

Nutraceuticals **στις** **Αγχώδεις Διαταραχές**

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Γ.Ν.Α. «Ο Ευαγγελισμός»
Αθήνα

neutraceuticals



- ✿ συνδυασμός των λέξεων “**nutrition**” (διατροφή) και “**pharmaceutical**” (φαρμακευτικός)
 - *Stephen De Felice ,1989*
- ✿ τρόφιμα είτε μέρη τροφίμων που εκτός από την βασική θρεπτική αξία.....
- ✿ παρέχουν **και** φαρμακευτικά οφέλη ή προάγουν την υγεία
- ✿ Για πρόληψη ή/και για θεραπεία



Τρόφιμα

- Ανάλογα με την μορφή και την δόση

Ή Φάρμακα ?

- *Μάλλον στην
διαχωριστική γραμμή*

Η επιστημονική έρευνα
οδήγησε στην μελέτη
καταστάσεων όπως ...



Γονιδιακή έκφραση

Προστασία της μιτοχondριακής δομής

Αντιοξειδωτική δράση

Κυτταρικός πολλαπλασιασμός

Ενίσχυση ανοσοποιητικού

Βελτίωση υγείας

Πρόληψη ασθενειών

Αντιγηραντική δράση

Τροφές με θεραπευτικές ιδιότητες : ορισμοί



Διαιτητικό συμπλήρωμα

- κατ ουσία τροφές
- Διάφορες μορφές (καψουλες , εναιώρημα κ.λ.π.)



Λειτουργική τροφή

- Πλήρεις τροφές ή ενισχυμένες τροφές για μείωση κινδύνου χρόνιας νόσου ή ωφέλεια πέραν των παραδοσιακών τροφών



Ιατρική τροφή

- Υπό την επίβλεψη ιατρού
- Παθήσεις όπου χρειάζεται ειδική διατροφή (με βάση επιστημονικά δεδομένα)



Φαρμα-κευτικό σκεύασμα

Από την «φάρμα» και τα φαρμακευτικά Η χρήση φυτικών παραγόντων εσοδείας ή και ζώων σαν φαρμακευτικά εργαστήρια πολύ αποτελεσματικότερα από ότι οι συμβατικές καλλιέργειες

Διαφορές με τα φάρμακα

Φάρμακα

- Έχουν προστασία από πατέντα
- Η διαδικασία εισαγωγής στην αγορά είναι χρονοβόρα και δαπανηρή
- Υφίσταται από το κράτος

Οι εταιρείες μπορούν να αναγράψουν τους ισχυρισμούς τους στις ετικέτες χωρίς κάποια τεκμηρίωση

Neutraceuticals

- Δεν χρειάζεται πατέντα η κυκλοφορία τους
 - ΧΡΕΙΑΖΕΤΑΙ ΟΜΩΣ ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΔΕΙΑ
- Δεν χρειάζονται διαδικασίες εισαγωγής
- Δεν υφίσταται αποζημίωση από το κράτος

Επιλογή Nutraceuticals

Common name	Biological name	Constituent	Health benefits
Garlic	Dried bulbs of <i>Allium sativum</i> (Liliaceae).	Alliin and allicin	Anti-inflammatory, antibacterial, antigout, nervine tonic
Maiden hair tree	Leaves of <i>Ginkgo biloba</i> (Ginkgoaceae).	Ginkgolide and bilobalide	PAF antagonist, memory enhancer, antioxidant
Ginger	Rhizomes of <i>Zingiber officinale</i> (Zingiberaceae.)	Zingiberene and gingerols	Stimulant, chronic bronchitis, hyperglycemia and throat ache
Echinacea	Dried herb of <i>Echinacea purpurea</i> (Asteraceae)	Alkylamide and echinacoside	Anti-inflammatory, immunomodulator, antiviral
Ginseng	Dried root of <i>Panax ginseng</i> (Araliaceae)	Ginsenosides and Panaxosides	Stimulating immune and nervous system and adaptogenic properties
Liquorice	Dried root of <i>Glycyrrhiza glabra</i> (leguminosae)	Glycyrrhizin and liquirtin	Anti-inflammatory and Anti-Allergic, Expectorant
St. John's wort	Dried aerial part of <i>Hypericum perforatum</i> (Hypericaceae)	Hypericin and hyperforin	Antidepressant, against HIV and hepatitis-c virus ^[18]
Turmeric	Rhizome of <i>Curcuma Longa</i> (Zingiberaceae)	Curcumin	Anti-inflammatory, antiarthritic, anticancer and antiseptic
Onion	Dried bulb of <i>Allium cepa</i> Linn. (Liliaceae)	Allicin and alliin	Hypoglycemic activity, Antibiotic and anti-atherosclerosis
Valeriana	Dried root of <i>Valeriana officinalis</i> Linn. (Valerianaceae)	Valerenic acid and valerate	Tranquillizer, migraine and menstrual pain, intestinal cramps, bronchial spasm.
Aloes	Dried juice of leaves <i>Aloe barbadensis</i> Mill. (Liliaceae)	Aloins and aloesin	Dilates capillaries, anti-inflammatory, emollient, wound healing properties
Goldenseal	Dried root of <i>Hydrastis Canadensis</i> . (Ranunculaceae)	Hydrastine and berberine	Antimicrobial, astringent, antihemorrhagic, treatment of mucosal inflammation
Senna	Dried leaves of <i>Cassia angustifolia</i> (Leguminosae)	Sennosides	Purgative,
Asafoetida	Oleo gum resin of <i>Ferula assafoetida</i> L. (Umbelliferae)	Ferulic acid and umbellic acid	Stimulant, carminative, expectorant
Bael	Unripe fruits of <i>Aegle marmelos</i> Corr. (Rutaceae)	Marmelosin	Digestive, appetizer, treatment of diarrhea and dysentery
Brahmi	Herbs of <i>Centella asiatica</i> (Umbelliferae)	Asiaticoside and madecassoside	Nervine tonic, spasmolytic, anti-anxiety



προέλευση

- Μέταλλα
- Φυτά
- Ζώα
- Μικροβιακά παράγωγα



Χημική κατηγορία

- Μέταλλα
- Βιταμίνες
- ω3 Nutrients
- Αμινοξέα



Διαιτητικά συμπληρώματα

- Δεν έχουν προορισμό την θεραπεία νόσων
- Αντιθέτως , την πρόληψη

Ιστορικό

- 252 βασικά φάρμακα
 - 11 % δρόγες
- Την τελευταία 30ετία
 - Το 50 % των εγκεκριμένων φαρμάκων από φυσικές πηγές
- Το πρώτο προϊόν : μορφίνη
 - Merck, 1826
- Ασπιρίνη
 - Bayer, 1899
- Διγτοξίνη
- Κινίνη
- **Πακλιταξέλη**
 - *Taxus brevifolia*

Πάνω από το 50% των αντικαρκινικών την τελευταία 30ετία φυτικά προϊόντα



WHO Model List of Essential Medicines

19th List
(April 2015)
(Amended August 2015)

Status of this document

This is a reprint of the text on the WHO Medicines website

<http://www.who.int/medicines/publications/essentialmedicines/en/>

Αλλά και ...

- ✿ Galantamine φυσικό αλκαλοειδές (*Galanthus nivalis*) για Alzheimer's
- ✿ Αρομορφίνη ημισυνθετικό προϊόν από morphine (*Papaver somniferum*) για Parkinson's disease
- ✿ Tiotropium από atropine *Atropa belladonna* στην ΧΑΠ
- ✿ Dronabinol and Cannabidiol (*Cannabis sativa*)
- ✿ Capsaicin από *Capsicum annuum* σαν αναλγητικό

Anxiety disorders & nutraceuticals

Unno K, Tanida N, Ishii N, Yamamoto H, Iguchi K, Hoshino M, Takeda A, Ozawa H, Ohkubo T, Juneja LR, Yamada. *Anti-stress effect of theanine on students during pharmacy practice: Positive correlation among salivary- amylase activity, trait anxiety and subjective stress.* *Pharmacol Biochem Behav.* 2013 Oct;111:128-35. doi: 10.1016/j.pbb.2013.09.004. Epub 2013 Sep 16. PubMed PMID: 24051231.

Lardner AL. *Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders.* *Nutr Neurosci.* 2014 Jul;17(4):145-55. doi: 10.1179/1476830513Y.0000000079.

Heese T, Jenkinson J, Love C, Milam R, Perkins L, Adams C, McCall S, Ceremuga TE. *Anxiolytic effects of L-theanine--a component of green tea-when combined with midazolam, in the male Sprague-Dawley rat.* *AANA J.* 2009 Dec;77(6):445-9. PubMed PMID: 20108732.

Ritsner MS, Miodownik C, Ratner Y, Shleifer T, Mar M, Pintov L, Lerner V. *L-theanine relieves positive, activation and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study.* *J Clin Psychiatry.* 2011 Jan;72(1):34-42. Epub 2010 Nov 30.

Miodownik C, Maayan R, Ratner Y, Lerner V, Pintov L, Mar M, Weizman A, Ritsner MS. *Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients.* *Clin Neuropharmacol.* 2011 Jul-Aug;34(4):155-60. doi: 10.1097/WNF.0b013e318220d8c6.

de Carvalho RS, Duarte FS, de Lima TC. *Involvement of GABAergic non-benzodiazepine sites in the anxiolytic- and sedative effects of the flavonoid baicalin in mice.* *Behav Brain Res.* 2011 Aug 1;221(1):75-82. doi: 10.1016/j.bbr.2011.02.038. Epub 2011 Mar 4.

Brock C, Whitehouse J, Tewfik I, Towell T. *American Skullcap (Scutellaria lateriflora): A Randomised, Double-Blind Placebo-Controlled Crossover Study of its Effects on Mood in Healthy Volunteers.* *Phytother Res.* 2014 May;28(5):692-8. doi: 10.1002/ptr.5044. Epub 2013 Jul 22.

Sarris J, McIntyre E, Camfield DA. *Plant-based medicines for anxiety disorders, part 2: a review of clinical studies with supportive preclinical evidence.* *CNS Drugs.* 2013 Apr;27(4):301-19. doi: 10.1007/s40263-013-0050-



Pharmaceutical



Drugs used in the TREATMENT of disease

Nutraceutical



Nutrients that may PREVENT disease



L - theanine



- Ευρίσκεται στο τσάι (πράσινο τσάι)
- Είναι αμινοξύ

T_{max} (μετά από ενδοπεριτοναϊκή έγχυση) 30 λεπτά
P.Os : ακολουθεί την οδό της μεταφοράς λευκίνης προς BBB με δόσοεξαρτώμενο τρόπο

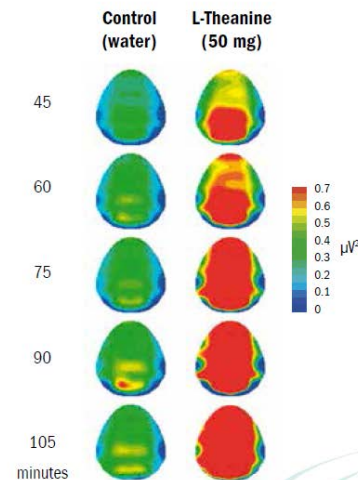
L-theanine, a natural constituent in tea, and its effect on mental stateAnna C Nobre PhD², Anling Rao PhD² and Gail N Owen PhD¹¹Unilever Food and Health Research Institute, Vlaardingen, The Netherlands
²Department of Experimental Psychology, Oxford University, UK

L - theanine

- **Αυξάνει την πυκνότητα των α κυμάτων στο ΗΕΓ**
 - Δρά σαν νευρομεταβιβαστής
- α κύματα : συσχετίζονται με ηρεμία χωρίς καταστολή
- Η L-theanine εξασκεί την δράση της με ελαφρώς μεγαλύτερη δόση από αυτήν σε ένα φλυτζάνι τσάι (20 mg vs. 50 mg)

N=16, υγιείς , ΗΕΓφική
καταμέτρηση $p < 0.05$ vs. controls

L-Theanine acts as a neurotransmitter in the brain, stimulating the production of alpha waves and causing a feeling of relaxation. (1, 2, 20)



In a recent clinical study the EEG of healthy subjects has evaluated at baseline and 45, 60, 75, 90 and 105 minutes after oral administration of L-Theanine 50 mg. (n = 16) or placebo (n = 19). Participants were in resting conditions and with closed eyes during the recording. It has been measured a significant increase activity of alpha waves in the group-1 (L-Theanine) compared to placebo ($p < 0.05$).⁽¹⁾

Anxiety measures	Placebo		L-Theanine		Alprazolam		Significance	η^2
	Baseline Mean (SD)	Post-drug Mean (SD)	Baseline Mean (SD)	Post-drug Mean (SD)	Baseline Mean (SD)	Post-drug Mean (SD)		
BAI	1.19 (2.20)	1.75 (3.51)	1.81 (2.81)	1.69 (2.91)	1.44 (3.22)	2.19 (2.40)	$F = 1.17; p = 0.32$	0.24
STAI State anxiety	26.50 (6.92)	26.12 (6.66)	24.56 (5.56)	25.25 (5.75)	26.50 (4.68)	31.50 (9.23)	$F = 4.54; p = 0.03^a$	0.63
VAMS								
Calm	10.56 (14.49)	13.94 (12.34)	9.94 (9.20)	10.56 (10.31)	9.00 (10.30)	16.69 (14.46)	$F = 1.49; p = 0.24$	0.29
Relaxed	9.06 (11.90)	16.50 (18.24)	11.62 (11.94)	12.69 (14.67)	9.69 (13.73)	17.94 (17.36)	$F = 0.88; p = 0.43$	0.19
Tranquil	8.37 (7.81)	16.44 (14.71)	13.19 (12.99)	9.94 (7.06)	11.87 (15.58)	20.00 (20.80)	$F = 4.05; p = 0.03^b$	0.68

$p < 0.05$ for L-Theanine (200 mg) vs Placebo and L-Theanine (200 mg) vs Alprazolam (1 mg).

Effect of placebo, L-Theanine and alprazolam on measures of “anticipatory anxiety”. The results expressed as averages and standard deviation (SD).

Ενίσχυση της ΑΨ Θεραπείας

Serum Levels of Brain-Derived Neurotrophic Factor and Cortisol to Sulfate of Dehydroepiandrosterone Molar Ratio Associated With Clinical Response to L-Theanine as Augmentation of Antipsychotic Therapy in Schizophrenia and Schizoaffective Disorder Patients

Miodownik, Chanoch MD*; Maayan, Rachel PhD†; Ratner, Yael MD‡; Lerner, Vladimir MD, PhD*; Pintov, Leonid MD‡; Mar, Maria MD‡; Weizman, Abraham MD†§; Ritsner, Michael S. MD, PhD‡||

Clinical Neuropharmacology: July/August 2011 - Volume 34 - Issue 4 - pp 155-160

doi: 10.1097/WNF.0b013e318220d8c6

Original Articles

Βελτίωση θετικών συμπτωμάτων και ενεργού οξείας ψυχοπαθολογίας σε σχιζοφρενείς και διπολικούς

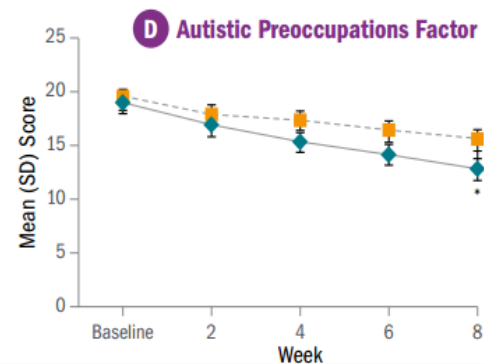
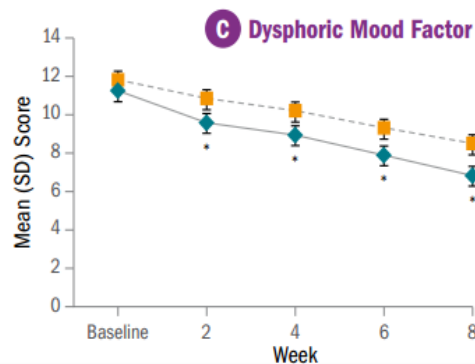
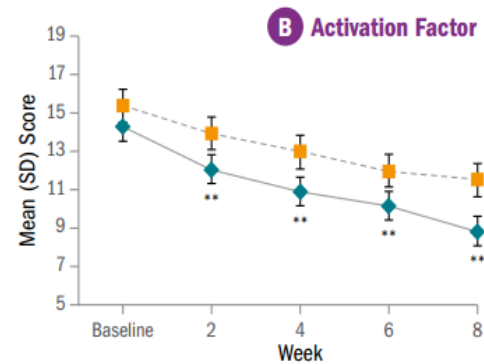
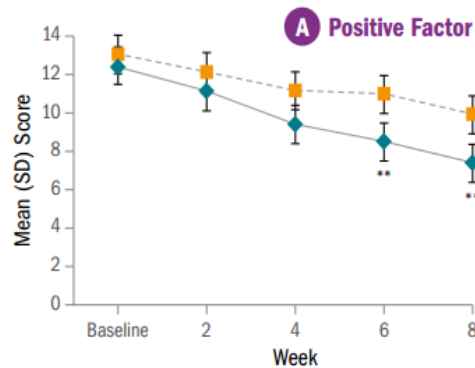
- Μελέτη 8 εβδομάδων , N=67
- Ενίσχυση της ΑΨ θεραπείας
- L-Θεανίνη 400 χλγ/ημ.

PANSS Scores

* $P < .05$; ** $P < .01$

Abbreviation:
PANSS = Positive
and Negative
Syndrome Scale

◆ L-Theanine
■ Placebo

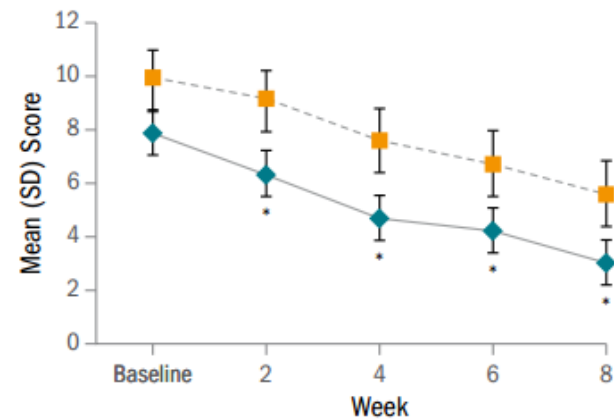


Από την ίδια μελέτη

Hamilton Anxiety Rating Scale Scores

* $P < .05$; onset of improvement occurred in week 2

- ◆ L-Theanine
- Placebo

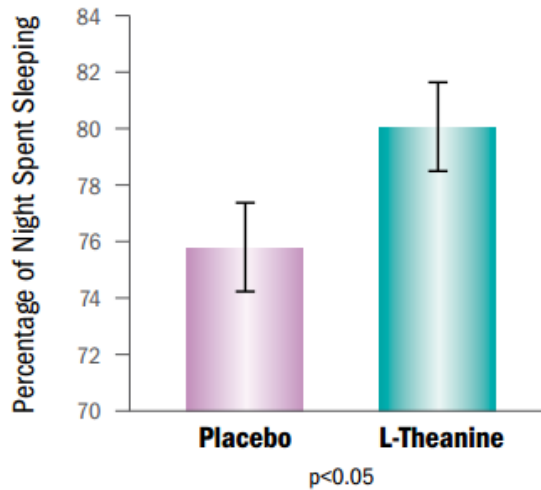


The action of L-Theanine in sleep disorders has been associated with its ability to induce relaxation and has also been tested in the presence of conditions, such as ADHD, in which sleep difficulties are comorbidities.⁽²²⁾

In the following double-blind study, actigraphic values of 100 young patients diagnosed with ADHD were assessed after a period of treatment with L-Theanine (200 mg) of 6 weeks.

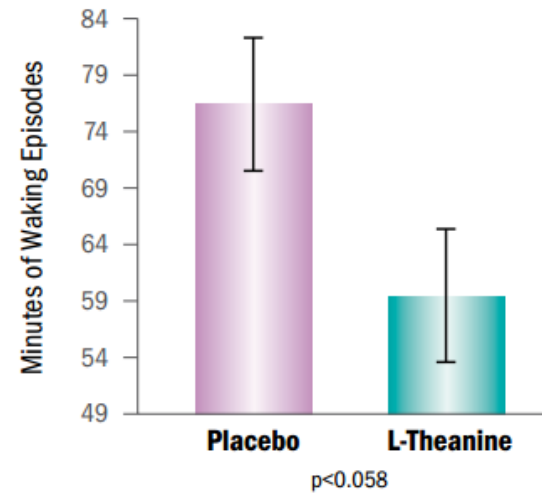
Sleep Efficiency

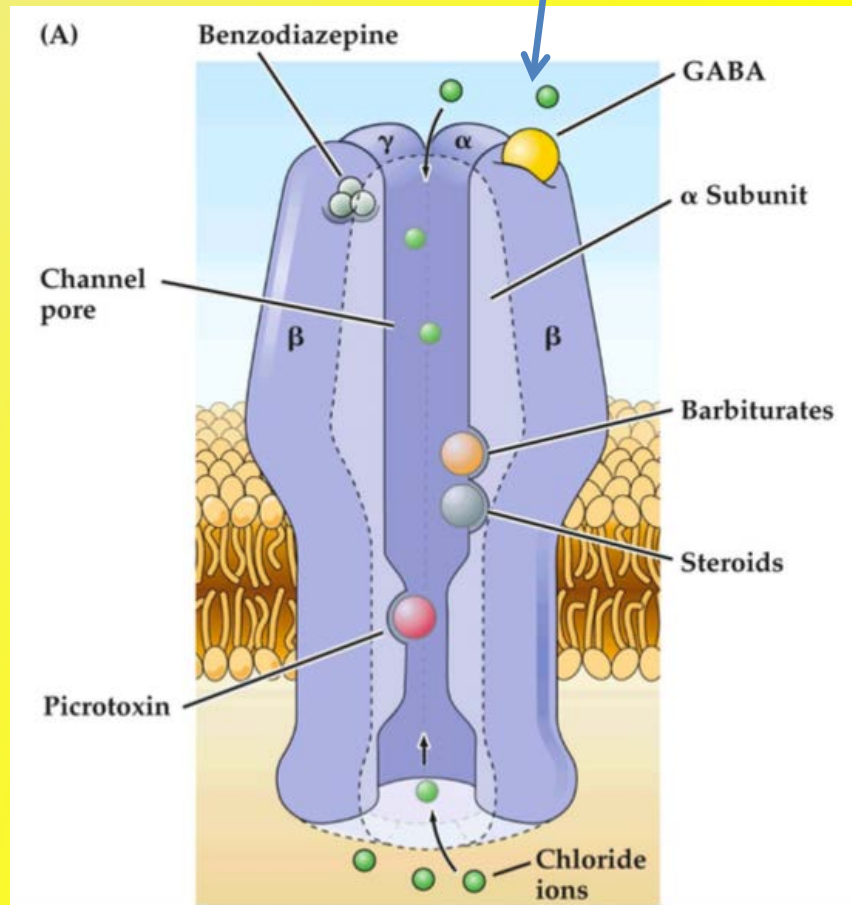
(Percentage of Night Spent Sleeping Restfully)



Wake After Sleep Onset

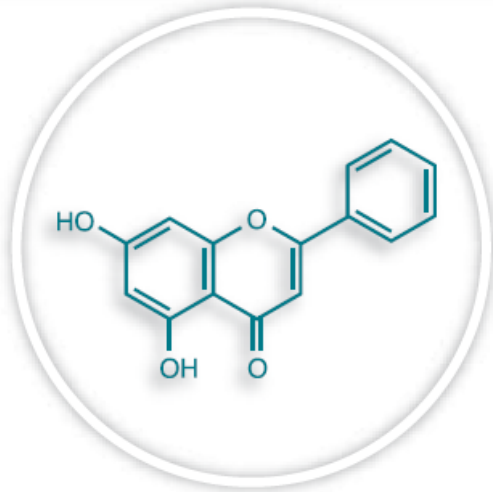
(Number of Minutes of Wakefulness After Onset of Sleep)





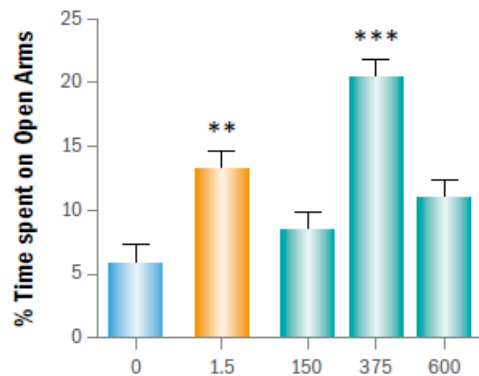
Χρυσίνη: αγχόλυση χωρίς καταστολή .Διαμόρφωση του GABA_A υποδοχέα

Χρυσίνη

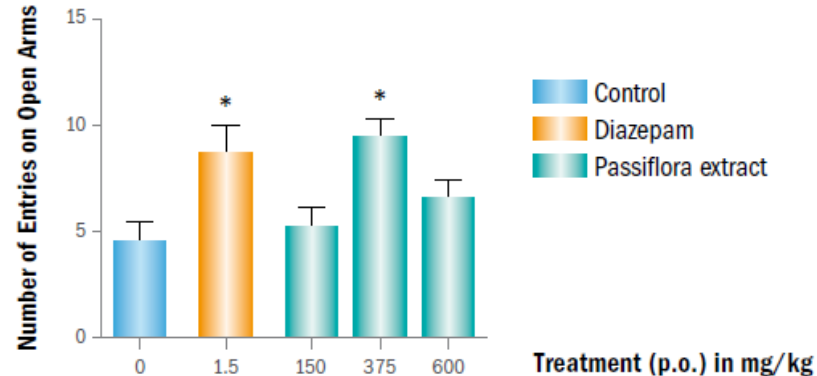


Chrysin and other flavonoids contained in the extract of *Passiflora* showed an anxiolytic, but not sedative, comparable to *diazepam* in tests of experimental models of anxiety. Also the use of the antagonist for the receptor binding site of benzodiazepines to GABA, *flumazenil*, has shown a remarkable antagonistic effect, demonstrating how the anxiolytic activity is mediated by the GABA receptor. ^(6, 8, 9, 10, 11, 13, 14, 17, 18)

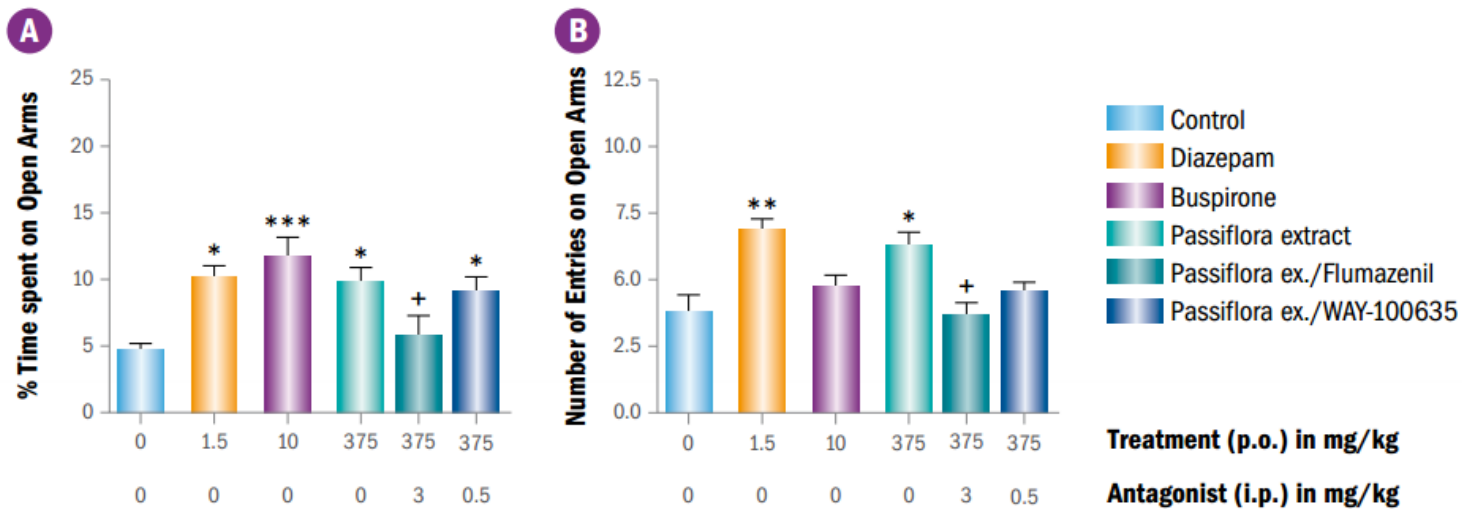
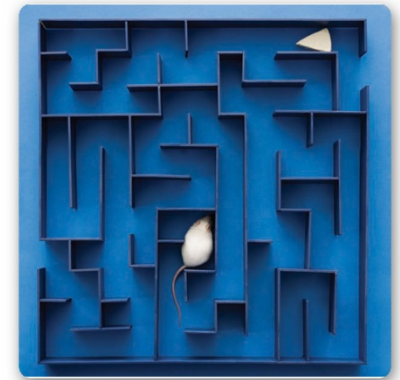
A



B

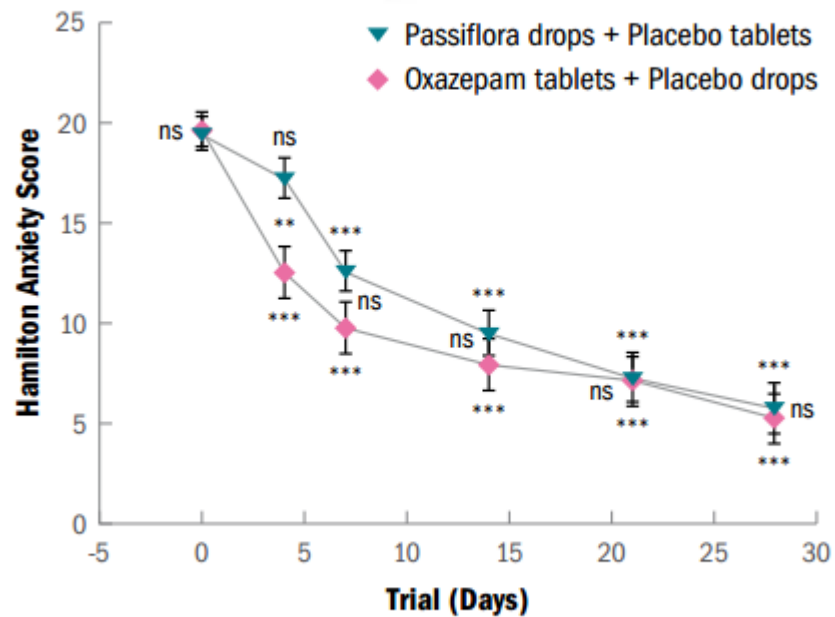


Flumazenil : ανταγωνιστής BZ υποδοχέων :
 συγχορήγηση με εκχύλισμα Passiflora :
 ανταγωνισμός
 Καταδεικνύεται η δράση της μέσω του
 GABA_A υποδοχέα



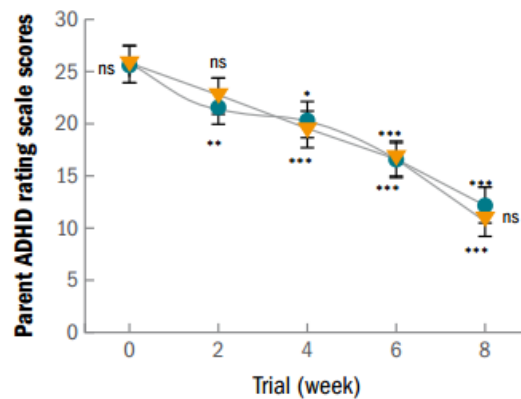
Influence of flumazenil (3 mg/kg. *i.p.*, 15 minutes prior to oral treatment with extract of Passiflora) and 5-HT_{1A} receptor antagonist WAY-100635 (0,5 mg/kg, *i.p.*, 15 minutes prior to oral treatment with extract of Passiflora) expressed as a percentage of time spent in the open arm (A) and number of entries in the open arm (B) in the elevated plus maze in mice. Results are expressed as mean ± standard deviation, n = 10 for each group. *** P < 0.001 vs control, ** p < 0.01 vs control (ANOVA with Student-Newman-Keuls post-hoc test).

Σύγκριση με oxazepam

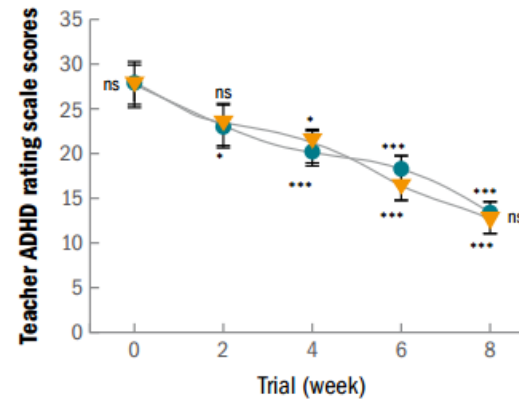


Passiflora extract proved to be useful in the management of ADHD in a randomized, parallel. Trial on 34 teenagers, lasting 8 weeks.⁽¹⁹⁾

Parent ADHD rating score



Teacher ADHD rating score



ns: not significant.
The horizontal symbols (***) are used to express statistical significance vs the respective baseline values.

● Passionflower extract 0,04 mg/kg/day ▼ Methylphenidate 1 mg/kg/day

ΑΕ : ελάχιστες

CLINICAL COMPLICATIONS											
Complications	Passiflora drops + Placebo tablets					Placebo drops + Oxazepam tablets					P
	None	Mild	Moderate	Severe	Severe, Disabling	None	Mild	Moderate	Severe	Severe, Disabling	
Dizziness	9	3	4	0	0	8	3	4	1	0	0.787
Drowsiness	10	6	0	0	0	9	5	2	0	0	0.342
Confusion	12	4	0	0	0	12	3	1	0	0	0.565
Slurred speech	16	0	0	0	0	16	0	0	0	0	None
Ataxia	14	1	1	0	0	12	3	1	0	0	0.562
Hyporeflexia	16	0	0	0	0	15	0	1	0	0	0.310
Respiratory depression	16	0	0	0	0	13	1	2	0	0	0.191
Dyspnea	16	0	0	0	0	14	0	2	0	0	0.144
Allergic reaction	14	1	1	0	0	13	2	1	0	0	0.831
Aggression	16	0	0	0	0	16	0	0	0	0	None
Disinhibition	16	0	0	0	0	16	0	0	0	0	None
Impairment of job performance	8	5	3	0	0	4	3	2	6	1	0.049*

*Problems related to dysfunctional labor were found in greater numbers and statistically significant in the group of patients treated with Oxazepam.

Baicaleine (Scutellaria extract)

Baicaleine (Scutellaria extract)

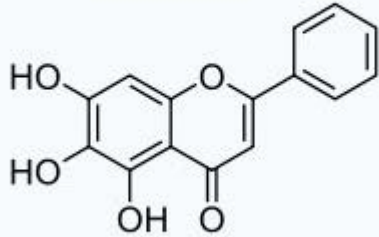
Baicaleine, the main flavone identified in the extract of Scutellaria, showed an anxiolytic activity that is mediated by the GABA_A receptor binding to a site different from the binding site for benzodiazepines. Furthermore, the **extract of Scutellaria** showed an inhibitory activity against the enzyme GABA-transaminase that has been put in relation with the anxiolytic effect.^(8, 9, 12, 16)



Scutellaria baicalensis

Scutellaria = σκούφος

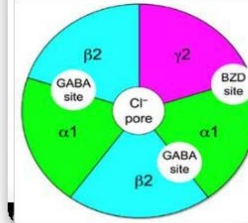
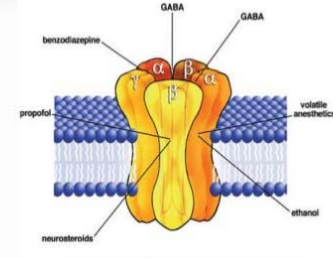
Baicalein



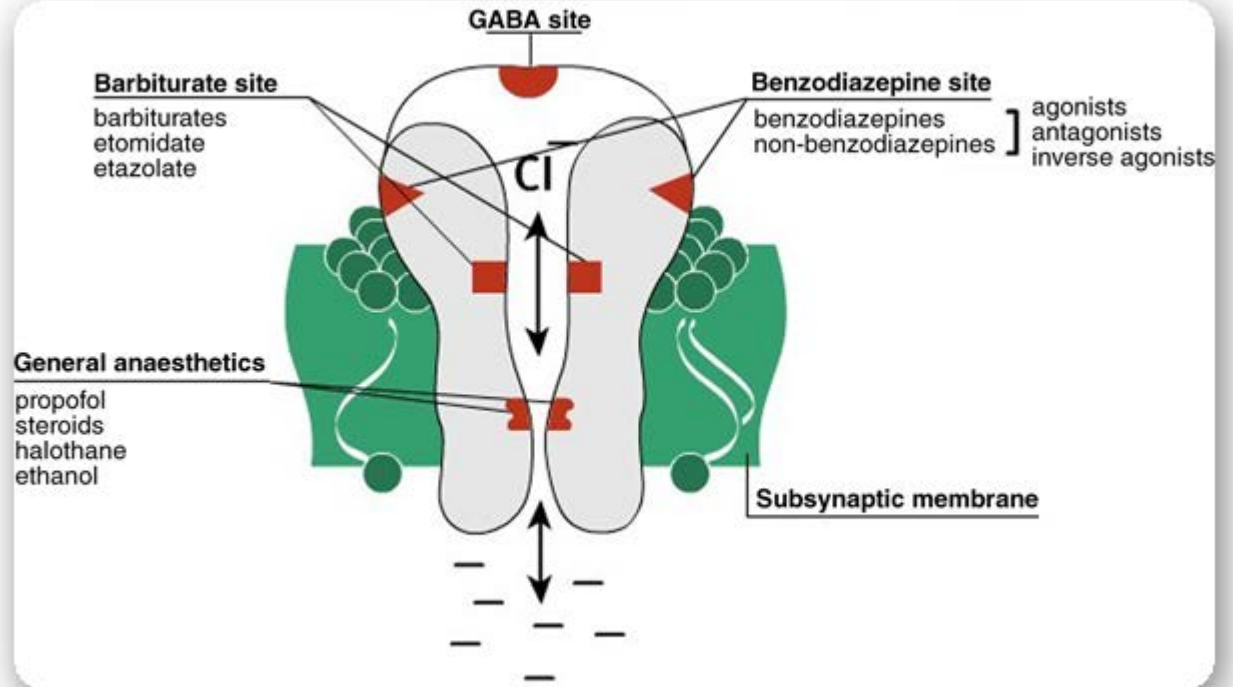
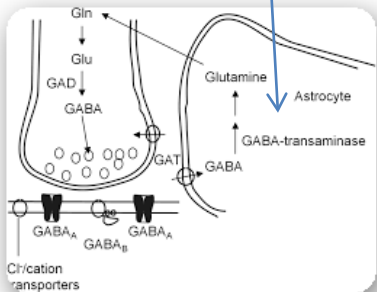
MECANISMO DE ACCIÓN

Receptores GABA

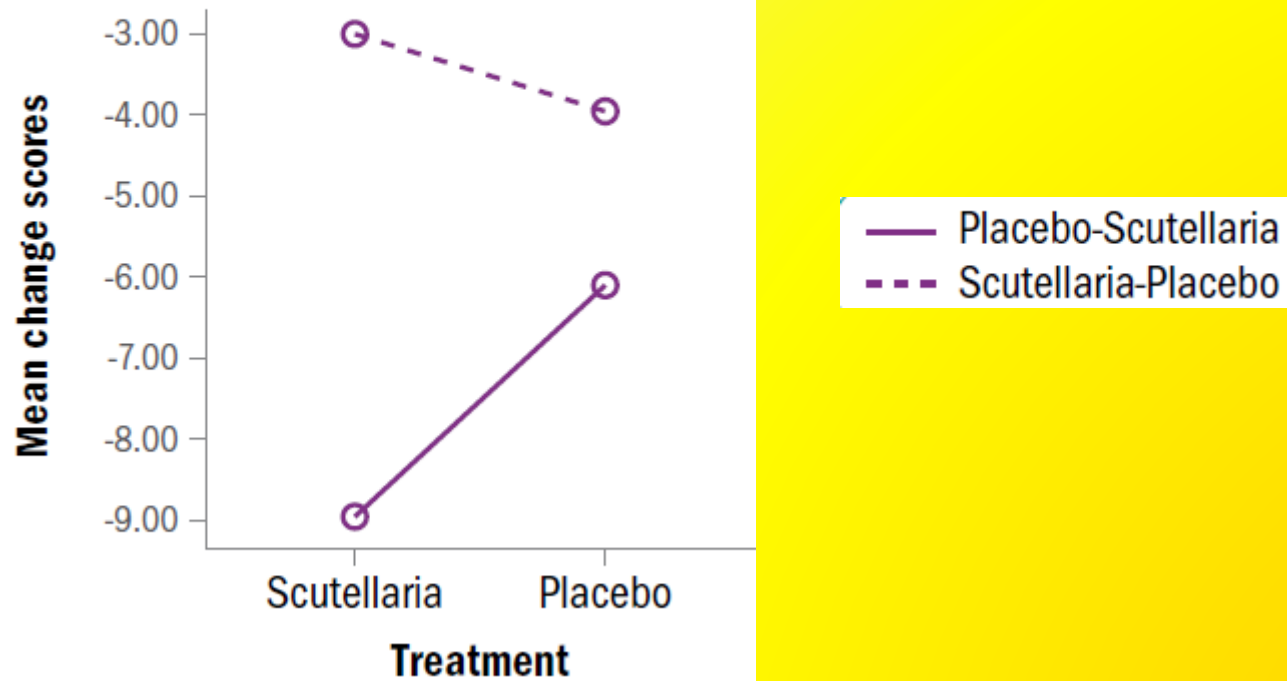
- Inotrópicos
 - GABA - A
- Metabotrópicos
 - GABA - B
 - GABA - C



Αναστολή του ενζύμου



Beck Anxiety Inventory



Brock C, Whitehouse J, Tewfik I, Towell T. American Skullcap (*Scutellaria lateriflora*): A Randomised, Double Blind Placebo-Controlled Crossover Study of its Effects on Mood in Healthy Volunteers.

Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. *Altern Ther Health Med*. 2003 Mar-Apr;9(2):74-8.

Συμπεράσματα

- ❖ τα Neutraceuticals μπορούν να χρησιμοποιηθούν είτε μόνα τους , είτε σαν συμπληρωματική θεραπεία στην ψυχιατρική
- ❖ Εχουν ελάχιστες παρενέργειες
- ❖ Η χρήση τους εξαπλώνεται συνεχώς και είναι αποδεκτά από τον ασθενή