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Side Effects of Cognizing, a Dietary Supplement Used to Improve the Brain Functioning, since its active substance, Citicoline, Allows Treating Cerebral Disorders, a study on Ants as Models

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Received: November 04, 2022; **Published:** November 08, 2022

Abstract

Since citicoline is efficient to treat cerebral disorders, cognizing which essentially contains this drug is sold as a dietary supplement to improve human adults' brain functioning. On ants, cognizing appeared to have only slightly this wanted effect, but to present side effects not reported in the product package. It induced agitation, stress, nervousness, what impacted the ants' locomotion, orientation, audacity, social relationships, correctly responding during tests. Cognizing did not affect the ants' sensory perception. The ants did not adapt to these side effects and did not habituate to the wanted effect. They developed a strong dependence on cognizing consumption. The effect of this product rapidly decreased after weaning, becoming different from its initial one as soon as two hours after weaning. These effects should be known by consumers who should be monitored as for the occurrence of dependence, social interactions impairments, locomotor problems and nervousness. Also, alternative methods allowing ameliorating the brain functioning should be used by human adults in good health.

Keywords: *Addiction; Dependence; Locomotion; Myrmica sabuleti; Nervousness; Social Relationships*

Abbreviations

ang.deg.: Angular Degrees; ang.deg./cm: Angular Degrees Per cm; mm/s: Millimeter Per Second; χ^2: Chi-Square; vs: Versus; n°: Number; cm: Centimeter; mm: Millimeter; mL: Milliliter; mg: Milligram; kg: Kilogram; s: Second; min: Minute; h: Hour; t: Time; %: Percentage

Introduction

Introduction to the studied topic

We here investigated on the side and wanted effects of the dietary supplement cognizing sold to human adults for improving their learning, memory, attention. Each tablet of this product contains 400 mg of citicoline, 80 mg of ginkgo biloba and 10 mg of pyrroloquinoline-quinone (PQQ). The active substance is thus essentially the citicoline. In a future work, we shall investigate on dietary supplements containing only the PQQ.

Citicoline, also named cytidine diphosphate choline or cytidine 5'- diphosphocholine, allows the generation of phosphatidylcholine from choline which occurs in the cellular membrane. This substance is the only or the most present substance of dietary supplements

sold under a lot of labels such as Cebroton, Ceraxon, Cidilin, Citifar, Cognizin, Difosfocin, Hypercol, NeurAxon, Nicholin, Sinkron and so on. After having been ingested, citicoline is hydrolyzed into choline and cytidine and after having crossed the brain barrier, the two latter substances are reformed into citicoline thanks to enzymes.

Citicoline is expected to ameliorate the brain functioning since it induces the production of phosphatidylcholine [1]. However, this statement is not unanimously accepted [2]. Citicoline may also be efficient for helping patients recovering after an ischemic stroke [3-6] and other neurological disorders [7,8]. However, also for those beneficial effects, the unanimity is not reached [9]. Nevertheless, citicoline has been proved to ameliorate the memory after traumatic injuries and for brain aging due to its efficiency to stabilizer the cell membrane [10]. Citicoline could also have a beneficial effect on patients suffering from glaucoma [11]. In fact, citicoline has a neuroprotective effect through several chemical mechanisms, which include an increase of the amount of choline and a beneficial effect on the cell membrane [12-17]. Such effects are particularly useful for elderly patients [18]. This is well documented in two reviews, one on the effects of citicoline after acute strokes [19], another one on all this drug effects including its efficiency to restore some neurotransmission functions [20].

Concerning the adverse effects induced by cognizing or citicoline consumption, very few ones are reported (on internet and in the notice for use joined to the substance packages). Psychiatric effects are sometimes reported, but they are not supported by the literature [21,22].

Since the beneficial effects of citicoline do not reach the unanimity and since nothing is known about this substance effect on the individuals' food intake, locomotion (muscle functioning), sensory perception, social relationships, stress, memory, adaptation to potential adverse effects, habituation to its presumed beneficial effect, dependence on its consumption and how its effect decreases after weaning, we intended to examine most of such physiological and ethological side effects of cognizing on ants used as models. Before relating our experiments and results, we here below recall why using ants, which species we used and what we know on it and the different traits we aimed to consider.

Why using ants

Basic biological processes, such as genetics, nervous cells functioning, muscles contractions, memorization, are identical for all animals including humans. Animals, invertebrates and vertebrates, are thus used as models for studying several physiological and ethological traits [23,24]. Invertebrates are often preferred because they are small, have a simple anatomy and a short life cycle, e.g. the fruit flies, nematode worms, mollusks, beetles, bees. Insects, among others *Hymenoptera*, are largely used [25,26]. Ants can thus be used as models. They are the more so since they can be easily maintained in any room, at a very low cost and detain many sophisticated biological traits on which the impact of drugs can be studied. They are eu-social, navigate using learned cues, recruit nestmates, differently mark the different parts of their living area, take care of their brood, clean their nest, build cemeteries and relocate their nest as necessary [27].

Which species was used and what is known on it

In the present work, we used the ant *Myrmica sabuleti* Meinert, 1861 as a model. Among others, we have studied its eyes morphology, visual perception, conditioning ability, recruitment strategy, navigation system, as well as the ontogenesis of some of their abilities [28,29]. They are imprinted to the appearance of their congeners, learn several behaviors in the presence of older congeners. These ants recognize themselves in a mirror [30]. The distance and size effects, as well as Weber's law can be applied to their perception [31,32]. They possess many rather sophisticated abilities, among other numerical ones, possess a number line, acquire the notion of zero, can expect the next element of an increasing or decreasing arithmetic or geometric sequence, can associate perceived elements with the time of day of their occurrence [33-36].

Which traits were examined

We examined the impact of cognizing on the following physiological and ethological traits: food intake, general activity, locomotion, orientation ability, audacity, tactile (pain) perception, social relationships, stress and cognition, cognition, conditioning acquisition and memory, adaptation to the side effects of citicoline, habituation to its wanted effect, dependence on its consumption and decrease of its effects after its consumption was stopped. The methods used were similar to those employed in previous works [54 products have been examined [37-39] i.e., six summaries of the studies of 51 products]. These methods are however here recalled for the readers' convenience, without avoiding inevitable self-plagiarism.

Aim of the Present Work

The aim of the present work was thus to define, using ants as models, the potential adverse as well as beneficial effects of the dietary product cognizing which contains essentially citicoline, a small amount of Ginkgo biloba and a very small amount of PQQ. This dietary supplement is nowadays sold for improving the brain functioning in human adults since citicoline has been proved to do so in humans suffering from brain damages and is considered as having very few negligeable side effects.

Materials and Methods

Collection and maintenance of the ants

The experiments were conducted on two colonies of *M. sabuleti* collected in September 2022 in the Aise valley (Ardenne, Belgium) from an abandoned quarry. These colonies contained about 600 workers, one or two queens and brood. They were nesting under stones and in grass. Each one was maintained in the laboratory in one to three glass tubes half filled with water, a cotton plug separating the ants from the water. The nest tubes of each colony were deposited in a tray (34 cm x 23 cm x 4 cm) the borders of which having been covered with talc to present ants from escaping. These trays served as a foraging area. In them, pieces of *Tenebrio molitor* larvae (Linnaeus, 1758) were provided three times per week and a small tube filled of a 15% aqueous solution of sugar was permanently present. The lighting of the laboratory varied between 110 and 330 lux, the ambient temperature constantly equaled *ca* 20°C, the humidity *ca* 80% and the electromagnetism 2 μWm^2. All these conditions were suitable to *M. sabuleti*. The ants are often here named workers or foragers or nestmates as do researchers on social insects.

Solution of citicoline given to the ants

A package of cognizing produced by the Laboratoire Therascience Belgum S.A. (Avenue Blonden, 52- 4000 Liège) was furnished by the pharmacist Wera (Brussels, Belgium). Humans consuming this dietary supplement are advised to intake two tablets of it per day. Humans consume this amount of cognizing per day while drinking about one liter of water. Insects, due to their physiology (excretory apparatus) and anatomy (cuticle), consume about ten less water than mammals. Consequently, to set the ants under a cognizing diet similar to that of humans, they must be provided with a solution of the content of two tablets of this dietary supplement into 100 ml of the sugar water commonly given to them, or what is enough for performing all the experiments, with a solution of the content of one tablet into 50 ml of sugar water. The realization of the latter solution is shown in figure 1. The adequate solution of cognizing was delivered to the ants in their usual sugar water cotton plugged tubes. The cotton plug was refreshed each 2 - 3 days and the entire solution was renewed each 7 days. Three times per day, it was checked if ants drunk the given solution and they did. All the control experiments were firstly performed on ants living under normal diet. Then, the tubes filled of sugar water were replaced by tubes filled of the sugared solution of cognizing and the test experiments begun after the ants were so maintained during one day.

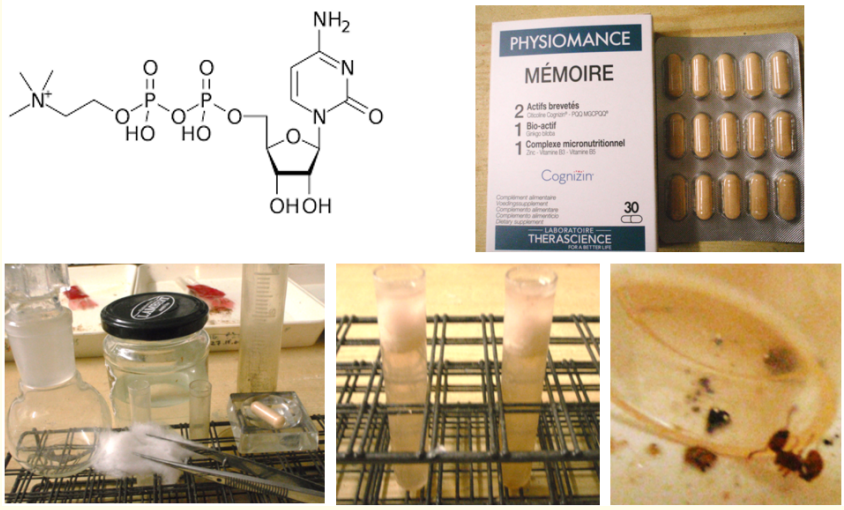

Figure 1: *Realization of the solution of cognizing given to the ants. Upper part: chemical structure of citicoline and an opened package of cognizing. Lower part: from left to right, the material used to make the solution, the two tubes given to the ants, an ant drinking the solution.*

Food intake and general activity

As in previous works [37-39], the ants present on the meat food, being at the entrance of the sugar water tube and being active at any place (foraging area, food sites, inside of the nest) were counted twice during the day and twice during the night during six consecutive days, this for the two used colonies and the kinds of diet (normal and with cognizing). For each kind of diet and each considered trait (meat intake, sugar water intake, activity), the daily mean of these 4 counts x 2 colonies = 8 counts was established (Table 1, lines I to VI) (total n° of counts = 8 x 6 days = 48 counts). The means of the six daily means were established (Table 1, line I- VI). For each examined trait, the six daily means obtained for ants under normal diet were compared to the six daily means obtained for ants under a diet with cognizing using the non-parametric test of Wilcoxon [40], the level of probability being set at 0.05.

Linear and angular speed, orientation ability

These traits were quantified, as in previous works [37-39] on foragers, the speeds without stimulating them, the orientation while stimulating them with a nestmate tied to a piece of paper (Figure 2A). Such a tied nestmate emits its attractive mandibular glands alarm pheromone and the foragers located in its surrounding orient themselves towards it. To assess the ants' speeds then to assess their orientation, the trajectory of 40 foragers were recorded. These trajectories were analyzed using appropriate software [41] set up on the basis of the following definitions. The linear speed (in mm/s) is the length of a trajectory divided by the time spent to travel it; the angular speed (in ang.deg./cm) is the sum of the angles made by successive adjacent segments, divided by the length of the trajectory; the orientation (in ang. deg.) towards a location is the sum of successive angles made between the direction of the location and the direction of the trajectory, divided by the number of measured angles. When the value of orientation is lower than 90°, the animal tends to orient itself towards the location; when the value of orientation is higher than 90°, the animal tends to avoid the location. For the linear speed, the angular speed and the orientation, the median and the quartiles of the distribution of the 40 recorded values was established (Table 2, lines 1, 2, 3). For

each variable, the distribution of the 40 values recorded for ants under normal diet was compared to that of the 40 values recorded for ants under a diet with cognizing using the non-parametric χ^2 test [40].

Audacity

This trait was examined through the ants' tendency to came onto an unknown apparatus. As in previous works [37-39], a cylindrical tower (height = 4 cm; diameter = 1.5 cm) tied to a squared platform (9 cm^2), both in white Steinbach® paper, was set in the ants' foraging area [26-29]. For the two used colonies, the ants present on the apparatus were counted 20 times over 10 min (total n° of counts = 20 x 2 colonies = 40) (Figure 2B). The numbers obtained for the two colonies were correspondingly added and the mean and the extremes of the recorded numbers were established (Table 2, line 4). To statistically analyze these data, the numbers of counted ants for the two colonies during two successive minutes were summed and the ten successive sums obtained for ants under normal diet were compared to the ten sums obtained for ants under a diet with cognizing using the non-parametric test of Wilcoxon [40].

Tactile (pain) perception

This trait was assessed through the ants' moving on a rough substrate as in several previous works [37-39]. Indeed, ants perceiving the uncomfortable character of a rough substrate walk on it with difficulty, slowly, sinuously and often touch the substrate with their antennae (Figure 2C). Ants poorly perceiving the uncomfortable character of a rough substrate walk on it more quickly, less sinuously and only seldom touch the substrate with their antennae. A folded piece (3 cm x 2 + 7 + 2 = 11 cm) of emery paper n° 280 paper was tied to the bottom and the borders of a tray (15 cm x 7 cm x 4.5 cm), dividing the tray in a first 3 cm long zone, a second 3 cm long zone covered with the emery paper and a last 9 cm long zone. To conduct an experiment on one colony, 20 ants were transported into the first zone of the apparatus and their trajectories were recorded while they walked on the emery paper. For each recorded trajectory (total n° = 20 x 2 colonies = 40), the ants' linear and angular speeds were assessed as they had been for ants walking in their foraging area (see the subsection relative to the speeds). The median and the quartiles of the distribution of each two kinds of recorded values were established (Tables 2, lines 5, 6) and each two distributions obtained for ants under normal diet were compared to each two distributions obtained for ants consuming cognizing using the non-parametric χ^2 test [40].

Brood caring behavior

As previously conducted [37-39], a few larvae of each colony were removed from the nest and deposited on the foraging area, near the entrance. For each colony, the ants' behavior towards five of these larvae were observed during five minutes (Figure 2D). The larvae among these 5 ones which were not re-entered in the nest after 30 seconds, 1, 2, 3, 4 and 5 minutes were counted. The numbers obtained for the two colonies were correspondingly added (Table 3, line 1). The six sums obtained for ants living under normal diet were compared to the six sums obtained for ants consuming cognizing using the non-parametric test of Wilcoxon [40].

Social relationships

Ants belonging to the same colony are normally not aggressive towards one another. Drugs could affect this peaceful social relationship. To assess potential aggressiveness against nestmates induced by cognizing, five dyadic encounters were performed, as in previous works [37-39], for ants under one and the other kinds of diet and for the two used colonies (10 encounters for each diet). Each encountering was conducted in a cylindrical cup (diameter = 2 cm, height = 1.6 cm), the borders of which being covered with talc to prevent ants from escaping. During each encountering, one ant of the pair was observed during 5 minutes and its behavior towards its opponent was characterized by the numbers of times it did nothing (level 0 of aggressiveness), touched its opponent with its antennae (level 1), opened its mandibles (level 2), gripped and/or pulled its opponent (level 3), tried to sting or stung it (level 4) (Figure 2E). The numbers of these five behaviors obtained for the two colonies were correspondingly added (Table 3, line 2). The distribution of the five sums obtained for

ant consuming cognizing was compared to the distribution of these five sums obtained for ants living under normal diet using the non-parametric χ^2 test [40]. Also, the ants' level of aggressiveness was evaluated by the variable 'a', which equaled the number of aggressiveness levels 2 + 3 + 4 divided by the number of levels 0 + 1.

Stress and cognition

This trait was assessed through the ants' ability to escape from an enclosure. Indeed, for doing so, the enclosed individuals must stay calm, look for an exit and have their cognitive abilities intact. Therefore, as in previous works [37-39], for each kind of died and each two colonies, six ants were enclosed under a reversed polyacetate cup (h = 8 cm, bottom diameter = 7 cm, ceiling diameter = 5 cm; its inner face being slightly covered with talc) set in the foraging area. To allow the ants escaping, a notch (3 mm height, 2 mm broad) had been made in the rim of the bottom of the cup (Figure 2F). The ants escaped after 2, 4, 6, 8, 10 and 12 minutes were each time counted. The numbers obtained for the two colonies were correspondingly added (Table 3, line 3). The six sums obtained for ants consuming cognizing were compared to those obtained for ants maintained under normal diet using the non-parametric Wilcoxon test [40].

Cognition

This trait was assessed as in previous wors [37-39] through the ants' ability to cross a twists and turns path. For each colony a simple apparatus was built. Two duly folded pieces of white extra strong paper (Steinbach®, 12 cm x 4.5 cm) were inserted into a tray (15 cm x 7 cm x 4.5 cm) in order to divide this tray in a first zone lying in front of a second zone containing the folded paper which created a twists and turns path and a third zone lying beyond this difficult path (Figure 3A). To make an experiment on a colony, 15 ants were transferred into the first zone of the apparatus and those still in this zone as well as those having reached the zone lying beyond the twists and turns path were counted after 2, 4, 6, 8, 10 and 12 minutes. The numbers obtained for the two colonies were correspondingly added (Table 3, line 4). The six sums obtained for ants consuming cognizing were compared to the six sums obtained for ants maintained under normal diet using the non-parametric Wilcoxon test [40].

Conditioning acquisition and memory

As in previous works [37-39], at a given time, a green hollow cube (made of strong green paper Canson®) was set above the entrance of the sugar water tube of each two colonies and the mealworms were relocated near this cube (Figure 3Ba). This having been done, the ants underwent visual conditioning. The control experiment was previously made on a distinct colony because when an individual has acquired a given conditioning, it keeps it for a rather long time and even after having lost its conditioning, it more quickly than initially acquires it again. Thus, it can no longer be used for assessing its native conditioning acquisition ability. Since the start of the ants' conditioning, over the ants' conditioning acquisition, then, after the cues' removal, during the ants' loss of conditioning, the ants of the two colonies were tested in an own Y-apparatus (Figure 3Bb). These Y-mazes were built in strong white paper, had their sides slightly covered with talc and their floor covered with a thin paper changed between each test and were set in a tray (30 cm x 15 cm x 4 cm). A green hollow cube was set randomly in one or in the other branch of each Y-apparatus. To make a test on a colony, 10 ants were transferred one by one inside the Y-maze before its division into two branches and each ant's first choice of a branch of the apparatus was recorded. Choosing the branch containing the green cube was considered as giving the correct response. After having been tested, each ant was kept in a cup until 10 ants of its colony were tested to avoid testing twice the same ant. After having tested 10 ants, all of them were transferred again into their foraging area. For each test, the numbers of ants of the two colonies having given the correct and the wrong responses were correspondingly added, while the numbers obtained during the control experiment were used as they were, what allowed establishing the conditional score obtained at each experimental time (Table 4). The successive scores obtained for ants consuming cognizing were compared to the successive scores obtained for ants living under normal diet by using the non-parametric Wilcoxon test [40].

Adaptation to side effects of cognizing

Adaptation to a substance occurs when an individual less and less suffers from the side effects of that substance over its consumption. To examine if such an adaptation occurs, a trait impacted by the considered substance must be quantified soon after the start of its consumption, then again after a longer time and the results of the two quantifications must be compared. In the present work, the ants' angular speed was impacted by cognizing. Consequently, this trait was again assessed after 6 days of the dietary supplement consumption, exactly as they had been assessed after one day of consumption and the results of the two assessments were compared to one another using the non-parametric χ^2 test [40].

Habituation to wanted effects of cognizing

Habituation to a product occurs when the individual consuming this product less and less perceives the wanted effect of the product over its consumption. To detect such a habituation, an effect improved by the product must be quantified soon after the individual has consumed it, then later, after some time of consumption and the results of the two quantifications must be compared. In the present work, the ants' memory appeared to be enhanced by cognizing consumption and since we examined this memory from 3 to 6 days after the ants consumed the dietary complement, we could evaluate the ants' potential habituation to this wanted effect on the memory. We also looked to another trait requiring some cognitive abilities, i.e., the ability to escape from an enclosure, after the ants had cognizing at their disposal for 7 days (See the subsection relative to the ants' habituation written in the Results and Discussion section).

Dependence on cognizing consumption

Dependence on a product occurs when the individual consuming this product enjoys doing so, wants to have it at any time at his disposal, consumes it even if suffering from adverse effects and finally can no longer live without using it. Briefly, he prefers having the substance than staying without it. In the present work, as in previous ones [37-39], dependence on cognizing was studied after the ants had it at their disposal during 9 days. On the tenth day, for each two experimented colonies, 15 ants were transferred into a tray (15 cm × 7 cm × 5 cm; the borders being covered with talc) inside of which two cotton-plugged tubes (h = 2.5 cm, diam. = 0.5 cm), one filled with sugar water, the other filled with the sugar solution of cognizing used over the experimental work had been deposited (Figure 3E). The tube containing the dietary supplement was set on the right for one colony and on the left for the other colony. Then, for each colony, the ants approaching each tube were counted 20 times over 10 minutes (Table 5, lower part) and the numbers obtained for the two colonies were correspondingly added. The two obtained sums allowed calculating the proportion of ants having chosen the drug solution and the drug-free one (Table 5, lower part). Also, the two obtained sums of counted ants were compared to the numbers expected if the ants had randomly approached each tube using the non-parametric χ^2 goodness-of-fit test [40].

Decrease of the effect of cognizing after its consumption was stopped

This decrease was studied after the ants had cognizing at their disposal for 11 days, according to a protocol similar to that used in previous works [37-39]. At the end of the 11th day, the ants were provided with a fresh solution of the dietary supplement and 12 hours later, so at the 12th day, their angular speed was assessed as they had been after 1 and 7 days of cognizing consumption, except that 20 instead of 40 ants' trajectories were recorded and analyzed in order to be able to make every assessment over the study of the decrease and so to evaluate the situation at any time. After that assessment made at the 12th day, which was that made at t = 0, weaning started, i.e., the tubes filled with the sugared solution of the dietary supplement were replaced by tubes filled with the usual drug-free sugared solution. From this time, the ants' angular speed was assessed every two hours until it became identical to that of ants maintained under normal diet, i.e., to the control. For each testing time, the median and the quartiles of the 20 recorded data were established (Table 6). Also, for each testing time, the obtained distribution of angular speed values was compared to that obtained at t = 0 and to the control one using

the non-parametric χ^2 test (Table 6) [40]. These results are in addition illustrated in figure 4. It was also tried to define the mathematical function best describing the decrease over time of the effect of cognizing after its consumption was stopped and this empirical function is given in the text.

Results and Discussion

Food intake and general activity

These three important physiological traits were affected by cognizing consumption (Table 1). While consuming this dietary supplement, the ants eat less meat, drunk less sugar water and were less active than while living under normal diet. This was statistically significant for each examined trait: each time: N = 6, T = -21, P = 0.016. The decrease of general activity may simply be a consequence of the less intake of meat and sugar and the latter fact should be taken into account when using cognizing for improving humans' brain functioning.

Days	Normal diet			Diet with Cognizing		
	Meat	Sugar water	Activity	Meat	Sugar water	Activity
I	0.63	1.00	20.13	0.50	0.25	10.50
II	0.75	1.00	20.75	0.38	0.38	11.25
II	0.88	1.25	20.25	0.25	0.25	10.88
IV	0.50	1.00	20.00	0.25	0.38	9.13
V	0.88	1.13	21.38	0.25	0.25	10.50
VI	0.88	1.13	21.00	0.38	0.25	10.25
I-VI	0.75	1.09	20.59	0.34	0.29	10.42

Table 1: *Impact of cognizing on the ants' food intake and activity. The dietary supplement affected these three ethological and physiological traits. Details and statistics are given in the text.*

Linear and angular speed

The observation of the ants walking while they were under a diet with cognizing leaded to the conclusion that they walked a little more quickly and essentially largely more sinuously than when they were under normal diet. Such an observation was confirmed by the numerical results (See table 2, lines 1,2) as well as by the statistical results. Indeed, we obtained for the linear speed $\chi^2 = 7.67$, df = 2, $0.02 < P < 0.05$; and for the angular speed: $\chi^2 = 9.33$, df = 2, $0.001 < P < 0.01$. Such an impact of cognizing on the locomotion may occur in humans and should be taken into account when intaking this dietary supplement.

Orientation ability

This ethological trait was affected by cognizing consumption. The observation of the ants consuming this product and presented with a tied nestmate incited to deduce that such ants seemed to oriented themselves towards the tied nestmate not as well as when they were under normal diet. Effectively, the numerical and the statistical results confirmed this presumption: see the numerical data in table 1, line 3; the statistical results were: $\chi^2 = 33.88$, df = 2, $P < 0.001$. Such a poor orientation may result from the ants' large sinuosity of movement (See the previous subsection), but might also be due to a decrease of the ants' sensory perception, a presumption examined in a following experiment (See the subsection relative to the ants' tactile (pain) perception).

Traits	Normal diet	Diet with Cognizing
Linear speed	10.0 (8.8 - 11.2)	9.2 (7.7 - 10.2)
Angular speed	109 (100 - 123)	132 (113 - 156)
Orientation	30.7 (20.2 - 39.8)	65.3 (44.7 - 74.9)
Audacity	2.90 [1 - 4]	2.65 [2 - 3]
Tactile perception		
Linear speed	3.7 (3.3 - 4.2)	4.6 (4.0 - 5.4)
Angular speed on a rough substrate	288 (273 -341)	283 (241 - 313)

Table 2: *Impact of cognizing on five ethological and physiological traits. The dietary supplement affected the ants' locomotion and orientation, slightly their audacity, but not their tactile (pain) perception.*

Audacity

This ethological trait was slightly affected by cognizing consumption (Table 2, line 4, figure 2B). While consuming this dietary supplement, the ants were somewhat less incline to come onto the unknown apparatus than when living under normal diet but this difference was not significant (N = 9, T = -34.5, P = 0.092). This result was in agreement was the previously observed slight decrease of activity of ants living under a diet with cognizing (See the subsection relative to the ants' activity).

Tactile (pain) perception

Cognizing did not affect this important physiological trait (Table 2, lines 5, 6; figure 2C). Ants under normal diet walked on a rough substrate at a lower linear speed and a higher angular speed than on their foraging area and this was significant: linear speed: $\chi^2 = 80.00$, df = 1, P < 0.001; angular speed: $\chi^2 = 65.45$, df = 1, P < 0.001. In the same way, while consuming cognizing, the ants walked more slowly and more sinuously on a rough substrate than on their foraging area and these two differences were also significant: linear speed: $\chi^2 = 65.45$, df = 1, P < 0.001; angular speed: $\chi^2 = 68.83$, df = 1, P < 0.001. The poor orientation to a tied nestmate of ants under a diet with the dietary supplement was thus not due to a decrease of their attractive pheromone perception, but simply to their large sinuosity of movement (See the above subsection relative to the ants' orientation).

Brood caring behavior

Cognizing affected this ethological trait. While ants under normal diet soon found the larvae removed from the nest, rapidly held them in their mandibles and quickly transported them towards, then in the nest, those consuming the dietary supplement delayed in taking the larvae in their mandibles (Figure 2D) and if having done so, they did not well orient themselves towards the nest entrance. All this leaded to a difference between the ants under one and the other kinds of diet as for the numbers of re-entered larvae over time (Table 3, line 1). This difference was significant: N = 5, T = 15, P = 0.031. The ants' poor orientation towards the nest entrance was in agreement with that towards a tied nestmate (See the above subsection relative to this trait) and the ants' delay to take the larvae may reflect an impact of cognizing on the ants' social relationships, a presumption examined through the following experiment (See the next subsection).

Social relationships

This trait was unexpectedly affected by cognizing consumption (Table 3, line 2; figure 2E). Under normal diet, the ants stayed side by side, making antennal contacts and seldom slightly opening their mandibles. While consuming the dietary supplement, the ants did not exactly do so, but rather often largely opened their mandibles. This difference of behavior between the ants maintained under one and the other kinds of diet was significant: $\chi^2 = 42.10$, df = 2, P < 0.001. Also, the variable evaluating the ants' aggressiveness equaled 0.10

for ants under normal diet and 0.92 for ants consuming cognizing. Effectively, we often observed aggressive postures in ants maintained under the dietary supplement all over our ants' maintenance and experiments. Such events may occur in humans consuming cognizing and attention should thus been paid to this potential occurrence.

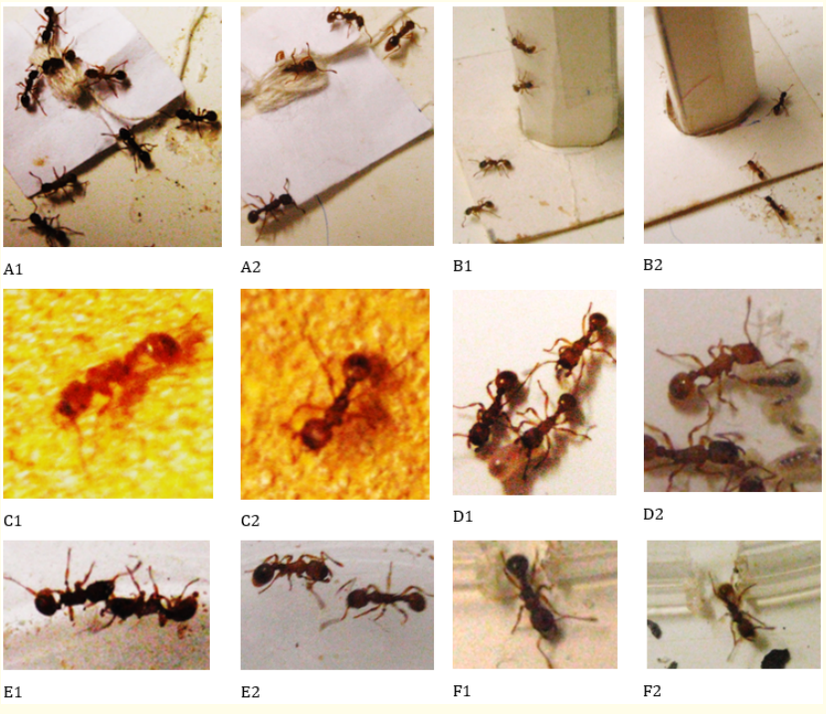

Figure 2: *Some views of the experiments made to know the impact of cognizing on six physiological and ethological traits. 1: Ants under normal diet, 2: Ants under a diet with cognizing. A: Ants coming near a tied nestmate very well while under normal diet, less well while consuming cognizing. B: Ants coming onto an unknown apparatus less frequently while consuming cognizing. C: Ants walking with difficulty on a rough substrate, whatever their diet. D: An ant under normal diet duly transporting a larva and delaying doing so while consuming cognizing. E: Two nestmates presenting some aggressive behavior (opening their mandibles) while consuming cognizing. F: An ant escaping from an enclosure whatever their diet.*

Traits	Normal diet	Diet with Cognizing
Brood caring: n° of not re-entered larvae over time	30'' 1' 2' 3' 4' 5' 10 8 6 4 0 0	30'' 1' 2' 3' 4' 5' 10 10 8 8 6 4
Social relationships: n° of 0 - 4 levels of aggressiveness; 'a'	0 1 2 3 4 'a' 53 46 9 0 0 0.10	0 1 2 3 4 'a' 23 29 48 0 0 0.92
Stress and cognition: n° of escaped ants over time	2' 4' 6' 8' 10' 12' 2 4 7 10 12 12	2' 4' 6' 8' 10' 12' 2 3 5 6 8 9
Cognition: n° of ants in front (f) and beyond (b) a twists and turns path	2' 4' 6' 8' 10' 12' f: 19 16 14 10 9 7 b: 0 1 4 6 9 11	2' 4' 6' 8' 10' 12' f: 16 16 13 11 9 8 b: 1 1 2 2 3 5

Table 3: *Effect of cognizing on four ethological and physiological traits. The dietary supplement affected the ants' brood caring behavior, social relationships and due to their increase of stress and agitation, their ability to escape from an enclosure and to cross a twists and turns path. Photos are shown in figure 2 and 3 and details are given in the text.*

Stress and cognition

Cognizing affected this ethological trait (Table 3, line 3; figure 2F). Under normal diet, the enclosed ants walked erratically during a short time, then more calmly all along the rim of the enclosure and if finding the exit, went out. While consuming the dietary supplement, the ants did not stop to walk erratically, very sinuously (even more than on their foraging area), were not attentive to the potential presence of an exit, often opened their mandibles and seldom found the exit. However, when they found this exit, they went out. Obviously, their state of stress was high but their cognition seemed to be intact. Nevertheless, since they largely delayed in finding the exit, the numbers of escaped ants over time were lower than those observed for ants under normal diet and this numerical difference was significant ($N = 5$, $T = 15$, $P = 0.031$).

Cognition

Cognizing seemed to not impact this ethological trait (Table 3, line 4; figure 3A). Under normal diet, the ants rather soon entered the twists and turns path and progressed inside of it over time. Eleven from 30 ones could reach the area lying beyond this difficult path. While consuming the dietary supplement, the ants also entered rather soon the twists and turns path, but moving erratically, sinuously, coming often back on their way, only 5 ones could reach the area lying beyond the difficult path over the 12 experimental minutes. Finally, the difference between the ants under one and the other kinds of diet as for their ability to cross the twists and turns path was not significant: in front of the path: $N = 4$, $T = -8$, $P = 0.188$; beyond the path: $N = 5$, $T = -15$, $P = 0.063$. On the basis of these results and of the observation of the experimented ants, it could be concluded that the ants' stress, nervosity, agitation was increased under cognizing consumption, but that their cognition was not decreased, was not affected and may even appear somewhat improved if the ants were not so agitated. The following experiment examined again the impact of cognizing on the ants' cognitive abilities.

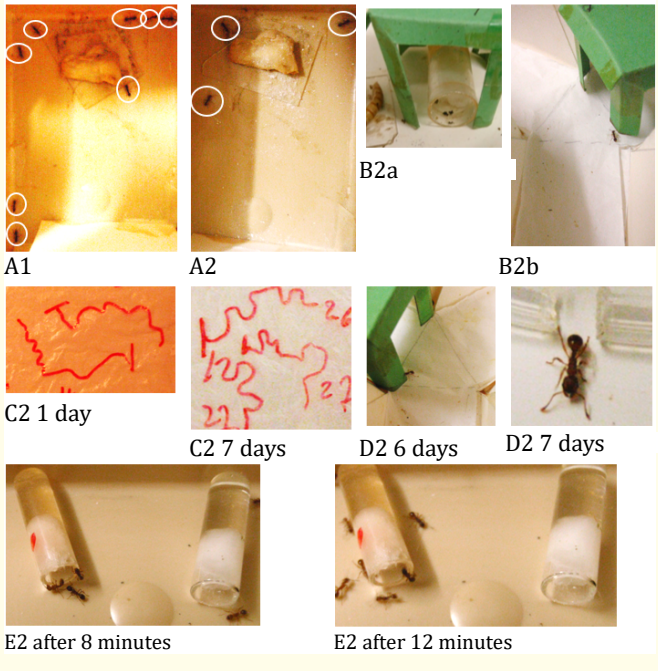

Figure 3: *Some views of the experiments made for studying five side effects of cognizing. 1: ants under normal diet; 2: ants under a diet with cognizing. A: The dietary drug somewhat affected the ants' cognition, through an increase of stress and agitation. B: Ants' training (a) and testing (b). C: The ants did not adapt themselves to the impact of cognizing on their locomotion. D: The ants did not habituate to the effect of cognizing on their memory and escaping behavior. E: Ants developed strong dependence on the dietary supplement (red dot = tube filled with the drug solution).*

Conditioning acquisition and memory

The ants' responses during the test were affected by cognizing consumptions (Table 4, figure 3B2). While under normal diet, the ants soon acquired conditioning and responded during the test with a score of finally 85%, those consuming the dietary supplement may learn the presented cue, but were so nervous, agitated and walked so erratically that they seldom gave the correct response. The difference between the ants under one and the other kinds of diet was significant: N = 6, T = 21, P = 0.016. After the cue removal, the ants under normal diet still presented a score of 80% after 72 hours (keeping thus 85.7% of their conditioning). Those consuming cognizing presented at that time a score of 70% (the difference between the two kinds of ants being thus significant: N = 6, T = 21, P = 0.016), keeping in fact all their conditioning. Consequently, even if at first sight the ants' memory was affected by the dietary supplement, the ants' memory was intact, but their affected locomotion and their nervosity prevent them often giving the correct response.

Time (hours)	Normal diet: conditioning scores	Diet + Cognizing: n° correct *vs* wrong responses for		
		Colony A	Colony B	Conditioning scores
7 hrs	60%	5 vs 5	5 vs 5	50%
24 hrs	60%	4 vs 6	6 vs 4	50%
31 hrs	70%	5 vs 5	6 vs 4	55%
48 hrs	70%	4 vs 6	5 vs 5	45%
55 hrs	80%	7 vs 3	6 vs 4	65%
72 hrs	85%	6 vs 4	6 vs 4	60%
Cue removal				
7 hrs	85%	7 vs 3	6 vs 4	65%
24 hrs	80%	7 vs 3	6 vs 4	65%
31 hrs	80%	7 vs 3	6 vs 4	65%
48 hrs	80%	7 vs 3	6 vs 4	65%
55 hrs	80%	6 vs 4	6 vs 4	60%
72 hrs	80%	7 vs 3	7 vs 3	70%

Table 4: *Impact of cognizing on the ants' conditioning acquisition and memory. Due to their nervousness, the ants poorly responded to the cue during testing. However, they have duly retained the cue and still responded to it 72 hours after its removal.*

Adaptation to side effects of cognizing

Briefly, the ants did not adapt themselves to the effect of cognizing on their locomotion (Table 5, upper part; figure 3C2). In details, this was obvious to observers and was confirmed by the numerical and the statistical results. Indeed, after 7 days on the dietary supplement diet, the ants walked at a linear speed somewhat lower (χ^2 = 10.26, df = 2, 0.001 < P < 0.01) and at an angular speed larger (χ^2 = 32.49, df = 2, P < 0.001) than those presented after 1 day of that substance consumption. Such a lack of adaptation is not in favor of cognizing use and may occur in humans who should be monitored as for such an occurrence. The ants' angular speed was definitively chosen as the considered trait impacted by cognizing for studying the decrease of this substance after its consumption was stopped (See the below subsection relative to this decrease).

Habituation to wanted effects of cognizing

According to the results obtained for the ants' memory, studied until after 8 days of cognizing consumption and which revealed that the ants could somewhat remember the learned cue (Figure 3D2a), it could be concluded that the dietary supplement kept its effect all over its consumption. We also checked if, at that time, the ants rather soon escaped from an enclosure and they did (Figure 3D2b). This is in favor of this substance consumption, but to the detriment of the occurrence of side effects (e.g. nervousness, stress, agitation).

Trait	Normal diet	+ Cognizing for 1 day		+ Cognizing for 7 days
Adaptation				
Linear speed (mm/s)	10.0 (8.8 - 11.2)	9.2 (7.7 - 10.2)		8.1 (7.1 - 8.7)
Angular speed (ang.deg./cm)	109 (100 - 123)	132 (113 - 156)		180 (165 - 208)
Dependence: n° of ants counted → % of ants on the Cognizing *vs* the Cognizing-free solutions		**Colony A**	**Colony B**	**Total %**
		34 vs 3	113 vs 25	81.88% vs 18.12%
89 vs 22				

Table 5: *Upper part: the ants did not adapt themselves to the effect of Cognizing on their locomotion (median and quartiles of ants' linear (mm/s) and angular (ang.deg./cm) speeds). They developed a strong dependence on this dietary supplement consumption.*

Dependence of cognizing consumption

When refreshing the sugared solution of the dietary supplement given to the ants after the latter had it at their disposal for seven days, three ants immediately came onto the solution and drunk it. This allowed presuming that ants developed some dependence on cognizing consumption. The experiment devoted to the study of such a dependence effectively revealed that ants developed a strong dependence on this dietary supplement (Table 5, lower part; figure 3E2). During the experiment, 89 ants of colony A came onto the drug solution and 22 ones onto the drug-free solution, while 34 ants of colony B came onto the drug solution and 3 ones onto the drug-free solution. This leaded to a total of 113 ants' visits to the drug solution and 25 ones to the drug-free solution, i.e., to 81.88% of ants' visits to the drug solution *versus* 18.12% ones to the drug-free solution. The numbers of counted ants (113, 25) statistically differed from those (69, 69) expected if ants randomly went onto the two kinds of solutions ($\chi^2 = 29.83$, df = 1, $P < 0.001$). Such a strong dependence is not in favor of cognizing use and may occur in humans who should thus be monitored as for such a dependence occurrence.

Decrease of the effect of cognizing after its consumption was stopped

Numerical and statistical results are given in table 6 and are illustrated in figure 4. Briefly, the effect of cognizing rapidly decreased in a total of about 11 hours, with two more rapid decreases, one soon after weaning, a second one at about 8 hours after weaning. In details, the effect of the dietary supplement became different from its initial one as soon as 2 hours after weaning ($P < 0.02$) and went on decreasing during the four following hours (after 4 as well as 6 hours: $P < 0.01$). Then, this effect rapidly decreased until 8 hours after weaning ($P < 0.001$) and went on decreasing until after a total of about 11 hours. Then, 12 and 14 hours after weaning, the effect of cognizing was fully vanished. The effect of cognizing stayed different from the control situation until after about 7 hours after weaning, then quickly decreased and became different from that control situation 8 eight hours after weaning ($P \leq 0.05$). The latter quick decrease was in agreement with that observed when comparing the effect of the dietary supplement with its initial effect (See just above). After this quick decrease at about 8 hours after weaning, the effect of cognizing went on decreasing more slowly until becoming similar to the control situation (10, 12 and 14 hours after weaning: $P < 0.20$), the control situation being reached at about 11 hours after weaning. We here once more observed a correspondence between a quick decrease of the effect of a substance and the development of dependence on that substance [39]. On the basis of the present work and on several ones previously made (we have studied the side effects of 53 substances or situations), we can add that the more rapid is the decrease of the effect of the substance, the stronger is the dependence developed on this substance. Though two particularly quick decreases occurred over the loss of the effect of cognizing after weaning, the entire such loss could be best described by the following linear function:

$E_t = E_i - 12.27\ t$

with E_t = Effect at time t; E_i = Initial effect; t = Time (E: in ang.deg./cm; t: in hours).

Time (hours)	Ants' sinuosity (ang.deg./cm)	*Versus* t = 0		Statistics	*Versus* control		
		χ^2	df	P	χ^2	df	P
t = 0	235 (213 - 252)	--			60.00	1	< 0.001
2h	199 (176 - 228)	8.9	2	< 0.02	55.81	1	< 0.001
4h	183 (163 - 211)	9.86	2	< 0.01	47.25	1	< 0.001
6h	160 (139 - 181)	10.33	2	< 0.01	26.79	1	< 0.001
8h	123 (114 - 143)	32.72	1	< 0.001	3.93	1	≤ 0.05
10h	116 (88 - 135)	29.56	1	< 0.001	2.35	1	< 0.20
12h	98 (85 - 116)	40.00	1	< 0.001	2.00	1	< 0.20
14h	96 (81 - 112)	40.00	1	< 0.001	2.00	1	< 0.20
Control	109 (100 - 123)	60.00	1	< 0.001	--		

Table 6: *Decrease of the effect of cognizing on the ants' sinuosity of movement after its consumption was stopped. The effect of the dietary supplement became different from its initial one as soon as after 2 hours after weaning, then more slowly decreased until 6 hours after weaning, after that, i.e., 8 hours after weaning, quickly decreased, then became no longer different from the control situation and finally fully vanished in a total of about 11 hours after weaning. These results are illustrated in figure 4.*

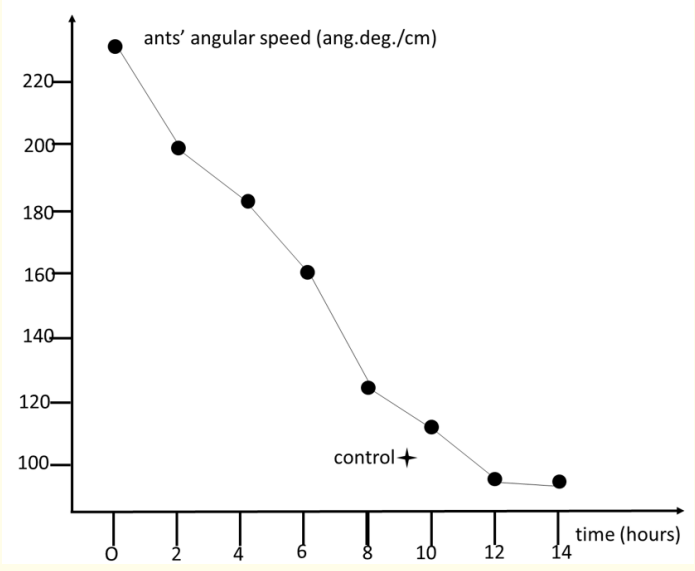

Figure 3: *Decrease of the effect of cognizing after its consumption was stopped. This effect decreased nearly linearly, with two more decreases one soon after weaning, the other 8 hours after weaning. The numerical and statistical results are given in table 6 and details can be found in the text.*

Cognizing lost thus about 12.3% of its effect each hour, losing more soon as well as 8 hours after weaning. This could be perceived by consumers who will then be tempted to intake again the dietary supplement, what could lead to dependence and accentuate the product side effects. This is not in favor of cognizing use, should be known by practitioners and consumers and the patients treated with this dietary supplement should be monitored as for the occurrence of dependence and other side effects revealed in the present work.

Discussion

Cognizing is a dietary supplement used for increasing adult humans' memory, cognition, brain functioning. Though very few adverse effects are reported, working on ants as models, we found that this product caused excitation, agitation, nervousness, stress, impacting consequently these insects' locomotion, orientation ability, social relationships, capability of correctly responding during several tests. Nevertheless, the ants' memory and maybe cognition were not affected. However, the ants did not adapt themselves to the observed side effects of cognizing and developed a strong dependence on its consumption, what accentuate the occurrence of its side effects. The active substance of cognizing is citicoline, a drug used e.g., to improve the brain functioning of elderly and persons having or having had some brain damage. Medicinally used, citicoline is very efficient and seemed to have few adverse effects. In addition to the references given in the Introduction section, here are ten more ones proving the efficiency of citicoline as a medicinal drug. In fact, these ten more references were taken out of a very large amount of works recently conducted on this promising drug. The methods used are detailed in [43]. The efficiency and safety of citicoline are again showed in [44-46]. Its long-term effect is proved in [47,48]. Its usefulness for caring of elderly persons is shown in [49]. Citicoline has also, maybe essentially a neuroprotective effect [50]. However, everything is not yet resolved as for this drug mode of action [51]. Finally, the most recent review on citicoline use is that of Yasielski [52]. Citicoline is also usefully used combined with other drugs [53].

Other medicinal therapies (old ones, Chinese ones) exist for improving the brain functioning and most of them seemed to be efficient without adverse effects [54].

As for the efficiency of cognizing in humans in good health put forward by THERASCIENCE (the firm which manufactures and sell this dietary supplement), tests in humans have shown that after 28 weeks these humans were more attentive than before the treatment [55]. This information is not easily available to anyone who wants having a soon improving effect on their cognition for accomplishing some current cerebral tasks. Therefore, cognizing does not give them exactly what they expect. In addition, these persons will probably suffer from the side effects of cognizing (e.g., agitation, stress, impairment of their social relationships) and could develop dependence on the dietary supplement consumption. Let us add that, after having experimented on a cognizing diet, the ants appeared to be tired, were far less active than usually and were sleeping nearly all day long. Such a tiredness after a rather long consumption of cognizing may also occur in humans. We are thus not in favor of this dietary supplement use. Looking at several internet links, stories written in magazines and summaries of interviews, we became conscious that most of the available dietary supplements are not efficient and have adverse effects such as some dependence on their use. The product PQQ present in a very small amount in cognizing is also sold as a dietary supplement allowing a brain functioning improvement. This substance is a co-enzyme present in the mitochondria of all the eucaryotic (any plants and animals). We intend to examine, in a future work, the side and wanted effects of this PQQ.

Conclusion

Cognizing used for humans in good health who want an immediate beneficial effect of their brain functioning is not exactly appropriated. It is only poorly efficient and has several important side effects such as excitation, nervousness, social relationships impairments and induces a strong dependence on its consumption. It should thus not be used, not only for children but also for adults. Other methods can ameliorate the brain functioning. Such an inefficiency and moderate dangerousness exist for numerous dietary supplements which are easily available and very expensive. This must be known by anyone. On the other hand, citicoline, the active substance of cognizing, is an efficient medicinal drug which allows patients recovering after having suffered or while suffering from cerebral damage.

Conflict of Interest

We affirm having not conflict of interest as for the marketing of cognizing or any similar dietary supplement or drug. We work on ants, on their behavior and cognitive abilities and use them as models for examining several topics. We receive no money for conducting our research. We maintained the ants in the best possible condition and collect on field only the smallest required amount of ant colonies.

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