



The Importance of Citicoline for Long-Term Brain Health & Memory Support

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COMPANY OVERVIEW

<p>Date of Incorporation February 23, 1907</p> <p>Number of Group Companies 178</p> <p>Number of Employees 30,000+</p>	<p>KIRIN HOLDINGS COMPANY, LTD.</p> <p>Joy brings us together</p> <p>KYOWA HAKKO BIO CO., LTD.</p> <p>Kyowa Hakko USA</p>
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SALES & MANUFACTURING PLANTS

Sales Offices
Head Office: Chiyoda, Tokyo
Kyowa Hakko USA, Inc.
Kyowa Hakko Europe GmbH
Kyowa Hakko Bio Italia S.p.A.
Kyowa Hakko Pharmaceutical CO., LTD. Beijing Branch
Kyowa Hakko Pharmaceutical CO., LTD. Shanghai Branch
Kyowa Hakko Bio Singapore PTE, LTD.

Manufacturing Plants
Biotryowa, Inc. USAIS
Shanghai Kyowa Amino Acid Co., LTD
Thai Kyowa Biotechnologies Co., LTD
Kyowa Hakko Bio Co., LTD

Missouri Plant

Shanghai Plant

Hofu Plant


Thailand Plant

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DIETARY SUPPLEMENT & NUTRITION PRODUCTS 



Glutathione



For the acquirer of your mind



Patented Performance Blend



Supports a healthy heart








<p>Amino Acids L-Alanine L-Arginine + L-Citrulline (VELOX®) L-Citrulline L-Glutamine</p> <p>New Product Development Human Milk Oligosaccharides (HMOs) Z - Fucosylactose 3 - Sialylactose Sodium Salt 6 - Sialylactose Sodium Salt</p>	<p>Nucleic Acids Citicoline (Cognizin®)</p> <p>Probiotics Kirin Holdings Co. Ltd. Product Offerings: Lactococcus lactis strain Plasma (IMMUSE®) Lactosaccharibacillus paracasei KW03116 (EYEMUSE®)</p> <p>Peptides L-Alanyl-L-Glutamine L-Glutathione Reduced (Setria®) L-Glutathione + L-Citrulline (Setria® Performance Blend)</p>	<p>Vitamins Vitamin K₁</p> <p>Vitamin B Derivatives Kyowa Pharms Chemical Co. Product Offerings: Vitamin B₆ derivatives Pantesin® L680 Pantesin® HF55 Vitamin B₁₂ derivatives Pyridoxal-5'-phosphate</p>
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AGENDA 

The Role of Citicoline in Long-Term Brain Health & Memory Support

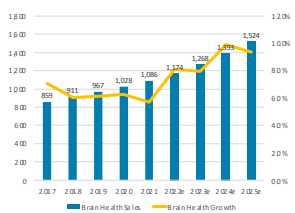
- Citicoline Overview
- Citicoline Metabolism and MoA
 - How does citicoline work?
- Citicoline Human Studies
 - Potential as nootropic

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TRENDS IN COGNITIVE HEALTH: SUPPLEMENTS 

Brain Supplement Sales and Growth

- In 2020, the brain health market grew to a **\$1 billion** value.
- The pandemic effect set the market up for **post-pandemic growth**, and projections now show an **8% gain** for 2023 and big growth for 2024



Year	Brain Health Sales (Billion \$)	Brain Health Growth (%)
2017	809	~
2018	911	~
2019	967	~
2020	1,028	~
2021	1,096	~
2022e	1,174	~
2023e	1,258	~
2024e	1,479	~
2025e	1,534	~

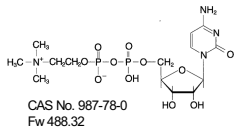
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What is Citicoline?



- A mononucleotide comprising cytosine, ribose, pyrophosphate and choline.
- An endogenous intermediate in the biosynthesis of structural membrane phospholipids, and Acetylcholine, a nerve system activator.

Citicoline



Application

USA: Dietary Supplement, Food/Beverage (GRAS)

EU: Dietary Supplement (Novel Food)

Asia:

- Japan: Pharmaceutical
- China: Pharmaceutical (as sodium salt)

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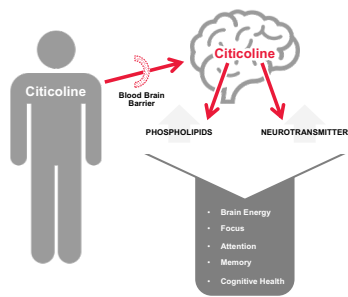
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How Does Citicoline Work?



Citicoline metabolizes to raise Acetylcholine levels and provide Phospholipid support

- Citicoline exists in our cells and is specifically critical for optimal brain cell performance.
- Citicoline is sourced for multiple Phospholipids which is a brain nutrient to consist of brain cell membrane.
- Citicoline also supports Neurotransmitters, the way our brain cells communicate, to activate the nerves system.

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How Does Citicoline Work?

Citicoline enhances brain function mainly via synthesis of **Phospholipids** that is a key component of brain cell membranes, and produce **Acetylcholine**, a nerve system activator.

Overall Brain Health

- Short Term Benefits
 - ✓ Focus
 - ✓ Attention
 - ✓ Brain energy
- Long Term Benefits
 - ✓ Memory
 - ✓ Cognitive health

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Cognizin® Citicoline: Features and Benefits

Cognizin® Citicoline, Kyowa HAKKO's branded form of citicoline, works as a brain nutrient to support acute performance as well as long term brain health.

Cognizin® is ideal for many different use occasions:

- Multitaskers
- Professional Workers
- Athletes
- E-Gamers
- Working Parents
- Aging Population

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Citicoline: Potential as a Nootropic



Definition of Nootropics

"Nootropics are drugs, supplements, and other substances that are claimed to improve cognitive function, particularly executive function, attention, memory, creativity, or motivation, in healthy individuals."

Oxford Dictionary
Current Neuropharmacology, 13 (1), 5-11, 2015

Several human studies have shown Citicoline has a function to increase brain energy production and improve focus, attention, and memory in healthy subjects.

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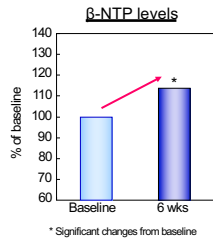
Cognizin® Citicoline Human Studies



Cognizin® Citicoline Increases Energy in Brain

- Subjects:** 16 physically and mentally healthy individuals (8M and 8F, 47.3±5.4 y, BMI = 25.3 ± 5.2)
- Dose:** Citicoline 500 mg or 2000 mg/day (n = 8 each)
- Term:** 6 wks
- Index:** Measurement of β-NTP as cellular energy by 31P-MRS in the frontal lobe: Anterior Cingulate Cortex (ACC)

ACC: area responsible for focus, attention, concentration



Silveri MM et al., NMR in Biomedicine, 21(10): 1066-75, 2008

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Cognizin® Citicoline Studies

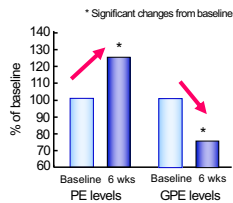


Cognizin® Citicoline Increases Phospholipid Synthesis (observed in humans)

Oral citicoline supplementation increased phospholipids synthesis in brain.


- Subjects:** 16 physically and mentally healthy individuals (8M and 8F, 47.3±5.4 y)
- Dose:** Citicoline 500 mg or 2,000 mg/day (n=8 each)
- Term:** 6 wks
- Index:** Membrane phospholipids in frontal lobe (ACC) measured by 31P-MRS; PE (anabolite) and GPE (catabolite)

ACC: Anterior cingulate cortex
PE: Phosphoethanolamine
GPE: Glycerophosphoethanolamine



Silveri MM et al., NMR in Biomedicine, 21(10): 1066-75, 2008

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Cognizin® Citicoline Human Studies 

Cognizin® Citicoline Increases Attention


- Design:** Double-blind, randomized, placebo-controlled three-arm study
- Subject:** 60 middle-aged women (40-60 y.o.)
- Dose:** Citicoline 250 mg/day or 500 mg/day
- Term:** 1 month
- Measurement:** Continuous Performance Test (CPT)

✓ On a PC screen "A, B, C, ..., X" appear in random letters.
 ✓ When letters other than "X" appear, press the Space bar.
 ✓ The test runs for 14 minutes and the timing of the display changes.

PC screen: 「C, Z, A, X, J, P, X, L, W, R, X, X,」




Commission Errors:
Participants incorrectly presses the space bar in response to "X"



Omission Errors:
Participant fails to press the space bar in response to any letter other than "X"

McGlade E et al., Food and Nutrition Sciences, 3, 769-773, 2012

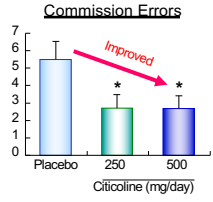
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Cognizin® Citicoline Human Studies 

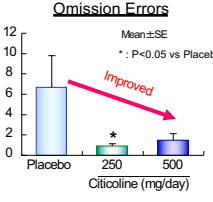
Cognizin® Citicoline Increases Attention

Oral Citicoline supplementation (250 mg/day) for 1 month improved attention in middle-aged women.

Commission Errors




Omission Errors



McGlade E et al., Food and Nutrition Sciences, 3, 769-773, 2012

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Cognizin® Citicoline Human Studies 

Cognizin® Citicoline Improves Motor Speed and Attention in Adolescents

- Design:** Randomized, placebo controlled, double blinded study
- Subjects:** Healthy adolescent males (N=75, 13-18 y.o.)
- Dose:** Citicoline (N=51, 250 or 500 mg/day) or Placebo (N=25)
- Term:** 28 days
- Measurements:** Finger tap test, Ruff 2&7 selective attention test MOSES interview (Side effects)


Table 3. Baseline Demographic Characteristics—Between-Group Differences.

	Treatment (n = 51)	Placebo (n = 24)	p
Age ± SD	15.41 ± 1.70	15.71 ± 1.73	0.98
Education (years) ± SD	9.00 ± 1.76	9.42 ± 1.82	0.48
Height (cm) ± SD	171.14 ± 9.24	171.95 ± 10.76	0.64
Weight (kg) ± SD	61.74 ± 14.80	62.90 ± 14.34	0.82
IQ (WASI) ± SD	106.04 ± 10.33	107.33 ± 9.50	0.45

Note: WASI = Wechsler Adult Intelligence Scale.

McGlade E et al., Journal of Attention Disorders, (Published Online: Jul 15th, 2015)


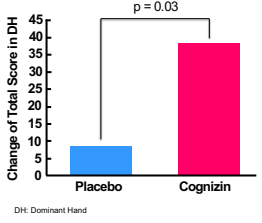
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Cognizin® Citicoline Human Studies 

Cognizin® Citicoline Improves Motor Speed and Attention in Adolescents

Finger Tap Test (motor function)

Subjects are instructed to tap as fast as they can for 10 seconds





Group	Change of Total Score in DH
Placebo	~10
Cognizin	~38

DH: Dominant Hand

McGlade E et al., Journal of Attention Disorders, (Published Online: Jul 15th, 2015)

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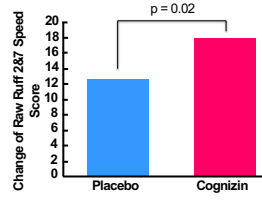
Cognizin® Citicoline Human Studies 

Cognizin® Citicoline improves motor speed and attention in adolescents

Ruff 2&7 selective attention test (Visual)

Cross out as many 2 & 7 per timed interval for a total of 5 minutes


1	8	9	2	5	4	7	1	5	4	6	6
9	2	3	7	3	5	8	6	5	9	6	3
3	6	4	7	9	8	0	5	8	6	3	7
8	2	2	9	5	8	1	6	9	3	4	9
7	8	2	9	8	4	4	1	9	8	2	0



Group	Change of Raw Ruff 2&7 Speed Score
Placebo	~13
Cognizin	~18

McGlade E et al., Journal of Attention Disorders, (Published Online: Jul 15th, 2015)

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Cognizin® Citicoline Human Studies 

Cognizin® Citicoline Improves Memory

- Design:** Randomized placebo-controlled parallel, double-blind study
- Subjects:** Healthy male/female age 50-85 years with AAMI*
- Dose:** Citicoline 500 mg/day (two-piece capsule) or placebo
- Term:** 12 weeks
- Outcome:** Cognitive test battery, which includes 7 tests

*Age-associated memory impairment (AAMI).


In order to investigate citicoline efficacy for memory properly, screened healthy subjects who have no health conditions that would prevent from fulfilling the study requirements but complaint or self-report memory loss.

NIH has proposed criteria for defining AAMI:

- (1) Males and females at least 50 years old
- (2) Complaints of memory loss and memory test performance that is at least 1 standard deviation (SD) below the mean established for young adults on a standardized test
- (3) Evidence of adequate intellectual function
- (4) Absence of dementia

J. Nutr. 21 August 2021, 2153-2160


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Cognizin® Citicoline Human Studies 

Method – Cognitive Test Battery


- A web-based platform for the assessment of cognitive function.
- Use several tasks to assess distinct components of cognition for evaluate memory function.

Memory [Spatial Span]




The patient will have to try to remember a sequence of flashing boxes that appear on the screen one after the other.

Memory [Paired Associates]




The patient must remember which object appeared in which box. Next, one at a time, objects appear in the center of the screen, and patients must point out which box each object was located in.

Verbal [Digit Span]



A sequence of numbers appears on the screen, one at a time. At the sound of the beep, users click the numbers in the same order.


Attention [Feature Match]



The patient will have to determine whether the array in the two boxes are identical or different by clicking MATCH or MISMATCH.

This is just an example, please visit their website to see more details
<http://www.cognizin.com/clinical-trials>
 J. Nutr. 21 August 2021, 2153-2160

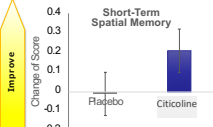
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Cognizin® Citicoline Human Studies 


Cognizin® Citicoline Improves Memory

- Citicoline significantly improved episodic memory.
- Other outcomes is not statistically significant though, showed a trend.

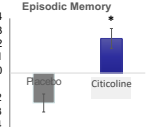
Short-Term Spatial Memory



Working Memory




Episodic Memory



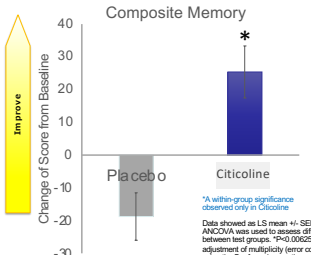
Data showed as LS mean +/- SEM. ANCOVA was used to assess differences between test groups. *P<0.00625

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Cognizin® Citicoline Human Studies 

Cognizin® Citicoline Improves Memory



*A within-group significance observed only in Citicoline

Data showed as LS mean +/- SEM. ANCOVA was used to assess differences between test groups. *P<0.00625, due to adjustment of multiplicity (error correction) using the Bonferroni correction.


- Composite memory, calculated using the scores of 4 memory tests*, also significantly improved.
- Conclusion
Dietary supplementation of citicoline for 12-week improved overall memory performance, especially episodic memory, in healthy older males and females with AAMI.

*To avoid "cherry picking", shown in the FDA guidance, it is appropriate to combine several tests into a single variable

* To account for multiplicity.

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Summary 


Citicoline is a mononucleotide comprising cytosine, ribose, pyrophosphate and choline.

Citicoline is an endogenous intermediate in the biosynthesis of structural membrane Phospholipids, and Acetylcholine, a nerve system activator.

Several human studies have shown **Cognizin® Citicoline** has a function to increase brain energy production and improve focus, attention, and memory in healthy subjects.

Citicoline has a potential as a Nootropic and applications for dietary supplements, sports/esports supplement or energy drinks.

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Thank you!

If you need more information, please email
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