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The subtle central effect of nutraceuticals: Is it placebo or nocebo?

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ABSTRACT

Background: Herbal medicines are often perceived by the general public as a "soft" alternative to Western Medicine, but the use of these substances can be risky since they can induce nocebo effect. **Aim:** The aim was to evaluate the nocebo effects of *Nigella sativa* oil, garlic and coenzyme Q10 (CoQ10) on the integrative function of the central nervous system and psychomotor performance. **Materials and Methods:** This is a randomized, double-blind, controlled, and prospective study conducted in the Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq during February 2013. A total of 160 medical students participated in this study were randomly assigned equally to one of the following groups: Group A: Received single dose of *N. sativa* oil (500 ml capsule); Group B: Received single dose of garlic (500 mg capsule); Group C: Received single dose of CoQ10 (120 mg capsule) and; Group D: received single dose of matching oral placebo (300 mg starch capsule). For all participants, reaction time and flicker fusion threshold were measured by the Leeds psychomotor performance test battery before and after 3 h of taking the drugs **Results:** Neither placebo nor nutraceuticals exerted significant effect on total reaction time. Although the recognition reaction time is insignificantly reduced by 2.77% (placebo), 5.83% (*Nigella sativa*), 7.21% (garlic) and 12.64% (CoQ10) from the pretreatment values, they are adversely affect the motor reaction time to reach the significant level in subjects pretreated with Garlic ($P = 0.02$). **Conclusion:** Nutraceuticals are not free from nocebo effect on psychomotor performance.

KEY WORDS: Garlic and coenzyme Q10, *Nigella sativa* oil, psychomotor performance

INTRODUCTION

Herbal medicines are often perceived by the general public as a "soft" alternative to Western Medicine, but the use of these substances can be risky since they can induce nocebo effect [1]. In 1961 Walter Kennedy chosen the term nocebo (Latin for I will harm) as the counterpart of placebo [2]. This term was introduced a few years after Henry Beecher published his paper on the placebo effect [3]. Most clinical studies explored the beneficial effects of nutraceuticals and ignored their nocebo effects, The seeds/oil of *Nigella sativa* has anti-inflammatory, analgesic, antipyretic, antimicrobial, hypotensive, hypoglycemic, antiepileptic and antineoplastic activity [4-7].

Garlic, considered either food or herbal medicine, possesses antimutagenic and antiproliferative properties that can be used in anticancer interventions, hypoglycemic [8-10].

Coenzyme Q10 (CoQ10) is an essential electron carrier in the mitochondrial respiratory chain and an important antioxidant. It exerts a beneficial effect on cognitive, digestive, cardiovascular and immune systems, and modulates inflammatory and degenerative processes in the body [11-13].

Nutraceuticals derived from such spices as turmeric, red pepper, black pepper, licorice, clove, ginger, garlic, coriander, and cinnamon target inflammatory pathways, thereby may prevent neurodegenerative diseases e.g., Parkinson's disease [14,15]. On the other hand, most clinical studies ignored the subtle central effect of the nutraceuticals, therefore the aim of this study is to show the nocebo effects of the nutraceuticals notably black cumin, garlic and CoQ10 on the integrative function of central nervous system and psychomotor performance in human using Leeds battery testing.

MATERIALS AND METHODS

This is a randomized, controlled, double-blind, prospective study conducted in the Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq in February 2013. A total of 160 healthy male volunteers were entered into the present study. They were randomly chosen from college medical students, aged ranges between 19 and 24 years (mean age 21 years). All participants were in good health, without any significant clinical history of physical or mental illness and not taking any concomitant medication that was likely to interfere with the study. Furthermore, caffeine and other beverages were forbidden on the study day. The study was approved by Local Scientific Committee of the Institution and written informed consent was obtained from all participants.

Prior to the study participants were trained to perform the psychomotor performance tests and practiced on three

separate occasions to exclude any learning bias. Then, they were randomly assigned equally to one of the following groups:

Group A: Received single dose of *N. sativa* oil (500 ml capsule, Sehapharma, Egypt).

Group B: Received single dose of garlic (500 mg capsule, private label nutraceuticals, USA).

Group C: Received single dose of CoQ10 (120 mg capsule, MaritzMayer Laboratories, USA).

Group D: Received a single dose of matching oral placebo (300 mg starch capsule).

All participants in the above 4 groups were subjected to Leeds battery psychomotor instrument before and after 3 h of taking the corresponding interventional agent (nutraceuticals or placebo) in order to assess their pre- and post-treatment psychomotor performance in term of choice reaction time (CRT), critical flicker fusion (CFF) and total reaction time (TRT).

It is well-known that CRT can be used to assess the sensory-motor alertness through measuring the speed of recognition and motor responding to particular sensory stimulus. In the present study, by using Leeds psychomotor tester, the participants instructed to respond to the bright red light that illuminated in one of six position in random way by pressing the button where the light presented. It's important to mention that the mean of 9 consecutive presentations is recorded as a response measure of three components of reaction time: recognition, motor, and TRT.

The recognition reaction time (RRT) represent the time spent between red light illumination in the Leeds psychomotor device and the beginning of participant responding toward that light (motor action), manifested by lifting of their finger from specific site (start button). The motor reaction time (MRT) represented by the time spent from the start of motor action to the end of it i.e., the time through which the finger of the participant moves from start button to the response button. Summation of RRT and MRT represent TRT.

The CFF task assessed the integrative capacity of the central nervous system (CNS) and, more specifically, the ability to discriminate discrete "bits" of sensory information. In this, the participants are asked to concentrate on 4 illuminated points and to response to the changes in illumination in these points from flickering to fusion and vice versa. Individual thresholds are determined by the psychophysical method of limits on 3 ascending (flicker to fusion) and 3 descending (fusion to flicker) scales. A decrease in the CFF threshold is indicative of a reduction in the overall integrative activity of the CNS.

All data were analyzed using the statistical package of social sciences (SPSS) version 15 for Windows program on the computer. Data were given as mean ± standard deviation (SD). Student's *t*-test was used to compare mean values between groups. Statistical significance was accepted as $P < 0.05$.

RESULTS

Table 1 shows that the neither placebo nor nutraceuticals exerted a significant effect on TRT. The RRT is insignificantly reduced by 2.77% (placebo), 5.83% (*N. Sativa*), 7.21% (Garlic) and 12.64% (CoQ10) from the pretreatment values [Table 1]. Nutraceuticals adversely affect the MRT to reach the significant level in subjects pretreated with Garlic [Table 1]. Placebo treatment reduced the MRT by 1.4% while the nutraceutical preparations prolonged the MRT by 12.22% (*N Sativa*), 30% (Garlic) and 8.82% (CoQ10).

Integrative activity of central nervous assessed by measuring the CFF threshold; ascending and descending components remained stable with placebo pretreatment and nutraceuticals [Table 2].

DISCUSSION

The results of this study show that garlic produces nocebo effect on the motor component of reaction time while *N. sativa* and CoQ10 produce placebo effect. All the nutraceuticals produce placebo like effect on the integrative activity of the CNS. The effects of *N. sativa* on the brain were extensively done on small animals and *in vitro* utilizing cell lines. These studies showed that *N. sativa* exert antiepileptic, anxiolytic, and cerebral protection against ischemia and reperfusion injury [16-19]. This study shows that *N. sativa* does not produce any effect on the healthy human brain in term of psychomotor performance or integration activity of CNS, i.e.; it is a safe nutraceutical. The neuroprotective effect of garlic was extensively studied in different experimental models of cerebral ischemia and

Table 1: Placebo and nocebo effects of nutraceuticals preparations

	N. Sativa oil	Garlic	CoQ10	Placebo
Total reaction time (min)				
Before	527.1±51,33	530.7±57.64	541.8±53.45	581.7±98.25
After	525.6±56.56	547.9±53.70	515.9±49.97	568.4±51.24
Recognition reaction time (min)				
Before	365.2±79.89	381.6±49.99	343.4±41.26	375.5±77.97
After	343.9±25.14	354.1±47.85	300.0±50.26	365.1±65.12
Motor reaction time (min)				
Before	161.9±63.16	149.1±47.64	198.4±66.24	206.2±49.20
After	181.7±49.17	193.8±42.12*	215.9±29.99	203.3±33.23

*P=0.02 compared with pretreatment value, *N. sativa: Nigella sativa*, CoQ10: Coenzyme Q10

Table 2: Effect of nutraceuticals on the integrative activity of CNS in humans

Nutraceutical	Critical flicker fusion threshold (ascending component)		Critical flicker fusion threshold (descending component)	
	Before	After	Before	After
N. Sativa oil	31.33±2.44	32.39±3.12	31.32±3.60	31.69±2.18
Garlic	31.61±4.03	31.04±3.18	30.62±2.25	31.83±3.59
CoQ10	32.39±3.12	32.39±1.91	32.11±4.22	32.21±2.24
Placebo	30.82±1.76	30.79±1.85	32.83±2.96	32.02±2.14

N. Sativa: Nigella sativa, CNS: Central nervous system

neurodegenerative diseases [20-22]. Other experimental animal studies showed that garlic improved the memory and cognitive function [23,24]. This study demonstrates the nocebo effect rather than the beneficial effect on the psychomotor function in the healthy human. Therefore, the garlic nutraceutical should prescribe with caution in conditions associated with impaired psychomotor performance, e.g., elderly age group or in concomitant use with CNS depressant agents, e.g., alcohol or antihistamines. CoQ10 protects the neurons from degenerative changes, e.g., Parkinson's disease, Huntington's chorea, optic nerve atrophy and it exerts a beneficial effect in the management of headache including migraine [25-27]. In this study, the effect CoQ10 on the psychomotor performance does not differ from the placebo effect. Short term therapy and one dose testing of each nutraceutical are the limitations of the study. It concludes that nutraceuticals are not free from nocebo effect on psychomotor performance.

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