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Double-blind placebo and active (Caffeine) controlled study to examine the effects of 3 doses of "Wake Up" herbal beverage on vigilance and function after lunch

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Abstract

Background Post-lunch dip is a well-established phenomenon associated with a substantial deterioration in cognitive function and productivity after lunch, resulting in potential increase in errors and accidents.
Wake-Up is a herbal based wake promoting beverage consisting of Guarana, Ginkgo Biloba, Elderberry and Fruit Up. A previous study showed that drinking Wake Up after lunch improved vigilance and performance similarly to caffeine. The aim of the current study was to test a novel composition of "Wake Up" beverage consisting of Guarana, Green Tea rich with polyphenols, Elderberry and Fruit Up in a double blind controlled methodology, with placebo and active control, and to examine the dose response effects of this beverage regarding alertness and function.

Methods Thirty healthy volunteers were studied in 5 visits, each time a similar regimen took place but different beverage was drank in a random and blinded order: placebo, WakeUp (in 3 doses: regular, double, tripple), or caffeine (100mg). They underwent a battery of functional tests at 3 time points in each visit: after lunce but prior to drinking, 30 and 120 minutes post-drinking. These tests included attention, executive function and memory tests, and hemodynamic measurements. The study results were compared (changes from baseline by the various beverages) utilizing one-way analysis of variance, with $P<0.05$ considered statistically significant.

Results The major findings were that in 3 measures: 2 attention tests and 1 executive test, there were significant improvements with Wake-Up beverage, Wake-Up double and triple dose, superior to the effect seen with 100 mg caffeine, during the 30 minutes and 120 minutes after lunch. In addition, unlike caffeine Wake up did not result in adverse hemodynamic effects, at any dose or time point.

Conclusions These results suggest that drinking Wake Up after lunch improves vigilance and performance significantly better than 100 mg caffeine. At 30 min and 120 minutes after drink the vigilance and performance remains high and is superior to caffeine, without adverse hemodynamic consequences. However, there was no classical dose-response curve and higher doses of Wake Up ingredients not necessarily responded in better functions.

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Introduction

The post-lunch dip is a well-established phenomenon of decreased cognitive function in the early afternoon hours typically after lunch consumption. It is thought to begin approximately 1 h after the start of lunch consumption. During the post-lunch dip, memory and vigilance are the most severely affected domains, and decreased mood, alertness and anxiety are also reported [1]. This phenomenon occurs in both adults and children, and may be further emphasized in individuals with nocturnal sleep disturbances or attention deficit hyperactive disorder [2-4]. [2-4]. There are several potential explanations for this phenomenon. One major possibility is that this is a circadian phenomenon, since it can be seen regardless of food intake in a constant routine study regimen [5]. This may be an evolutionary phenomenon since animals in savannas prefer to take a mid-day nap [6]. Another potential mechanism to explain this phenomenon is a sharp drop in cortisone/cortisol levels in the early afternoon which could explain the tendency to sleep [7]. Additional explanation lies in body temperature changes. When body temperature decreases, such as in early afternoon hours, tendency to sleep increases [6]. A heavy meal may alter the distribution of blood flow resulting in an increased flow to the intestine and a decreased one to the brain, which causes sleepiness [8]. Regardless of the mechanism, a reduction in alertness during this period may lead to poor judgment and increased human error, resulting in an increase in the accident rate and reduced performance in the workplace [9]. Experimental research has consistently demonstrated that napping during the day improves objective and subjective alertness, cognitive functioning, psycho-motor performance, memory and even mood [10]. Unfortunately, western society not frequently allows napping during the day. Studies have shown that this post lunch dip phenomenon has also a substantial economic burden. The cost of errors reduced productivity and fatigue has been estimated to cost employers $136.4 billion annually in US workers [11]. Thus, fighting this phenomenon is important for both individuals and societies.
One potential way to fight this Post Lunch Dip is by drinking coffee- The most widely consumed stimulant in the world [12]. The caffeine molecule is structurally similar to adenosine, which is an endogenous neurotransmitter with mostly inhibitory effects in the central nervous system, when acting through high affinity – A1- receptors. In general, adenosine inhibits adenyl1 cyclase via A1 receptors and stimulates adenyl cyclase via low affinity- A2- receptors. Caffeine is capable of non- specific binding to A1/A2 receptors and may act as a drug stimulating central nervous system via acetylcholine receptors. In higher concentrations of caffeine consumption, may explicate other mechanisms of action, including phosphodiesterase inhibition and calcium mobilization from intracellular storage sites in skeletal and cardiac muscles and neuronal tissue [13-14]. Indeed, it was found that drinking coffee at lunch improves alertness and performance compared to decaffeinated coffee [15]. On the other hand, caffeine results in a rebound phenomenon: sleepiness following a decrease in caffeine levels in blood and possible dependence. Moreover, caffeine has a relatively short half-life and potential side effects such as increased pulse rate and blood pressure. In addition, regular coffee drinking results in tolerance and substantial reduction of the effect of caffeine [16].

Another alternative which may reduce the post- lunch dip phenomenon is Wake-Up beverage - a wake promoting nutritional supplement. The relatively newly developed "WakeUp®" beverage (InnoBev Ltd, Tel Aviv, Israel) is a wake-promoting nutritional supplement based on herbal extracts of guarana, ginkgo biloba, elderberry and fruit-up. Guarana is a plant native to the Amazon. It has been previously shown that guarana seeds provide additional stimulation over caffeine alone and improves memory performance, mood and increases alertness without any additional impairment of the autonomic nervous system regulation [17-19]. The "Fruit-up" (which is a fruit extract containing predominantly fructose) predominantly adds taste to WakeUp, although its glucose content may also improve alertness [20]. In a previous study it has been shown that WakeUp may improve vigilance and function following lunch, compared to caffeine and placebo. It has been shown to improved short-term memory and function similarly to caffeine, but better than placebo, and that the effect was longer with WakeUp compared to caffeine. While drinking WakeUp after lunch improved vigilance and performance similarly to caffeine and significantly better than placebo 30 min following the drink, 120min following the drink, performance and vigilance with WakeUp remained high, significantly superior to both placebo and caffeine[21]. While Caffeine increased blood pressure and pulse rate, WakeUp had no such an adverse effect [21]. Thus, WakeUp may be an appropriate and effective drink to counteract the somnolence and reduced performance during the post-lunch hours, without hemodynamic side effects.

Recently the content of the beverage has been changed and instead of ginkgo biloba, green tea rich with polyphenols has been added. In a preliminary open proof of concept study of 20 volunteers we found that this change did not deteriorate the wake-

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promoting capabilities of this drink (data not published). Thus, the current study was planned to test the new composition in a double-blind controlled methodology, and also to examine the dose response effects of this beverage regarding alertness and function. We hypothesized that drinking WAKE UP after lunch will improve short time memory, attention and executive function compared to placebo and similarly or more than caffeine. We expected to find a dose response effect, with no effect on blood pressure and pulse rate.

SUBJECTS AND METHODS

Wake Up new formula

The current composition of the WakeUp beverage consists of herbal extracts of guarana, green tea, elderberry and Fruit-up, with the following characteristics:

	Amount per Serving
Calories	20
Total Carbohydrates	14 g
Sugars	11 g
Added Sugars	11 g
Green tea powder	75 mg
Guarana seed extract	50 mg
Elderberry extract	50 mg

Serving size (1 bottle): 200ml

Other Ingredients: Water, Fruit Syrup, Natural Flavors, Lemon Juice, Malic Acid

Manufactured by Frutarom USA, Inc, safety approved by EAGLE Food Registrations, Inc.

Study participants

This was a randomized, double-blind, controlled study with placebo and active control. The study took place in Carmel medical center. Thirty healthy volunteers participated. Initial assessment of inclusion and exclusion criteria took place on a screening visit. Inclusion criteria consisted of age over 18 years, who could understand and signed an informed consent. Exclusion criteria consisted of shift work, usage of hypnotics or stimulants, unstable medical condition. Once participants have met criteria for participation and signed an informed consent, they were enrolled and undergone randomization. Subjects were asked to avoid any caffeine-containing beverage or food after 7:00 in the morning of any test day.

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Study procedure

After the screening visit, the study consisted of 6 more visits. In the first 5 visits, each time a similar regimen took place, but different beverage was drank in a random and blinded order: placebo, WakeUp® (in 3 doses: regular, double, tripple), or caffeine (100mg).

Study schedule:

.1 Visit 1: Participants had their regular lunch following which a first set of performnce studies took place (see below, studying attention, executive function and memory). Immediately thereafter, the participant drank the tested beverage (marked A, B, C, D or E in a randomized order). Thirty minutes after drinking, a second set of studies will took place (exactly equal to the previous set of studies). A third set of studies (exactly the same as the previous two) took place 2 hours following the drink.

.2 Visits 2, 3, 4, and 5 were exactly like visit 1, just that the beverage was different, such that each participants after completing 5 visits had all tested beverages: placebo, 100mg Caffeine, WakeUp® regular dose, WakeUp® double dose, WakeUp® triple dose.

.3 Visit 6: A telephone call or a face-to-face visit (based on the preference of the participants) one week after the study to make sure there were no side effects and to close participation.

The time between screening and visit 1 was up to 1 month. The time between any two other visits (visit 1 to 2, 2 to 3 etc) was up to 14 days. Each one of visits 1 to 5 begun after lunch, between 11:30 and 15:00, preferable at the same time in all visits 1 to 5. Treatment was randomized for the order of tested beverages (A to E) in visits 1 to 5 by the researcher. Blinding was kept by the manufacturer of the beverages (Frutarom USA, Inc). All 5 beverages (placebo, 100mg Caffeine, WakeUp® regular dose, WakeUp® double dose, and WakeUp® triple dose) were marked by a letter between A to E, which was blinded to the participants and the staff of the study. Only after the completion of the study and statistical analyses and reporting, the various beverages (letters) were unblinded.

Attention, Executive Function and memory tests

At all testing times (3 times at every visit from visit 1 to 5) the following tests were performed:

Vital signs (blood pressure and pulse rate)

5 Neurocognitive function tests, by Cambridge Cognition company, were performed on an iPad tablet. The following tests were completed:

Attention:

RTI- Reaction Time (a 2-3-minute test). Outcome measures are divided into reaction time and movement time for both the simple and five-choice variants.

RVP - Rapid Visual Information Processing (a 7-minute test). Outcome measures cover latency (speed of response), probability of false alarms and sensitivity.

Executive Function:

MTT- Multitasking Test (an 8-minute test). Outcome measures for the Multitasking Test include response latencies and error scores that reflect the participant's ability to manage multitasking and the interference of incongruent task-irrelevant information on task performance

SSP- Spatial Span (a 5-minute test). Outcome measures cover span length (the longest sequence successfully recalled), errors, number of attempts and latency (speed of response).

Memory:

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SWM-Spatial Working Memory (a 4-minute test). Outcome measures include errors (selecting boxes that have already been found to be empty and revisiting boxes which have already been found to contain a token) and strategy and latency.

The data from the iPads were compiled by Cambridge Cognition and the raw data were put into a CSV file which was downloaded from the tablet directly. The secure private cloud environment was provided by HIPAA-accredited supplier Armor. The study data were analyzed in Microsoft Excel and the results were compared utilizing one-way analysis of variance, with $P<0.05$ considered statistically significant.

RESULTS

Of the 30 participants 8 were men, and 22 were women. The average age was 38±10 years (range 18-59 years). The mean Height was 167±7cm (range 156-180cm) and mean weight was 70±14Kg (range 46-105 Kg).

The major findings are that in 3 of the 5 measures: two attention tests and one executive test, there were significant improvements with Wake-Up beverage superior to caffeine after lunch.
In reaction time (RTI) attention test the reaction time in milliseconds, 30 minutes after the drink, was better with wake up beverage and wake up double dose compared to caffeine: 364±39, 362±47, 358±41 msec respectively, $p<0.05$. 120 min after drinking the caffeine containing drink the reaction time deteriorated (tended to increase, not significantly) while reaction time after wake up double and triple beverages remained significantly better (Fig 1, table 1). Similar results showing wake up, wake up double and Wake Up triple superior to caffeine after 120 minutes were observed also in another executive test reflecting reaction time (Fig 2). As can be seen, with all doses of Wake up reaction time was faster (albeit not in all doses and times it was significant, and there was no classical dose response relationships). Interestingly, this test also showed a significant improvement in reaction time after placebo drink, but not after caffeine drink.

The total number of target sequences (Correct Hits within the allowed time) that were correctly responded to during assessment sequence blocks (RVPTH, an attention test) also showed improvement with wake up beverage (2 times significant and the rest just trend) which was not seen with Caffeine (Fig 3, table 1).

The remaining of the tests (SSP- Spacial Span and SWM-Spatial Working Memory) did not show improvement following wake up drinking or caffeine, Table 1).
Interestingly, while all doses of Wake Up beverage did not result in significant hemodynamic changes, Caffeine resulted in significant elevation of systolic blood pressure 120 minutes following drinking it (118±15 vs 125±14 respectively, $p<0.05$, Table 2).
None of the participants reported any side effects for any of the beverages, during the study or one week after the end of the study at visit 6.

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Fig 1. RTIFMDRT (Reaction Time Five-Choice Median Reaction Time) Attention Test- assessed by reaction time in milliseconds.
*p<0.05 wake up vs caffeine and placebo

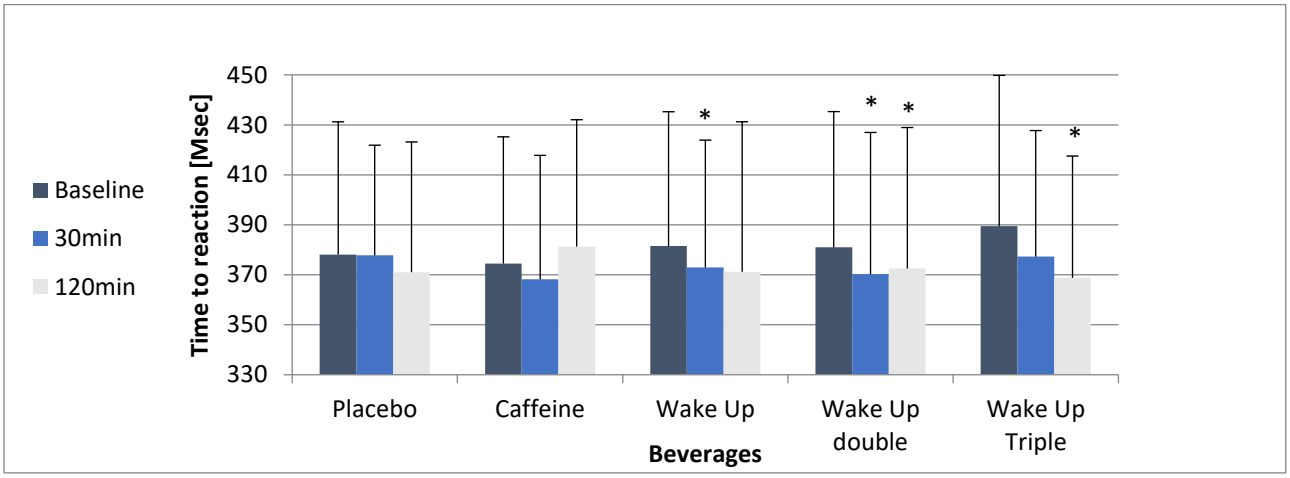

Fig 2: Reaction time- MTTLM (The mean latency of response from stimulus appearance to button press) - executive function test measured in milliseconds

*p<0.05 wake up vs caffeine

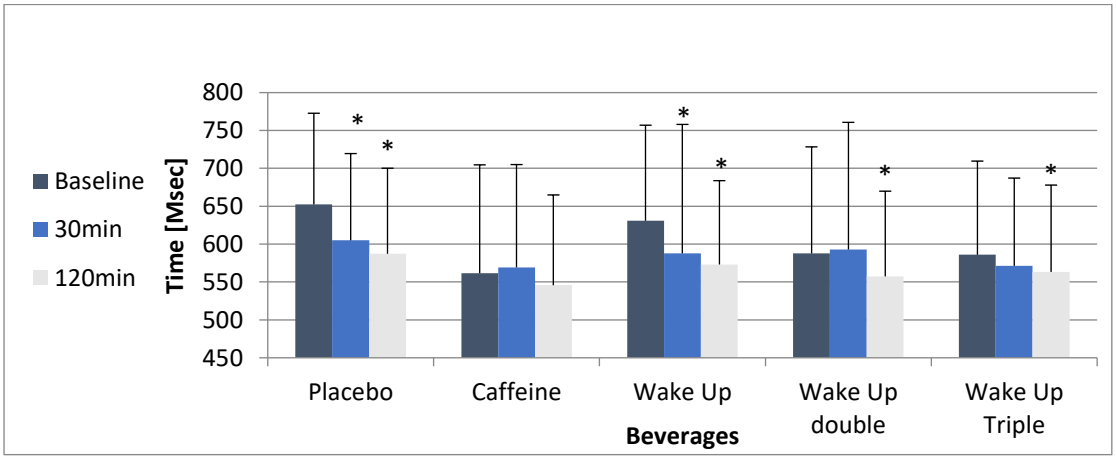

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Fig 3. RVPTH attention test measured in milliseconds

*p<0.05 wake up vs caffeine and placebo

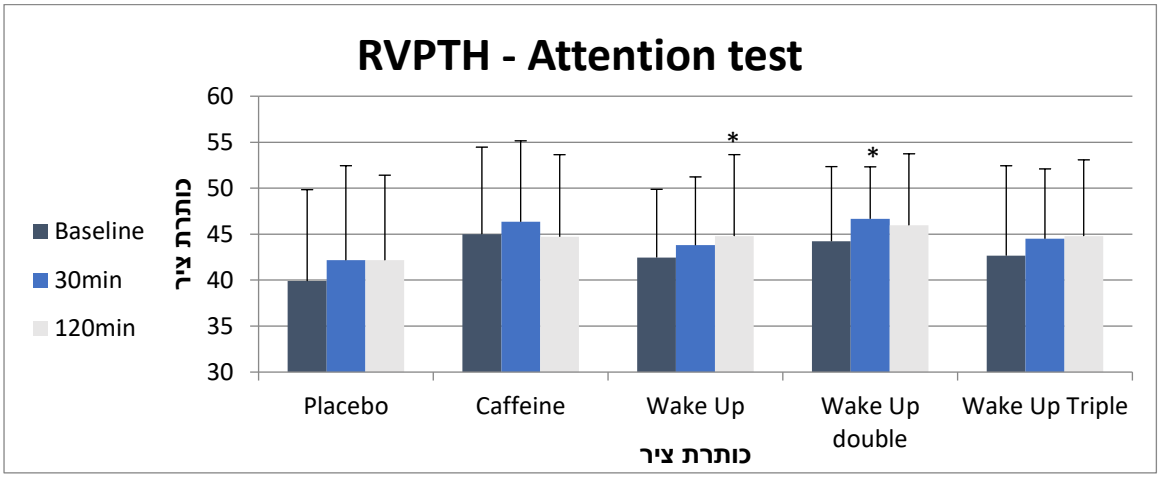

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Table 1. results of several tests with the various beverages at baseline, 30 and 120 minutes after the drink
*p value<0.05 wake up vs caffeine

Test:	RTIFMDRT (Msec)	RVPTH (number)	MTTLM (Msec)	SSPFSL (number)	SWMTE468 (number)
Placebo					
Baseline	378 ± 53	40 ± 10	652 ± 120	6.9 ± 1.7	11 ± 10
30min	378 ± 44	42 ± 10	605 ± 114 *	7.4 ± 1.6	10 ± 10
120min	371 ± 52	42 ± 9	587 ± 113 *	7.1 ± 1.9	8 ± 9
Caffeine					
Baseline	375 ± 54	45 ± 7	561 ± 126	7.4 ± 1.4	7 ± 8
30min	368 ± 51	46 ± 7	569 ± 170	7.7 ± 1.9	9 ± 11
120min	381 ± 60	45 ± 9	546 ± 111	7.3 ± 1.7	7 ± 9
WU Single					
Baseline	381 ± 51	42 ± 9	631 ± 143	7.0 ± 1.5	10 ± 11
30min	373 ± 50 *	44 ± 9	588 ± 136 *	7.7 ± 2.5 *	8 ± 8
120min	371 ± 51 *	45 ± 9 *	573 ± 119 *	7.3 ± 1.6	9 ± 10
WU double					
Baseline	381 ± 54	44 ± 8	588 ± 141	7.5 ± 1.4	8 ± 7
30min	370 ± 57 *	47 ± 6 *	593 ± 158	8.3 ± 3.0	8 ± 11
120min	372 ± 56 *	46 ± 8	557 ± 112 *	7.5 ± 1.6	7 ± 7
WU Triple					
Baseline	390 ± 90	43 ± 10	586 ± 123	7.5 ± 1.5	7 ± 9
30min	377 ± 50 *	45 ± 8	571 ± 116	7.5 ± 1.4	7 ± 8
120min	369 ± 49 *	45 ± 8	563 ± 115 *	7.8 ± 1.5	8 ± 9

RTIFMDRT- RTI Median Five-Choice Reaction Time: The median duration it took for a subject to release the response button after the presentation of a target stimulus. Measured in milliseconds. **RVPTH**- The total number of target sequences that were correctly responded to

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(Correct Hits) within the allowed time during assessment sequence blocks. **MTTLM**: The mean latency of response (from stimulus appearance to button press). Calculated across all correct, assessed trials. Measured in Msec. **SSPFSL**- Forward Span Length: The longest sequence of boxes successfully recalled by the subject. **SWMTE468**- Total Errors: The total number of times a box is selected that is certain not to contain a token and therefore should not have been visited by the subject.

Table 2. Hemodynamic measures with the various beverages at baseline, 30 and 120 minutes after the drink.
*p<0.05 caffeine vs wake up

	Baseline			30 min following drink			120 min following drink		
	Pulse rate	Systolic BP	Diastolic BP	Pulse rate	Systolic BP	Diastolic BP	Pulse rate	Systolic BP	Diastolic BP
Placebo	75±11	120±13	78±9	72±9	118±13	76±7	76±8	122±15	77±8
Caffeine	78±10	119±15	77±9	75±9	120±12	79±9	79±9	125±14*	77±9
WU Single	77±10	119±13	78±10	76±12	119±16	78±12	77±8	118±15	78±11
WU Double	77±11	118±15	78±10	72±9	120±17	78±10	76±8	120±16	78±10
WU Triple	76±9	121±14	77±9	73±8	121±14	79±10	77±7	119±16	77±9

DISCUSSION

This was a very carefully methodologically planned study to test the effects of a relatively novel herbal beverage based on guarana, green tea rich with polyphenols, elderberry and Fruit-up on function following lunch. It was tested in a double blind and controlled study (both placebo and active control) fashion (actually triple blind if we take into consideration that the statistician group were blinded to the key of beverage as well). The major findings were that in 3 measures: 2 attention and 1 executive tests, there were significant improvements with Wake-Up beverage, Wake-Up double and triple dose, superior to the effect seen with 100 mg caffeine, during the 30 minutes and 120 minutes after lunch. In addition, unlike caffeine Wake up did

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not result in adverse hemodynamic effects, at any dose. Yet, the results are not simple to understand, and merit deep discussion. First, there was no classical dose response improvement with the 3 doses of Wake up. Second, there was no improvement with caffeine. Third, in one measure (MTTLM) there was an improvement with caffeine.

A herbal based wake promoting beverage, has a very important potential with huge likely implications. An excessive meta-analysis which was done about the relationship between sleep and work shows that daytime fatigue has tremendous importance to organizations because of its relationship with employee performance, safety, health and attitudes [22]. Thus, a wake promoting drink may reduce this phenomenon of post-lunch dip and improve work performance and productivity after lunch time. One example for such a beverage is caffeine containing drink. However, several factors should be considered: first, there may be habituation and tolerance to caffeine [23]. Second, caffeine intake has been associated with a range of reversible and transient physiological effects broadly and cardiovascular effects specifically [24]. The question as to whether coffee intake increases the risk of coronary heart disease remains controversial [25]. Populations at risk for hypertension or already with hypertension may be more sensitive to some effects of caffeine and experience acute increases in blood pressure following caffeine consumption [26]. In addition, the impact of coffee intake on chronic diseases has been a matter of debate in the last two decades, with some conflicting result due the retrospective nature of most of the studies [27]. Thus, caffeine containing drinks may be effective for reducing post-lunch dip phenomenon but these disadvantages should be considered. We cannot know the reason why in the current study caffein containing beverage did not result in functional tests improvement, and was inferior to wake up beverage. We postulate that our participants were regular coffee drinkers (very common in Israel) and developed tolerance to caffeine. We did eliminate coffee drink in the day of each visit after 7:00 a.m. but did not monitor coffee drinking habits of our participants (see under limitations of the study). Regardless of caffeine, a vigilance promoting beverage which is not associated with adverse hemodynamic changes could be beneficial.

The newly developed Wake Up beverage tested in the current study consists of herbal extracts of guarana, green tea, elderberry and Fruit-up (fructose). It has already been shown that Guarana improves mood and memory performance and increases alertness [18]. The combination of these extracts with ginkgo biloba instead of green tea had also been shown to result in counteracting the post lunch dip fatigue [21]. The newly contained ingredient in the current formula was green tea. Green tea has been shown to have beneficial effects against a variety of diseases such as cancer, obesity, diabetes, cardiovascular diseases, and neurodegenerative diseases [28]. Systematic review aimed to establish the current knowledge regarding the effects of green tea consumption on cognition and human brain function showed that Green tea and it's main ingredients: EGCG and L- theanine, can enhance cognition, neuropsychology and brain functions, as the majority of the studies suggest [29]. Another study of green tea consumption on brain wave activities showed highly significant changes between 30 minutes and 1 hour post-consumption of green tea which may indicate its putative role in relaxation and cognitive function [30]. The Fruit up component enhances the taste of the beverage, while its glucose content may also improve alertness [31]. When blood glucose levels drop, such as in the post lunch dip, fatigue and reduced function occur [32]. Since neither placebo nor caffeine beverage contain fructose, this study cannot differentiate between the effects of the various components of the beverage.

Our study showed that Wake up has the potential to alleviate the undesired effects of the post lunch dip. In fact, not only that reaction times and executive function not deteriorated after lunch, they improved with wake-up beverage. Single, double and triple dose of wake-up showed superiority over 100 mg caffeine in 2 tests of attention reflected in reaction time and one executive test, 30 and 120 minutes after the drink. However, the magnitude of the improvements was subtle. Some of the changes showed only trend for improvement, while in some the changes were significant, and significantly better than the results seen with caffeine. We believe that the reason that some changes were significant while others did not results from two observations: first, the improvement was not dramatic, ranging between 3 to 29% improvement in the various tests. Second, there was high variability between the function test results both for each individual and between individuals, which made statistical analyses less prominent. Finally, there may be many additional various factors except for the beverage drank after

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lunch which may affect test results (mental status, sleep quality and quantity in the previous night, ambient temperature, work related events the same day etc.). These factors may also explain why in one of the tests placebo showed significant improvements. Another explanation for this finding (see limitations below) is that post hoc it turned out that randomization was not equal, and about 50% of the tests begun with placebo. Although each session consisted of training in order to avoid learning curve of the results, the fact that in many tests placebo was first to assess may contribute to the finding that here was an improvement with placebo due to learning of the study (learning curve).

This study has several limitations. First, as already mentioned, we did not monitor coffee drinking habits of our participants and cannot determine whether the lack of wake promoting effect with caffeine in this study results from tolerance. Second, as discussed above, we had used a complete randomization order for beverages usage (random for each participant) instead of ordered randomization which turned out as non-random, and some 50% of participants started the test with placebo. This possibly led to the improvement of functions following placebo. In the first visit the participants were also first introduced with the tests. Therefor, the improvement showed after drinking placebo could be explained by learning curve, no matter which beverage was consumed. Third, although participants were asked to avoid any caffeine-containing beverage or food in the morning of the tests day, we did not control for other factors that have an influence on vigilance: sleep on the night prior to the tests, physical activity during the day, content of the lunch. However, there is no reason to believe that there was a directional skew in this regard, and the participants or study researcher could not know what every participant would drink on each visit. Thus, we beliave this potential bias is random and does not effect the results. Forth, we used executive and functional tests as surogate of allertness. We could not use a direct allertness test such as MWT (maintenance of Wakefulness Test) due to the nature of the test and study, and the need to assess allertness in a timely test directly following beverage. Finally, the participants in our study were healthy. We can not predict how these beverages would affect specific patients such as those with obstructive sleep apnea, fibromialgia, heart failure or other illnesses resulting in fatigue. Thus, generalization should be avoided at this time.

CONCLUSIONS

Despite the above mentioned limitations, our findings suggest that drinking Wake up, containing green tea, guarana elderbery and fructose, after lunch improve vigilance and performance significantly better than 100 mg caffeine. At 30 min and 120 minutes after drink the vigilance and performance remains high and is superior to caffeine. Compared with caffeine, Wake up was not associated with increased pulse and blood pressure in the short term. This is the second study on Wake up that shows these results. Thus, Wake up appears to be an appropriate and effective drink to counteract the fatigue and reduced performance during the post lunch hours. Future larger studies are required to establish these results and to examine the long term effects and potential usage of this beverage.

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