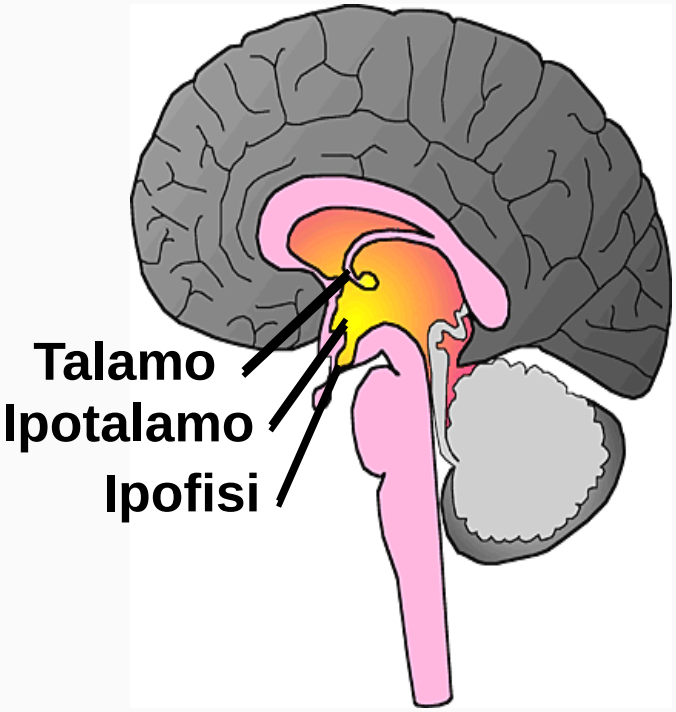

FABRIZIO MURATORI
UNITA' OPERATIVA DI ENDOCRINOLOGIA
DIABETOLOGIA E NUTRIZIONE CLINICA
OSPEDALE SANT'ANNA DI COMO

# Nutraceutica ed eccesso ponderale

# Principali piante medicinali impiegate nel sovrappeso/obesità

| Nome comune della droga | Principali costituenti chimici | Dose consigliata die |
|---|---|---|
| **Arancia amara** | Sinefrina | Non superare i 30 mg die |
| **Efedra sinica/Ma Huang** | Efedrina, pseudoefedrina | Non più in commercio in Italia |
| **Guaranà** | Alcaloidi purinici (caffeina), tannini | 1-3 grammi |
| **Fucus vesciculosos (Fuco)** | Iodio, polisaccaridi | Non sono disponibili dati attendibili |
| **Griffonia simplicifolia** | 5 OH triptofano (5OHT) | 100 – 600 mg die in 5OHT |
| **Cissus quadrangolaris** | Fitosteroli . Ketosteroidi flavonoidi | 200-300 mg die **Non in commercio in Italia** |
| **Rhodiola Rosea** | Rosavin, Salidroside | |
| **Garcinia Cambogia** | Acido idrossicitrico | 1,5 grammi |
| **Fagiolo** | Faseolamina | |
| **Orthosiphon** | Flavonoidi, cumarine terpenoidi | Secondo prescrizione medica |
| **Tarassaco** | Olio essenziale, flavonoidi, derivati dell'acido caffeico | Secondo prescrizione medica |
| **Gomma Guar** | Galattomannano, proteine | 9-30 grammi |
| **Psillio** | mucillagini | 10-30 grammi |

# Circuiti Monoaminergici che Intervengono nella Assunzione di Cibo e nella Sazietà




**Serotonina (5-HT)**
Favorisce la sazietà

**Noradrenalina (NA)**
Inibisce l'assunzione di cibo (sistema β-adrenergico)

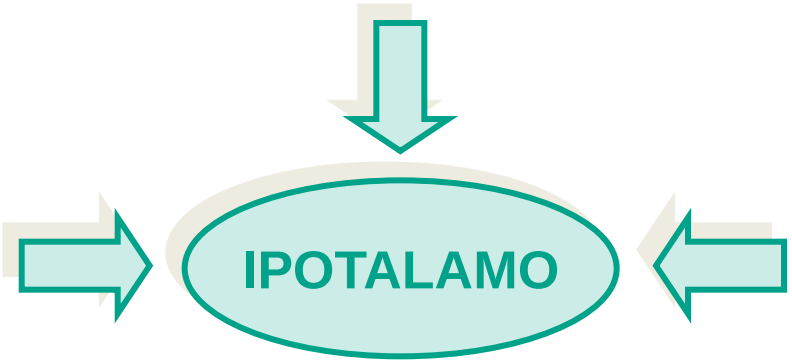
**Dopamina (DA)**
Inibisce l'assunzione di cibo

1. Obesity: advances in understanding and treatments. 1995 (May 22) 22; 6 (2-3): 26-41
2. Hoebel et al. *Brain Behav Bodily Dis.* 1981; 59: 103-142.

# INFLUENZE SULL'ASSUNZIONE DI CIBO

**AFFERENZE**
visive-limbiche-motorie

**INIBIZIONE**
- serotonina
- dopamina
- leptina
- insulina
- alfa-MSH
- CRF
- GLP-1
- CCK
- POMC
- catecolamine
- CART
- Antagonisti dei cannabinoidi
- PYY




**STIMOLO**
- NPY
- glucocorticoidi
- oppioidi
- GABA
- GHrH
- galanina
- norepinefrina
- Ghrelina
- cannabinoidi

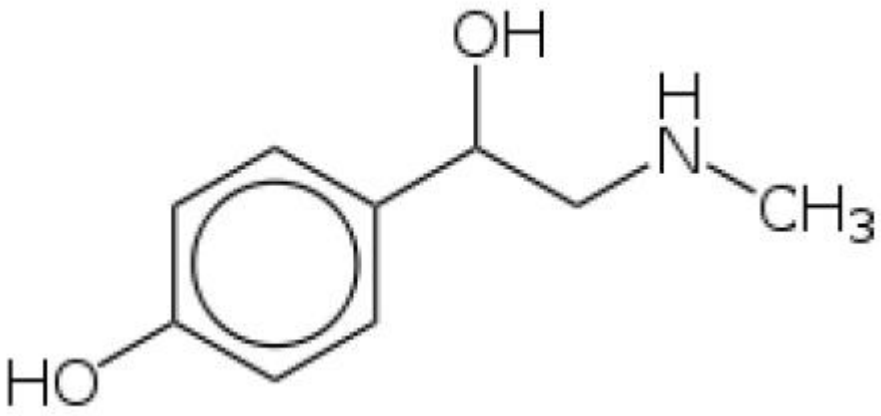
# AGENTI COADIUVANTI IL CALO PONDERALE

## FITOTERAPICI di più frequente utilizzo

| Stimolanti | Modulatori umore | Metabolici | Drenanti | Coleretici epatoprotettori | Fibre |
|---|---|---|---|---|---|
| Guaranà | Griffonia | Garcinia cambogia | Orthosifon | Boldo | Psyllo |
| Matè | Rhodiola rosea | Estratto fagiolo | Pilosella | Cardo | Gomma guar |
| Citrus aurantium | | Fucus | | tarassaco | |
| Rhodiola rosea | | | | | |

# sinefrina

da estratto di frutti immaturi di **Citrus**
(*Citrus aurantium var. amara L.*)



# Citrus Aurantium

Il principale composto farmacologicamente attivo del Citrus è la p-sinefrina (para-sinefrina o ossedrina)

L'impiego di Citrus Aurantium, come integratore, è consentito e regolamentato dal Ministero della Salute

Dose massima giornaliera di sinefrina 30 mg da estratto secco

Corrispondenti a 800 mg di Citrus titolato al 4%

Altre formalità:

- Va riportata la titolazione in sinefrina
- Si sconsiglia l'uso in gravidanza e durante l'allattamento e al di sotto dei 12 anni
- Consultare il medico prima dell'uso se le condizioni CV non sono nella norma

# Citrus Aurantium

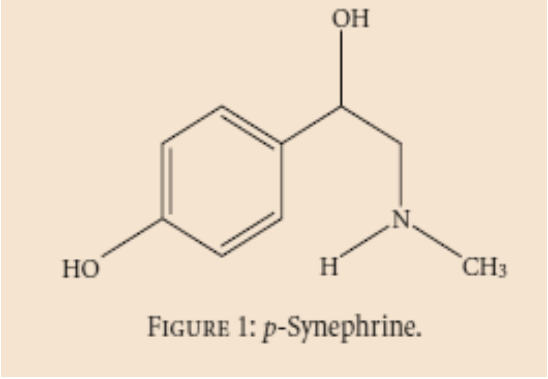


FIGURE 1: *p*-Synephrine.

**Indicazioni ministeriali** per l'utilizzo di citrus negli integratori:

Indicazioni: Equilibrio del peso corporeo. Stimolo metabolico e metabolismo dei lipidi. Funzione digestiva. Regolare motilità gastrointestinale ed eliminazione dei gas.

Occorre indicare in etichetta la titolazione in sinefrina: l'apporto massimo di sinefrina non deve superare i 30 mg/die

AVVERTENZA SUPPLEMENTARE da aggiungere in etichetta: Si sconsiglia l'uso del prodotto in gravidanza, durante l'allattamento e al di sotto dei 12 anni.

**Consultare il medico prima dell'uso se condizioni cardiovascolari non sono nella norma**.

Esistono 6 possibili isomeri della sinefrina (orto, meta, para e, per ciascuno di essi la forma d (+) o l (-)

Il composto principale farmacologicamente attivo del Citrus è la p-sinefrina (para sinefrina o ossedrina)

La p-sinefrina avrebbe un'azione stimolante i beta 3 recettori e quindi lipolitica, termogenica

*International Journal of Medical Sciences*
2011; 8(4):295-301

Research Paper

# Effects of *p*-Synephrine alone and in Combination with Selected Bioflavonoids on Resting Metabolism, Blood Pressure, Heart Rate and Self-Reported Mood Changes

**Sidney J. Stohs[1], Harry G Preuss[2]✉, Samuel C. Keith[3], Patti L. Keith[3], Howard Miller[4], Gilbert R. Kaats[3]**

1. Dean Emeritus, Creighton University Health Sciences Center, Omaha, NE 68178, USA
2. Department of Physiology, Georgetown University Medical Center, Washington, DC, USA
3. Integrative Health Technologies, Inc., 4940 Broadway, San Antonio, TX 78209, USA
4. Nutratech Inc., West Caldwell, NJ 07006, USA

## Abstract

Bitter orange (*Citrus aurantium*) extract is widely used in dietary supplements for weight management and sports performance. Its primary protoalkaloid is *p*-synephrine. Most studies involving bitter orange extract and *p*-synephrine have used products with multiple ingredients. The current study assessed the thermogenic effects of *p*-synephrine alone and in conjunction with the flavonoids naringin and hesperidin in a double-blinded, randomized, placebo-controlled protocol with 10 subjects per treatment group. Resting metabolic rates (RMR), blood pressure, heart rates and a self-reported rating scale were determined at baseline and 75 min after oral ingestion of the test products in V-8 juice. A decrease of 30 kcal occurred in the placebo control relative to baseline. The group receiving *p*-synephrine (50 mg) alone exhibited a 65 kcal increase in RMR as compared to the placebo group. The consumption of 600 mg naringin with 50 mg *p*-synephrine resulted in a 129 kcal increase in RMR relative to the placebo group. In the group receiving 100 mg hesperidin in addition to the 50 mg *p*-synephrine plus 600 mg naringin, the RMR increased by 183 kcal, an increase that was statistically significant with respect to the placebo control ($p<0.02$). However, consuming 1000 mg hesperidin with 50 mg *p*-synephrine plus 600 mg naringin resulted in a RMR that was only 79 kcal greater than the placebo group. None of the treatment groups exhibited changes in heart rate or blood pressure relative to the control group, nor there were no differences in self-reported ratings of 10 symptoms between the treatment groups and the control group. This unusual finding of a thermogenic combination of ingredients that elevated metabolic rates without corresponding elevations in blood pressure and heart-rates warrants longer term studies to assess its value as a weight control agent.

Key words: *p*-Synephrine, naringin, hesperidin, resting metabolic rate, heart rate, blood pressure

# Effetto sinergico della sinefrina , della esperidina e della naringina sul consumo calorico

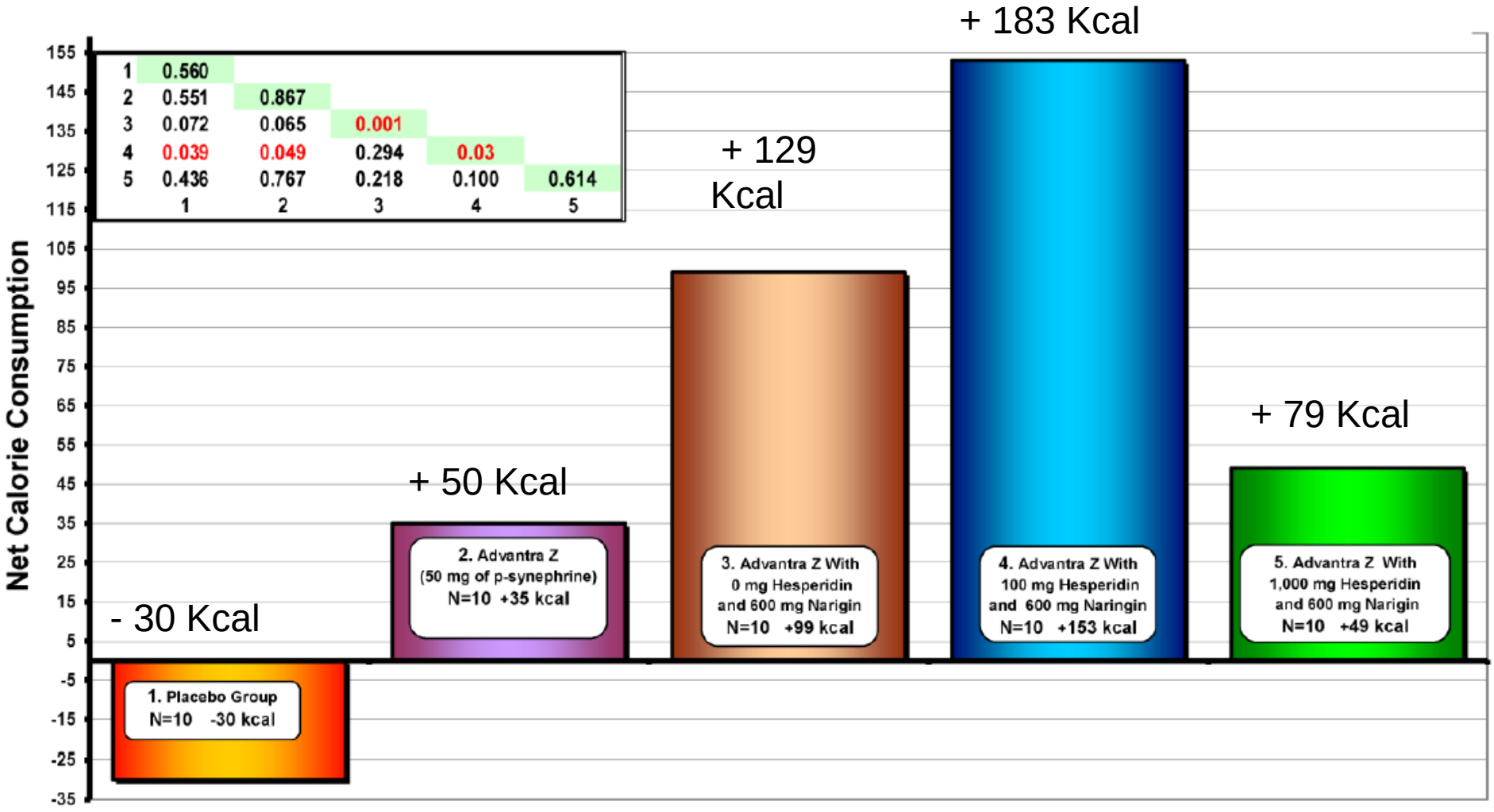



**Figure 1**. Over-Placebo Comparisons of Changes in Resting Metabolic Rates 75 Minutes from Baseline (Expressed in kcal) With a Supplement Containing the Variations in Advantra Z, Naringin, and Hesperidin

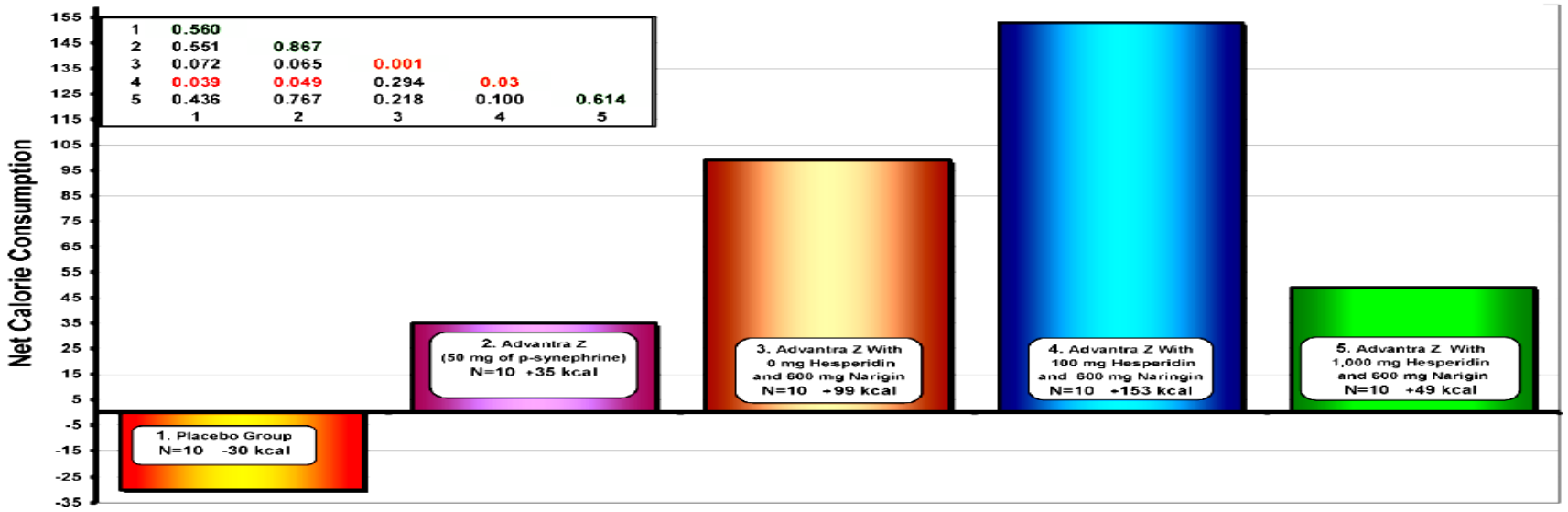



**Figure 1**. Over-Placebo Comparisons of Changes in Resting Metabolic Rates 75 Minutes from Baseline (Expressed in kcal) With a Supplement Containing the Variations in Advantra Z, Naringin, and Hesperidin

**Table 2**. Blood Pressures and Resting heart Rates

| Treatment Variable | Placebo | T2 | T3 | T4 | T5 | P-Value[1] |
|---|---|---|---|---|---|---|
| SYSTOLIC | | | | | | |
| Baseline | 122.9(17.7) | 120.5(14.5) | 120.0(12.3) | 117.9(14.4) | 125.6(12.6) | 0.794 |
| Ending | 123.3(18.3) | 120.3(9.0) | 120.9(11.4) | 119.3(15.5) | 130.8(10.2) | 0.317 |
| DIASTOLIC | | | | | | |
| Baseline | 71.3(6.9) | 73.8(6.4) | 77.0(6.3) | 72.7(9.8) | 76.9(6.4) | 0.316 |
| Ending | 75.0(9.1) | 74.6(8.3) | 75.5(10.0) | 71.8(10.0) | 75.3(7.8) | 0.891 |
| HEART RATE | | | | | | |
| Baseline | 64.5(11.2) | 72.3(5.1) | 70.0(14.0) | 71.6(13.3) | 69.4(6.4) | 0.518 |
| Ending | 62.7(9.4) | 71.6(6.7) | 65.7(9.0) | 68.6(9.5) | 68.0(8.4) | 0.206 |

[1]ANOVA. Placebo: V-8 juice only, T2: 50 mg of *p*-synephrine (Advantra Z®). T3: *p*-synephrine + 600 mg naringin. T4: *p*-synephrine + 600 mg naringin + 100 mg hesperidin. T5: *p*-synephrine + 600 mg naringin + 1,000 mg hesperidin. Each value is the mean with the standard deviation for 10 subjects.

# Citrus Aurantium

Hindawi Publishing Corporation
Oxidative Medicine and Cellular Longevity
Volume 2011, Article ID 482973, 9 pages
doi:10.1155/2011/482973

*Review Article*

## A Review of the Receptor-Binding Properties of *p*-Synephrine as Related to Its Pharmacological Effects

**Sidney J. Stohs,[1] Harry G. Preuss,[2] and Mohd Shara[3]**

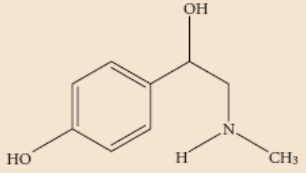


FIGURE 1: *p*-Synephrine.

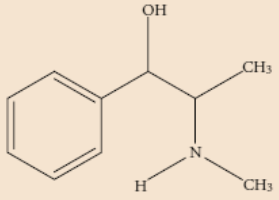


FIGURE 2: Ephedrine.

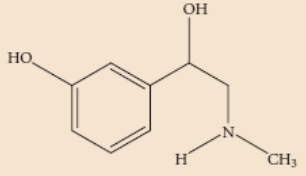


FIGURE 3: *m*-Synephrine.

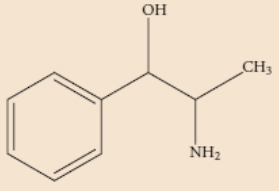


FIGURE 4: Phenylpropanolamine.

A causa della somiglianza strutturale della p-sinefrina con m-sinefrina, efedrina, noradrenalina e amfetamina è diffusa la percezione che tutte queste molecole abbiano proprietà simili e simile profilo di rischio

Invece esistono notevoli differenze

- La p-sinefrina non passa facilmente la barriera ematoencefalica
- La p-sinefrina è meno lipo-solubile dell'efedrina
- Ha un'azione stimolante il SNC e CV minima o assente rispetto a efedrina, noradrenalina, amfetamina
- **Diversa affinità recettoriale**

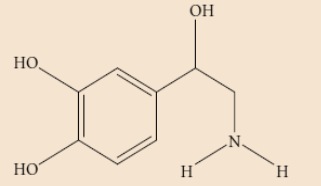


FIGURE 5: Nor-epinephrine (Nor-adrenaline).

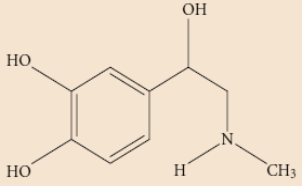


FIGURE 6: Epinephrine (Adrenaline).

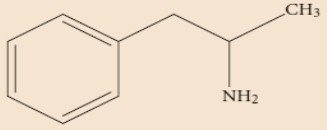


FIGURE 7: Amphetamine.

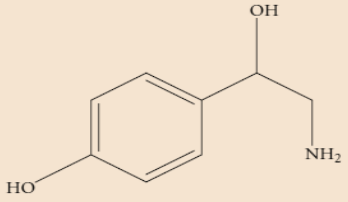
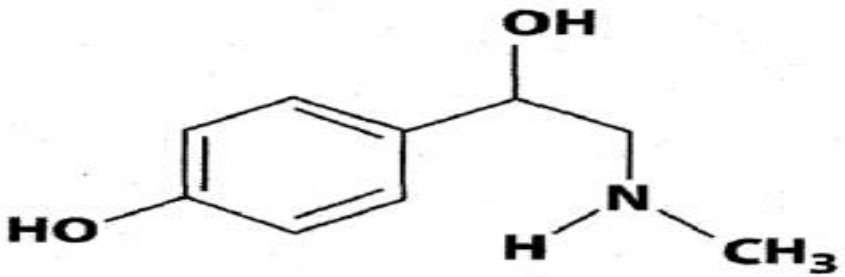
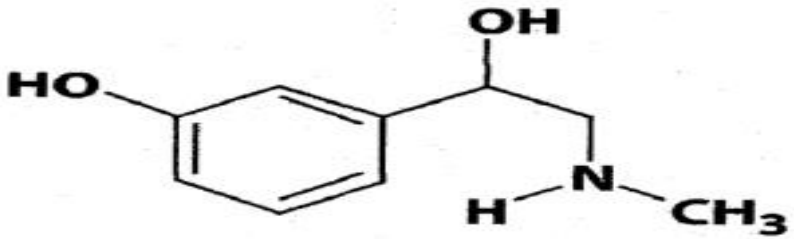


FIGURE 8: *p*-Octopamine.



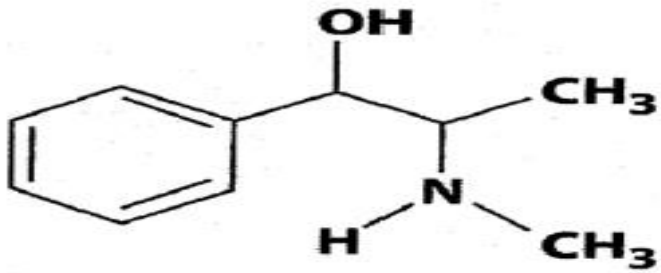

*p*-synephrine

**Fig. 1** Chemical structure of *p*-synephrine.




*m*-synephrine

**Fig. 2** Chemical structure of *m*-synephrine.




ephedrine

**Fig. 3** Chemical structure of ephedrine

**Lipids in Health and Disease**

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Research

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# Effect of the dietary supplement Meltdown on catecholamine secretion, markers of lipolysis, and metabolic rate in men and women: a randomized, placebo controlled, cross-over study

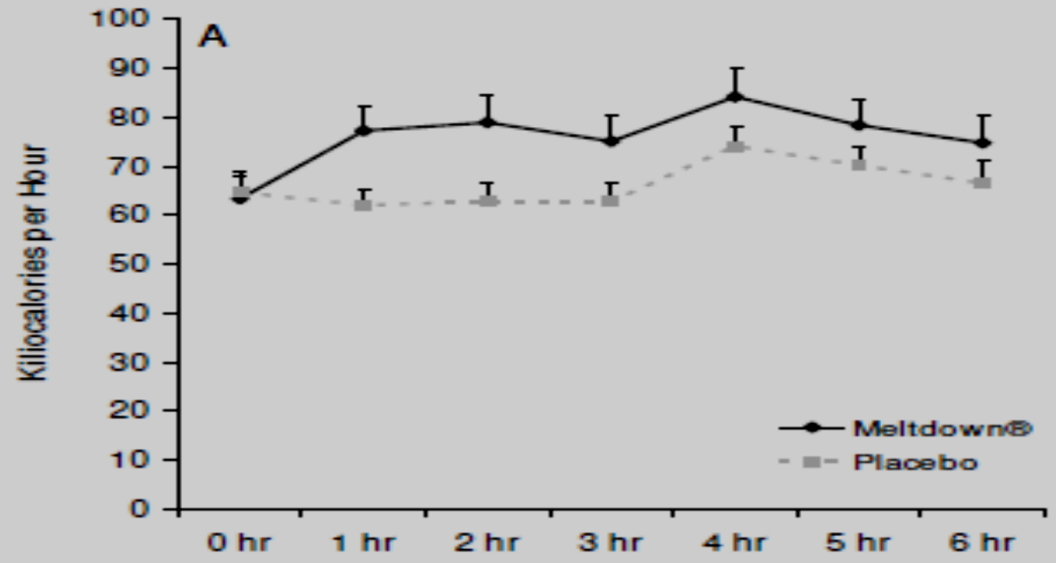
Richard J Bloomer*, Robert E Canale, Megan M Blankenship, Kelley G Hammond, Kelsey H Fisher-Wellman and Brian K Schilling

Address: Cardiorespiratory/Metabolic Laboratory, Department of Health and Sport Sciences, University of Memphis, Memphis, TN, USA

Email: Richard J Bloomer* - rbloomer@memphis.edu; Robert E Canale - rcanale@memphis.edu; Megan M Blankenship - mmblnkns@memphis.edu; Kelley G Hammond - kghmmond@memphis.edu; Kelsey H Fisher-Wellman - kfshrwll@memphis.edu; Brian K Schilling - bschllng@memphis.edu

* Corresponding author

*Lipids in Health and Disease* 2009, 8:32




## SUPPLEMENT FACTS

Serving Size: 3 Capsules — Servings Per Container: 40

| | Amount per Serving | %DV* |
|---|---|---|
| Calories 0 | | |
| Total Carbohydrates | 0 g | 0% |
| Total Fat | 0 g | 0% |
| **Fat Catabolizor™ & β-3 Potentiator** | **317 mg** | ** |
| Caffeine Anhydrous | | ** |
| a-MTTA (alpha-Methyl Tetradecylthioacetic Acid) | | ** |
| Yerba Mate Extract | | ** |
| **Lipolytic Trigger™** | | ** |
| 3'-5'-cAMP (3'-5'-Cyclic Adenosine Monophosphate) | | ** |
| **Super Synephrine™ β-3 Activator™** | **20 mg** | ** |
| Methyl-Synephrine HCl | | ** |
| **Iphoric® Potent Methyl β-PEA Matrix** | **138 mg** | ** |
| R-beta-Methylphenylethylamine | | ** |
| N-Methyl-beta-Phenylethylamine | | ** |
| **NorEpiphex™ α2-Andrenergic Blockade Complex** | **9 mg** | ** |
| 11-Hydroxy Yohimbine | | ** |
| Yohimbine HCl | | ** |
| alpha-Yohimbine | | ** |
| **NorEpiphex™ M-MAOxidizor-I™** | **20 mg** | ** |
| Methyl-Hordenine HCl | | ** |

* Percent daily values (DV%) are based on a 2000 calorie diet.
** Daily values not established.

**Other Ingredients: BIOLIQUID™ PolyLipid™ (polymer-lipid based) Delivery System:** Contains one or more of the following: Super Refined Sesamum Indicum (Sesame) Seed Oil, Propylene Glycol Fatty Acid Ester, Safflower Oil, Sunflower Oil, Purified Water, Gelatin, Titanium Dioxide.

Figure 1
Label description of Meltdown®.

**Caffeina, sinefrina e yohimbina**

**Lipids in Health and Disease**

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# Effect of the dietary supplement Meltdown on catecholamine secretion, markers of lipolysis, and metabolic rate in men and women: a randomized, placebo controlled, cross-over study

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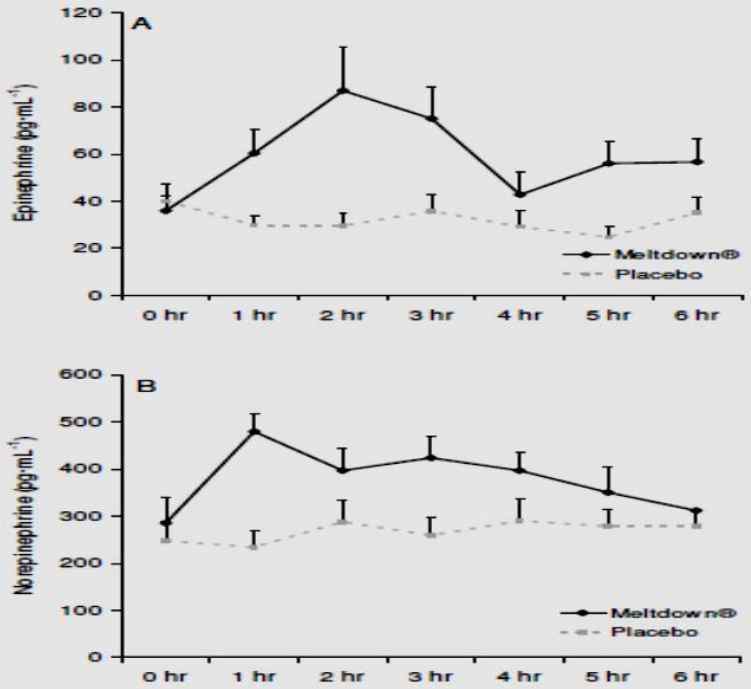


**Figure 2**
**Plasma epinephrine (A) and norepinephrine (B) data for men and women consuming Meltdown® and placebo in a randomized cross-over design.** Data are mean ± SEM. * Greater epinephrine (367 ± 58 pg·mL$^{-1}$·6 hr$^{-1}$ vs. 183 ± 27 pg·mL$^{-1}$·6 hr$^{-1}$; p = 0.01) and norepinephrine (2345 ± 205 pg·mL$^{-1}$·6 hr$^{-1}$ vs. 1659 ± 184 pg·mL$^{-1}$·6 hr$^{-1}$; p = 0.02) AUC for Meltdown® compared to placebo.

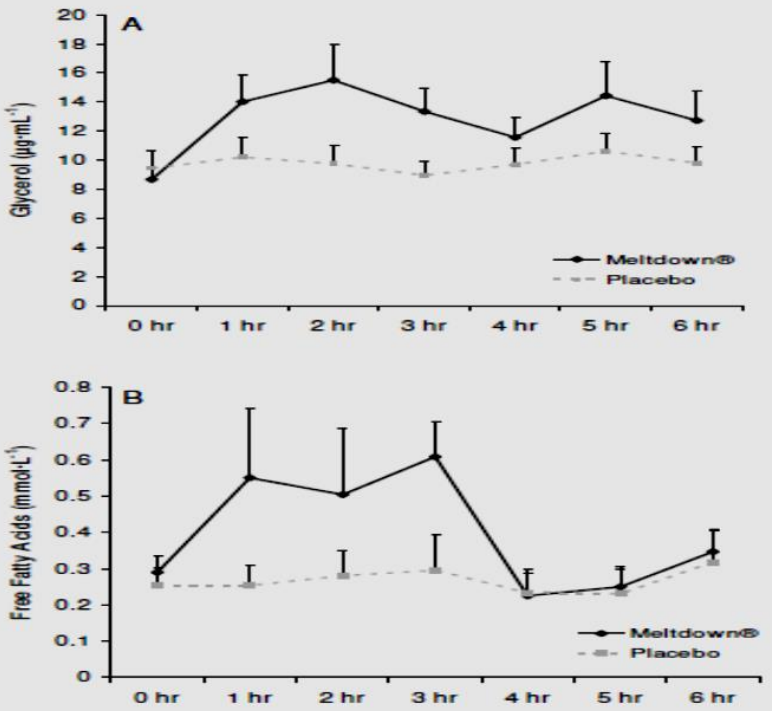


**Figure 3**
**Plasma glycerol (A) and free fatty acid (B) data for men and women consuming Meltdown® and placebo in a randomized cross-over design.** Data are mean ± SEM. * Greater glycerol (79 ± 8 μg·mL$^{-1}$·6 hr$^{-1}$ vs. 59 ± 6 μg·mL$^{-1}$·6 hr$^{-1}$; p = 0.03), and FFA (2.46 ± 0.64 mmol·L$^{-1}$·6 hr$^{-1}$ vs. 1.57 ± 0.42 mmol·L$^{-1}$·6 hr$^{-1}$; p = 0.05) AUC for Meltdown® compared to placebo.

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Several other ingredients are included within Meltdown® including the amphetamine-like/thyroid stimulating agent phenylethylamine (PEA), which is known to stimulate a rise in blood catecholamine levels and inhibiting their reuptake [26]. The monoamine oxidase inhibitor methyl hordinine is also contained within this supplement. Hordinine is structurally similar to EPI and has been shown to liberate NE from its storage site, in addition to inhibiting NE metabolism [27]. Methyl tetradecylthioacetic acid is also included, and known to stimulate beta oxidation [28] and to be involved in lipid transport and utilization [29].

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* Percent daily values (DV%) are based on a 2000 calorie diet.
** Daily values not established.

**Other Ingredients: BIOLIQUID™ PolyLipid™ (polymer-lipid based) Delivery System:** Contains one or more of the following: Super Refined Sesamum Indicum (Sesame) Seed Oil, Propylene Glycol Fatty Acid Ester, Safflower Oil, Sunflower Oil, Purified Water, Gelatin, Titanium Dioxide.

**Figure 1**
**Label description of Meltdown®.**

Caffeina , sinefrina, phenylethylamina, yohimbina, monoaminossidasi inibitore hordinina : cosa ne pensiamo ?

CURRENT
THERAPEUTIC
RESEARCH®
VOL. 60, NO. 3, MARCH 1999

# Effects of *Citrus aurantium* Extract, Caffeine, and St. John's Wort on Body Fat Loss, Lipid Levels, and Mood States in Overweight Healthy Adults

Carlon M. Colker,[1] Douglas S. Kalman,[2] Georgeann C. Torina,[1] Theresa Perlis,[3] and Chris Street[4]

[1]Greenwich Hospital, [2]Peak Wellness, Greenwich, Connecticut, [3]National Drug Research Institute, New York, New York, and [4]TSI University Laboratories, Houston, Texas

## CONCLUSIONS

*C aurantium extract* is a noncentrally acting, beta-sympathicomimetic agent, which, when combined with caffeine and St. John's Wort—as well as caloric restriction and exercise—can induce weight loss to a greater extent than diet and exercise alone. This investigation shows that a combination of *C aurantium* extract, caffeine, and St. John's Wort is viable and effective in reducing body fat in obese healthy adults.

IVYSPRING INTERNATIONAL PUBLISHER

*International Journal of Medical Sciences*

2012; 9(7):527-538. doi: 10.7150/ijms.4446

Review

# A Review of the Human Clinical Studies Involving *Citrus aurantium* (Bitter Orange) Extract and its Primary Protoalkaloid *p*-Synephrine

**Sidney J. Stohs[1], Harry G. Preuss[2]✉, Mohd Shara[3]**

**Table 1**. Summary of published human studies involving bitter orange extract and *p*-synephrine

| Product | Treated Subjects | overwt/ obese | Duration | *p*-Synephrine dose (mg) | Caffeine dose (mg) | End Point | Adverse events | Reference |
|---|---|---|---|---|---|---|---|---|
| Complex | 9 | 9 | 42 days | 58.5 | 528 | Wt. loss, ↑BMR | No | Colker et al., 1999[15] |
| Bitter orange juice | 12 | -- | 1 day | 27 | --- | CV | No | Penzak et al., 2001[6] |
| Complex | 15 | 15 | 56 days | 10 | 400 | Wt. loss Multiple | No | Kalman et al., 2000[21] |
| Complex | 13 | 13 | 14 days | 10 | 400 | CV | No | Kalman et al., 2002[22] |
| Bitter orange extract | 12 | -- | 28 days | 30.6 | -- | Cyt.P450 enzymes | No | Gurley et al., 2004[24] |
| Complex | 18 | 18 | 56 days | 36 | 132 | No wt. loss ↑RMR | No | Zenk et al., 2005[26] |
| Bitter orange extract | 18 | -- | 8 hrs | 27 | --- | CV | No | Min et al., 2005[27] |
| Complex | 10 | -- | 6 hrs | 5.5 | 239 | CV | ↑HR, ↑BP | Haller et al., 2005[28] |
| Bitter orange extract | 10 | -- | 6 hrs | 46.9 | --- | CV | ↑HR | Haller et al., 2005[28] |
| Bitter orange extract | 15 | -- | 6 hrs | 54 | --- | CV | ↑HR, ↑BP | Bui et al., 2006[29] |
| Complex | 10 | 10 | 7 hrs | 12 | 150 | ↑ RMR, ↑ Kcal use | No | Sale et al., 2006[30] |
| Bitter orange extract | 22 | 22 | 8 hrs | 30 | --- | ↑RQ | No | Gougeon et al., 2006[31] |
| Complex | 10 | -- | 3 hrs | 21.6 | 450 | ↑RQ, ↑RMR | ↑BP | Hoffman et al., 2007[32] |
| Complex | 10 | -- | 2 hrs | 21 | 304 | CV | ↑↑DBP | Haller et al., 2008[34] |
| Complex | 23 | 23 | 25 hrs | 52 | 704 | ↑ kcal use, ↓RER | No | Seifert et al., 2011[35] |
| Bitter orange extract | 40 | -- | 2 hrs | 50 | --- | ↑RMR | No | Stohs et al., 2011[36] |

BMR=basal metabolic rate; RMR=resting metabolic rate; CV=cardiovascular; RQ=respiratory quotient; RER=respiratory exchange ratio

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Review

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**Sidney J. Stohs[1], Harry G. Preuss[2]✉, Mohd Shara[3]**

## Summary and Conclusions

The results involving both published and unpublished clinical studies indicate that *p*-synephrine alone or in combination with caffeine does not appear to produce significant adverse cardiovascular effects or pose a risk to human health at doses commonly ingested orally. No adverse effects have been directly attributable to bitter orange extract or *p*-synephrine. *p*-Synephrine/bitter orange extract alone as well as in combination with other ingredients results in significant increases in resting metabolic rate, and when taken for periods of time up to 12 weeks may result in modest weight loss.

*Int. J. Med. Sci.* 2012, 9

The results indicate that bitter orange extract and *p*-synephrine increase metabolism and energy expenditure. The data accumulated to date do not support hypothesized concerns regarding potential adverse effects of *p*-synephrine particularly with respect to the cardiovascular system due to a paucity of binding to α-, β-1 and β-2 adrenergic receptors while exhibiting modest binding to β-3 adrenergic receptors. However, a need exists for additional well controlled, long term human efficacy and safety studies involving *p*-synephrine/bitter orange extract.

Acknowledgements

**Lipids in Health and Disease**

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# The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

Julius E Oben*[1], Judith L Ngondi[1], Claudia N Momo[1], Gabriel A Agbor[1,2] and Caroline S Makamto Sobgui[1,2]

**Methods:** The study was a 10 week randomized, double-blind, placebo-controlled design involving 72 obese or overweight participants (45.8% male; 54.2% female; ages 21–44; mean age = 29.3). The participants were randomly divided into three equal (n = 24) groups: placebo, *Cissus quadrangularis*-only, and *Cissus quadrangularis/Irvingia gabonensis* combination. Capsules containing the placebo or active formulations were administered twice daily before meals; no major dietary changes nor exercises were suggested during the study. A total of six anthropomorphic and serological measurements (body weight, body fat, waist size; total plasma cholesterol, LDL cholesterol, fasting blood glucose level) were taken at baseline and at 4, 8 and 10 weeks.

**Conclusion:** Although the *Cissus quadrangularis*-only group showed significant reductions on all variables compared to the placebo group, the *Cissus quadrangularis/Irvingia gabonensis* combination resulted in even larger reductions. This apparently synergistic formulation should prove helpful in the management of obesity and its related complications.

## Due fitoterapici con azione sinergica : Cissus Quadrangolaris e Irvingia gabonensis

Cissus : inibisce le lipasi e le amilasi

Irvingia iniobisce la alfa amilasi

Lipids in Health and Disease

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# The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

Julius E Oben*[1], Judith L Ngondi[1], Claudia N Momo[1], Gabriel A Agbor[1,2] and Caroline S Makamto Sobgui[1,2]

**Table 1: Body weight: effectiveness of treatments**

| | Body weight (mean kg) | | | | Weight change (%) | | |
|---|---|---|---|---|---|---|---|
| | Initial | 4 weeks | 8 weeks | 10 weeks | 4 Weeks-Initial | 8 Weeks-Initial | 10 Weeks-Initial |
| Placebo | 98.05 ± 12.30 | 98.76 ± 8.20 | 96.74 ± 10.60 | 95.99 ± 15.20 | 0.72 | -1.33 | -2.10 |
| CQ | 98.92 ± 10.60 | 95.77 ± 12.32[a] | 91.47 ± 8.69[a] | 90.19 ± 7.60[b] | -3.19 | -7.53† | -8.82† |
| CQ-IG | 99.79 ± 13.50 | 95.77 ± 7.40 | 90.91 ± 5.72[b]* | 87.95 ± 3.17[c]** | -4.02† | -8.90† | -11.86† |

[a]$p < 0.05$; [b]$p < 0.001$; [c]$p < 0.0001$ compared with **Placebo**
*$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$ compared with **CQ**
†$p < 0.05$; ‡$p < 0.001$ compared with **Initial**; intra-group analysis

**Table 4: Plasma total cholesterol level: effectiveness of treatments**

| | Total cholesterol (mean mg/dL) | | | | Change (%) | | |
|---|---|---|---|---|---|---|---|
| | Initial | 4 weeks | 8 weeks | 10 weeks | 4 Weeks-Initial | 8 Weeks-Initial | 10 Weeks-Initial |
| Placebo | 146.20 ± 38.14 | 140.40 ± 11.11 | 150.06 ± 13.20 | 149.47 ± 19.16 | -3.965 | 2.64 | 2.23 |
| CQ | 150.34 ± 21.24 | 122.31 ± 15.56[b] | 116.40 ± 17.30[b] | 110.21 ± 9.34[b] | -18.64† | -22.57† | -26.69† |
| CQ-IG | 153.21 ± 20.21 | 108.45 ± 18.21[b] ** | 89.48 ± 10.66[b] *** | 85.33 ± 7.80[b] *** | -29.21† | -41.59† | -44.30† |

[a]$p < 0.05$; [b]$p < 0.001$; [c]$p < 0.0001$ compared with **Placebo**
*$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$ compared with **CQ**
†$p < 0.05$; ‡$p < 0.001$ compared with **Initial**; intra-group analysis

# Guaranà e caffè

La caffeina, un antagonista del recettore per l'adenosina, è uno **stimolante** che può influenzare **il Sistema Nervoso Centrale**, l'apparato **cardiovascolare**, il rilascio delle catecolamine, l'acidità a livello gastrico e **il metabolismo** in generale.

:

# Guaranà e caffè

## Farmacocinetica

L'assorbimento orale è molto rapido, con il picco di concentrazione plasmatica dopo 29,8 minuti.

Biodisponibilità sostanzialmente completa

Emivita plasmatica varia 2,7-9,9 ore.

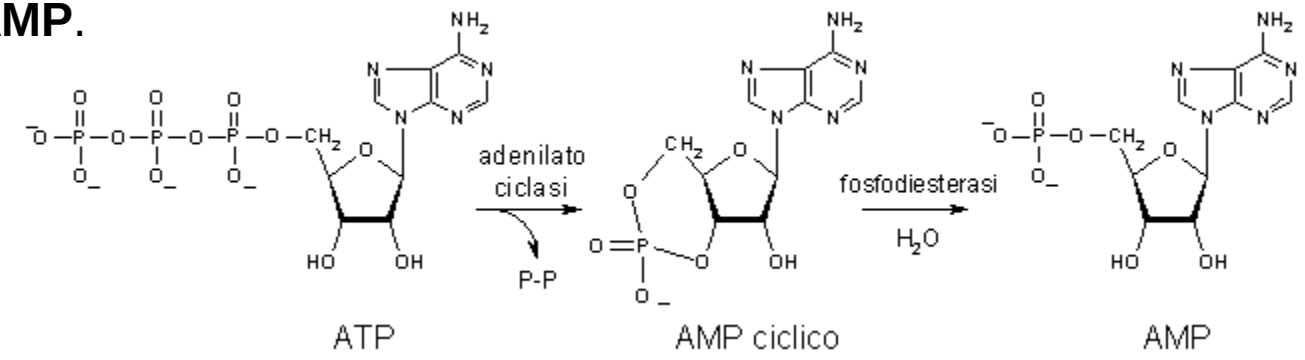
Blanchard J. Eur J Clin Pharmacol. 1983;24(1):93-8.

# Guaranà e caffè

L’effetto della caffeina è biologicamente mediato dall’**aumento di AMP ciclico** (adenosina 5’-monofosfato ciclico) con un’azione combinata su due livelli:

**1) Aumento della sintesi di cAMP:**
la caffeina blocca l’inibitore dell’enzima **adenilato-ciclasi** che trasforma ATP in cAMP

2) **Rallentamento della degradazione di cAMP:**
la caffeina inibisce l’enzima **fosfodiesterasi**, che trasforma c**AMP** in **AMP**.



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# Guaranà e caffè

## Effetti caffeina

- **Sulla muscolatura scheletrica la caffeina ha effetto contrattile**
- **Effetto inotropo e cronoptropo positivo**
- **Aumento pressione arteriosa** (ogni tazza aumenta la PAS di 0,8 e la PAD di 0,5 mmHg) (transitorio)
- **Aumento della diuresi** (transitorio)
- **Antiemicranico** in associazione all'**ergotamina** (vasocostrizione extracranica)
- **Antidolorifica** per riduzione del rilascio dei mediatori dolorifici indotto dall'adenosina ed attivazione delle vie noradrenenergiche
- **Stimola la secrezione acida a livello gastrico** per azione sui recettori $H_2$

:

# Guaranà e caffè

## Effetti caffeina

- Caffeina **mobilita le riserve di grasso** e stimola i muscoli a utilizzare il grasso come combustibile
- Ciò **ritarda l'esaurimento del glicogeno** muscolare e consente l'esercizio fisico prolungato.
- Il periodo critico di risparmio del glicogeno sembra verificarsi **durante i primi 15 minuti di esercizio**, quando la caffeina ha dimostrato di diminuire l'utilizzo di glicogeno fino al 50%.
- Così**, glicogeno** risparmiato all'inizio è disponibile **durante le fasi successive di esercizio**.

# Guaranà e caffè

## Tossicità acuta e cronica

*Una tazza di caffè americano contiene  100 - 150 mg di caffeina*
*La tazzina di caffè espresso italiano 40 - 80 mg*

- **Eventi avversi** compaiono a dosi superiori ai **200 mg**
- **Effetti letali**  per assunzioni generalmente superiori a 5 grammi in un'unica somministrazione
- Dosaggi alti (650 mg), causano la sindrome del "caffeinismo", caratterizzata da ansietà, irrequietezza e disordini nel sonno molto simile allo stato ansioso da stress.
- **L'assunzione prolungata di quantità moderate di caffeina non ha evidenziato effetti tossici**. Inoltre, pazienti con ipertensione conclamata non hanno manifestato modificazioni pressorie collegabili al consumo di caffè, né sono stati confermati maggiori rischi di infarto al miocardio.

# Guaranà e caffè

La maggior parte dei lavori sull'impiego della caffeina  nel calo ponderale sono incentrati sull'associazione **efedrina/caffeina**.

Tale terapia meriterebbe una trattazione a parte ma per sommi capi:

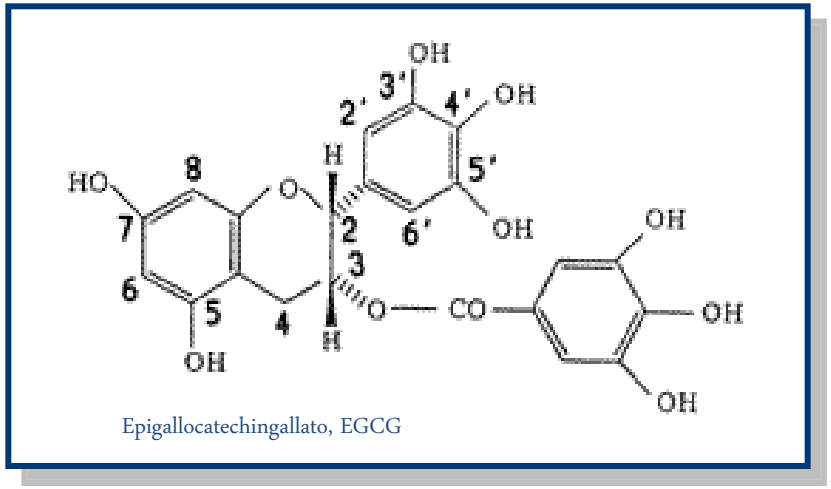
A.L' ephedra, ma non l'efedrina, è vietata negli USA  e in Italia

B.Tale associazione è quella con il maggior numero di lavori e la sua efficacia è documentata(1)

1) G Bray and F. Greenway Pharmacological treatment of the overweight patient. Pharmacol Rev 59:151-184, 2007

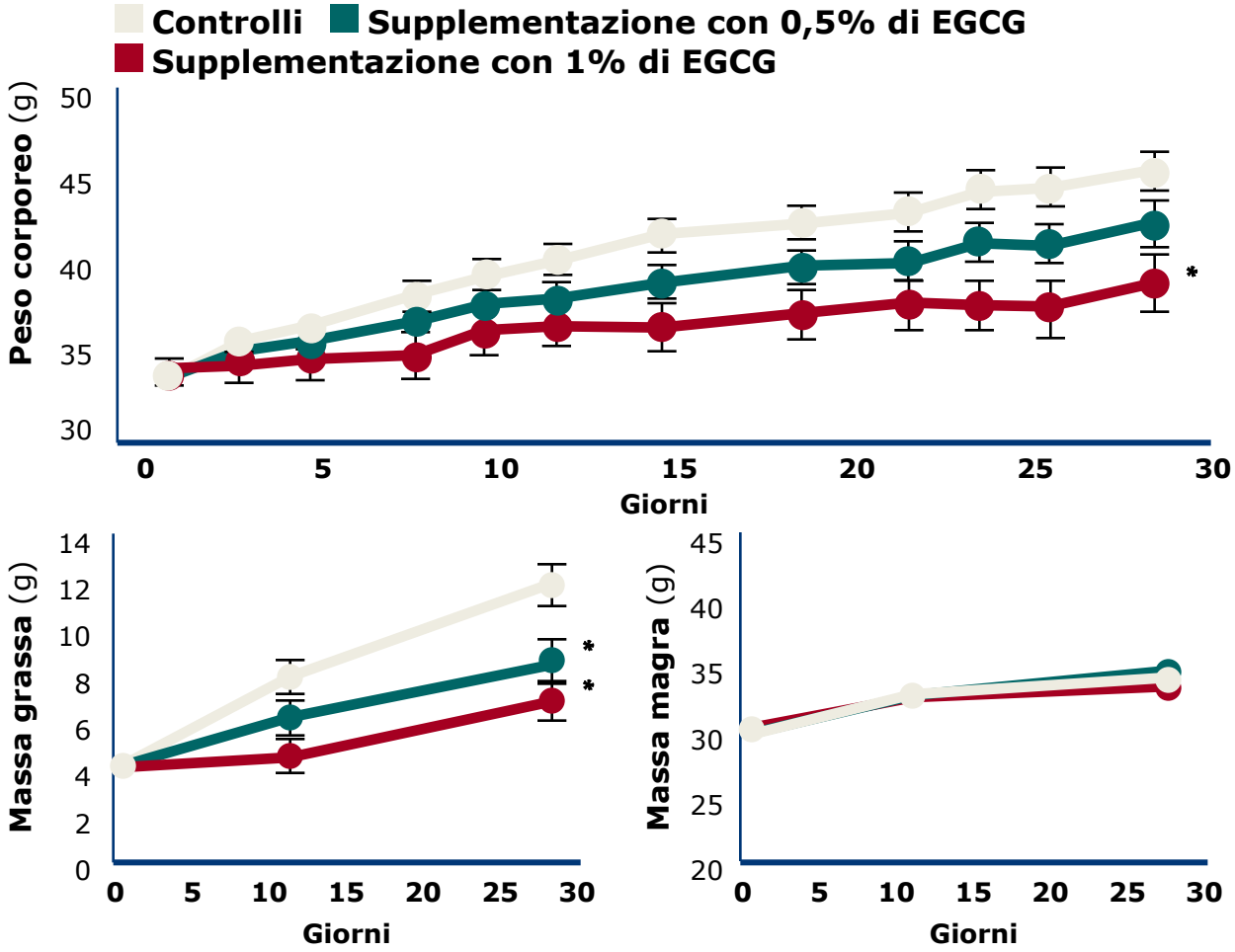
# Epigallocatechingallato, EGCG

- È una catechina del tè, particolarmente abbondante nel tè verde, ha:
  - azione ipolipemizzante
  - azione sul dispendio energetico
  - azione antiossidante



Epigallocatechingallato, EGCG

# EGCG evidenze sperimentali dispendio energetico e catabolismo lipidico

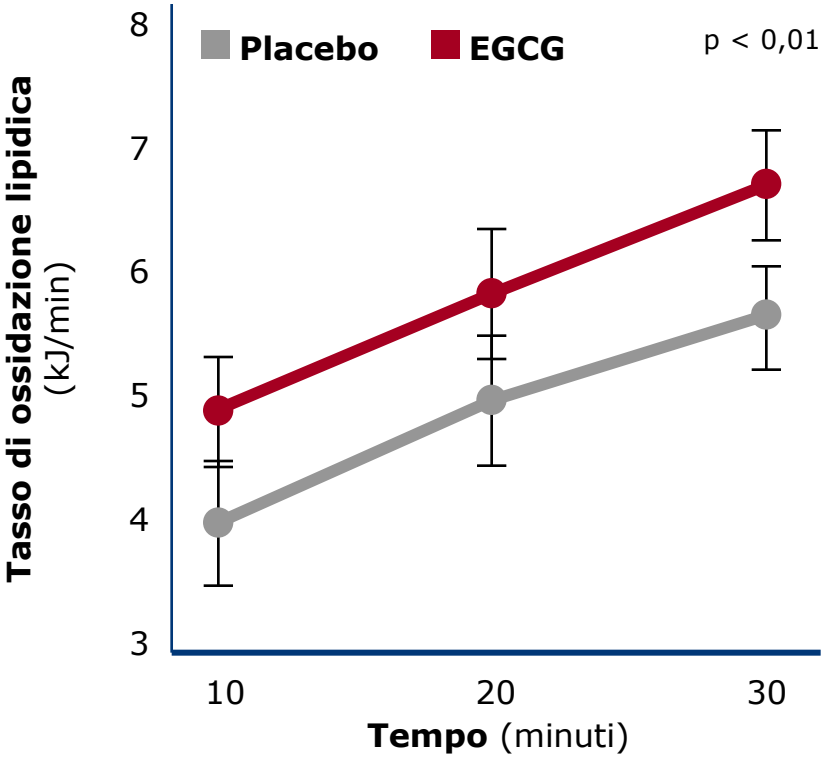


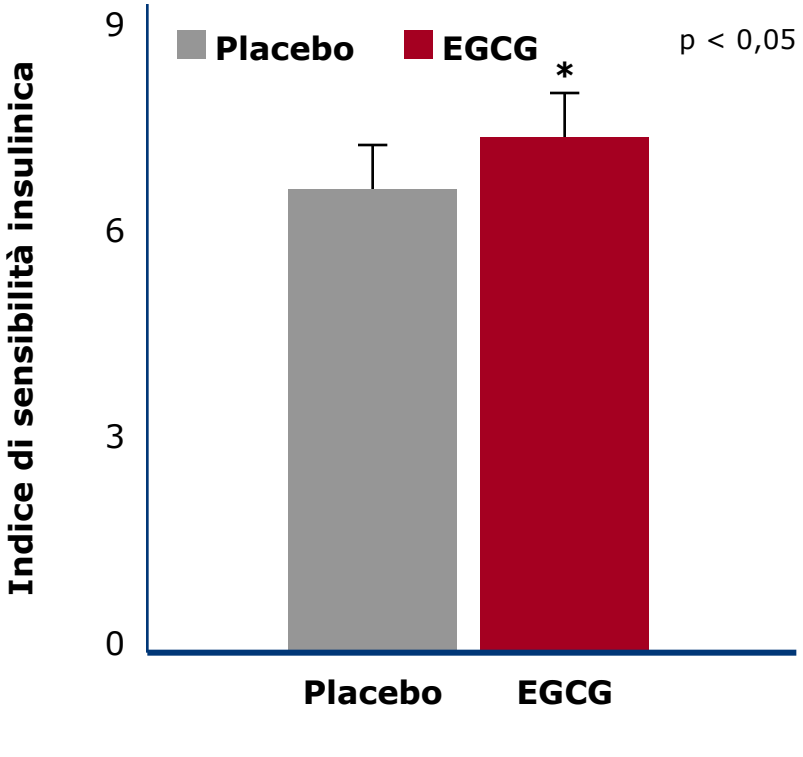

- Dosi di EGCG pari allo 0,5-1% in aggiunta a una dieta standard, in topi suscettibili all'obesità, sono necessarie e sufficienti a controllare l'incremento di peso e l'accumulo di massa grassa, senza alterazioni della massa magra.
- *L'aumento del consumo energetico è dovuto all'attivazione a livello epatico delle UCP2 e delle UCP3 con conseguente aumento del catabolismo lipidico.*

"EGCG attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation"
International Journal of Obesity

# EGCG evidenze sperimentali sull'aumento del dispendio energetico e del catabolismo lipidico

– Uno studio pubblicato nel 2008, su *The American Journal of Clinical Nutrition* ha dimostrato come, in soggetti giovani sani, l'esercizio fisico associato ad integrazione con ECGC aumenti l'ossidazione lipidica e la sensibilità periferica all'insulina




Am J.Clin.Nutr; 2008; 87:778-84

## Fucus vescicolosus

Il *Fucus vesiculosus* è molto ricco di iodio e, in passato, era utilizzato nella terapia dei gozzi da carenza iodica ed è sulla scorta di tali dati che spesso viene somministrato come "acceleratore metabolico": in realtà lo iodio non ha alcuna azione dimagrante nei soggetti normali.

Oltre a ciò il fucus è potenzialmente pericoloso per l'effetto di biomagnificazione della pianta che trattiene e concentra gli inquinanti contenuti nell'acqua. Svariati casi di grave insufficienza renale acuta dovuti a intossicazione da metalli pesanti sono stati descritti in soggetti che assumevano fucus ai fini dimagranti.

Sempre a causa degli inquinanti, vi sono numerose descrizioni di fibrosi dell'interstizio renale in pazienti che assumevano misture di fitoterapici a scopo dimagrante.

Abt AB, Oh JY, Huntington RA, et al: Chinese Herbal Medicine Induce Acute Renal Faiture. Arch Intern Med 1995; 155: 211-212.
Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbal. Lancet 1993;

# Garcinia Gambogia

Il costituente attivo e più studiato della *Garcinia* è l'acido idrossicitrico (HCA)

Possibile meccanismo d'azione di HCA

- Inibizione competitiva dell'enzima adenosin-trifosfato-citrato-liasi
- Incremento del rilascio o della disponibilità di serotonina
- Inibizione della alfa-amilasi pancreatica e dell'alfa-glucosidasi intestinale con riduzione del metabolismo dei carboidrati

# Garcinia Cambogia

## l'acido idrossicitrico da estratto di frutti di Garcinia (*Garcinia cambogia Desr.*)

**l'acido idrossicitrico:**

è in grado di ridurre la produzione di acidi grassi e lipidi che derivano dal metabolismo degli zuccheri → ne consegue una **riduzione del deposito di grassi.**

### MECCANISMO D'AZIONE

**Quando l'ingestione di zuccheri eccede le necessità dell'organismo** una parte del citrato prodotto nel ciclo di Krebs viene immesso nel citoplasma, dove viene scisso in acido ossalacetico e acetil-CoA ad opera dell'enzima ATP-citrato liasi. L'acido ossalacetico costituisce il prodotto di partenza per la sintesi dei grassi, che vengono poi immagazzinati principalmente nel tessuto adiposo sottocutaneo.

L'ac. idrossicitrico **inibisce nettamente l'azione della citrato-liasi**, **e quindi limita molto l'immagazzinamento di calorie sotto forma di grassi di deposito (ac.grassi e colesterolo**

Amin et al. Lipids in Health and Disease 2011, 10:74
http://www.lipidworld.com/content/10/1/74

LIPIDS IN HEALTH AND DISEASE

RESEARCH Open Access

# The relation of high fat diet, metabolic disturbances and brain oxidative dysfunction: modulation by hydroxy citric acid

Kamal A Amin[1*], Hamdy H Kamel[2] and Mohamed A Abd Eltawab[1]

## Abstract

**Aims:** This study aimed to examine the effect of high fat diet (HFD) to modulate brain dysfunction, and understand the linkages between obesity, metabolic disturbances and the brain oxidative stress (BOS) dysfunction and modulation with hydroxyl citric acid of *G. Cambogia*.

**Methods:** Rats were divided into 3 groups; 1st control, maintained on standard normal rat chow diet, 2nd HFD, maintained on high fat diet along 12 week and 3rd HFD+G, administered *G. Cambogia* for 4 weeks and each group include 8 rats. Blood, brain and abdominal fat were collected for biochemical measurements.

**Results:** HFD group showed significant increase in energy intake, final BW and BW gain. Also significant increase in weight of abdominal fat in HFD group. HFD induce metabolic disturbance through increasing the lipid profile (LDL, TG, TC), γGT and α-amylase activity, uric acid level and hyperglycemia, while decreasing creatine kinase (CK) activity.

These changes associated with lowering in brain nitric oxide (NO) level and rising in serum butyrylcholinesterase (BChE), brain catalase activity and MDA levels as oxidative stress markers. These alterations improved by *G. Cambogia* that decrease BOS and increased NO level.

**Conclusions:** Rats fed HFD showed, metabolic disturbances produce hyperglycemia, hypertriglyceridemia, hypercholesterolemia and increased LDL associated with increased BOS. Involvement of BuChE, NO and oxidative stress associated with metabolic disturbances in the pathophysiological progression in brain, suggesting association between obesity, metabolic disorders and brain alteration while, using *G. Cambogia*, ameliorate the damaging effects of the HFD via lowering feed intake and BOS.

Amin *et al. Lipids in Health and Disease* 2011, **10**:74
http://www.lipidworld.com/content/10/1/74

LIPIDS IN HEALTH AND DISEASE

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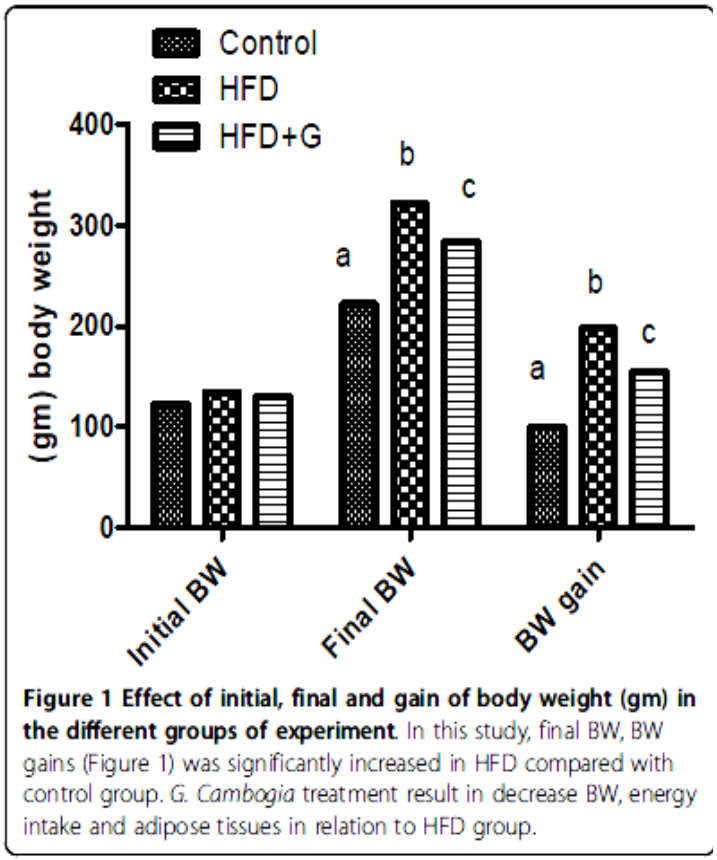



**Figure 1 Effect of initial, final and gain of body weight (gm) in the different groups of experiment**. In this study, final BW, BW gains (Figure 1) was significantly increased in HFD compared with control group. *G. Cambogia* treatment result in decrease BW, energy intake and adipose tissues in relation to HFD group.

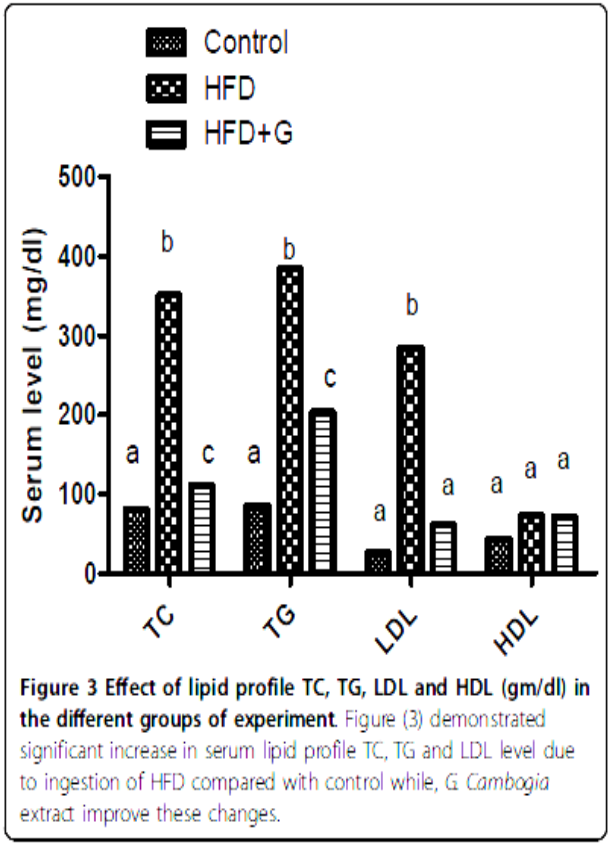



**Figure 3 Effect of lipid profile TC, TG, LDL and HDL (gm/dl) in the different groups of experiment**. Figure (3) demonstrated significant increase in serum lipid profile TC, TG and LDL level due to ingestion of HFD compared with control while, *G. Cambogia* extract improve these changes.

**Table 2 Means of brain catalase, MDA and Nitric oxide levels in different groups of rats (3 months)**

| *Groups Parameters* | Control | HFD | HFD+G |
|---|---|---|---|
| Brain Catalase (U/gm) | $5.1 \pm 0.69^{a}$ | $12.2 \pm 0.63^{b}$ | $10.3 \pm 0.32^{b}$ |
| Brain MDA (nmol/g) | $2.6 \pm 0.24a$ | $5.7 \pm 0.31^{b}$ | $4.9 \pm 0.61^{c}$ |
| Brain Nitric oxide | $1.3 \pm 0.08^{a}$ | $0.8 \pm 0.11^{b}$ | $1.1 \pm 0.12^{ab}$ |

In brain tissues, MDA level and catalase activities were significantly increased in HFD compared with control group and treatment with *G. Cambogia* ameliorated these changes (Table 2).

*Values are statically analyzed by one way ANOVA and reported as means ± SEM. Means have different letters indicate significant variation at ($P \leq 0.05$), while the same letters indicate non significant variation*

# Garcinia Gambogia

*Review Article*

**The Use of *Garcinia* Extract (Hydroxycitric Acid) as a Weight loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials**

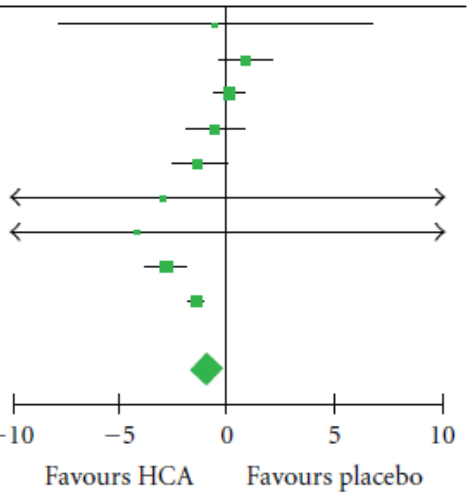
**Igho Onakpoya, Shao Kang Hung, Rachel Perry, Barbara Wider, and Edzard Ernst**

Hindawi Publishing Corporation
Journal of Obesity
Volume 2011, Article ID 509038, 9 pages
doi:10.1155/2011/509038

| | HCA | | | Placebo | | | | Mean difference | Mean difference |
|---|---|---|---|---|---|---|---|---|---|
| Study or subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, random, 95% CI | IV, random, 95% CI |
| Hayamizu 2001 | 0 | 11.5 | 20 | 0.5 | 11.7 | 20 | 1.4% | −0.5 [−7.69, 6.69] | |
| Heymsfield 1998 | −3.2 | 3.3 | 66 | −4.1 | 3.9 | 69 | 14.7% | 0.9 [−0.32, 2.12] | |
| Kovacs 2001a | −0.4 | 0.9 | 21 | −0.5 | 1.4 | 21 | 18% | 0.1 [−0.61, 0.81] | |
| Kovacs 2001b | −1.5 | 1.66 | 11 | −1 | 1.34 | 11 | 14.4% | −0.5 [−1.76, 0.76] | |
| Mattes 2000 | −3.7 | 3.1 | 42 | −2.4 | 2.9 | 47 | 14.4% | −1.3 [−2.55, −0.05] | |
| Preuss 2004a | −4.5 | 16.6 | 19 | −1.6 | 34.1 | 16 | 0.2% | −2.9 [−21.2, 15.4] | |
| Preuss 2004b | −5.5 | 23.7 | 9 | −1.4 | 17.3 | 10 | 0.2% | −4.1 [−22.93, 14.73] | |
| Ramos 1995 | −4.1 | 1.8 | 18 | −1.3 | 0.9 | 17 | 16.6% | −2.8 [−3.74, −1.86] | |
| Roongpisuthipong 2007 | −2.8 | 0.5 | 23 | −1.4 | 0.5 | 19 | 20% | −1.4 [−1.7, −1.1] | |
| Total (95% CI) | | | 229 | | | 230 | 100% | −0.88 [−1.75, −0] | |

Heterogeneity: $\tau^2 = 0.98$; $\chi^2 = 38.5$, df = 8 ($P < .00001$); $I^2 = 79\%$

Test for overall effect: $Z = 1.96$ ($P = .05$)



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**The Use of *Garcinia* Extract (Hydroxycitric Acid) as a Weight loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials**

**Igho Onakpoya, Shao Kang Hung, Rachel Perry, Barbara Wider, and Edzard Ernst**

## 5. Conclusion

The evidence from RCTs suggests that *Garcinia* extracts/HCA generate weight loss on the short term. However, the magnitude of this effect is small, is no longer statistically significant when only rigorous RCTs are considered, and its clinical relevance seems questionable. Future trials should be more rigorous, longer in duration, and better reported.

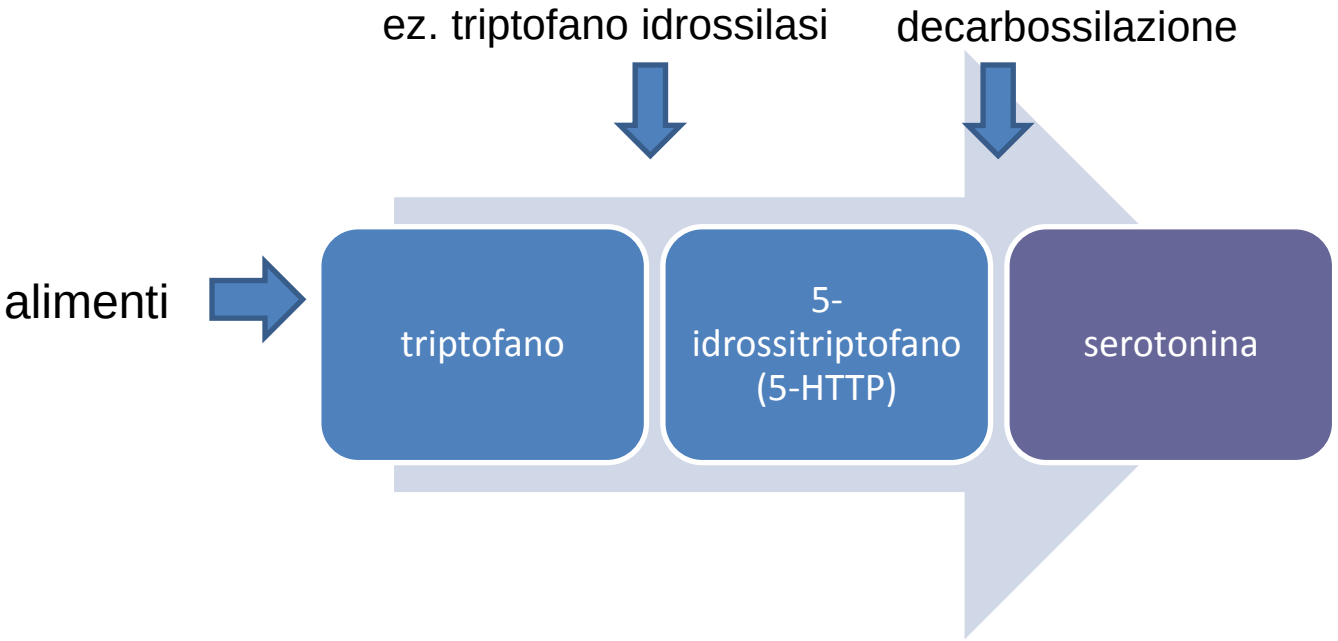
# Griffonia Simplicifolia

**L'interesse verso questa pianta in Europa è relativamente recente, ed è dovuto alla scoperta che i suoi semi contengono la sostanza definita con la sigla 5-HTP (5-idrossitriptofano), un precursore endogeno della serotonina.**

| *NOME BOTANICO* | *PARTE UTILIZZATA* | *RIFERIMENTO PER GLI EFFETTI* | *NOTE* |
|---|---|---|---|
| GRIFFONIA SIMPLICIFOLIA (DC.) BAILL. | semen | **semen:** Normale tono dell'umore. Rilassamento e benessere mentale. Rilassamento e sonno. Controllo del senso di fame. | |

# 5-**idrossitriptofano** da estratto di semi di **Griffonia** (*Griffonia simplicifolia Baill.*)

Il triptofano è una aminoacido essenziale quindi deve essere assunto con gli alimenti. Ne sono particolarmente ricchi i legumi, i latticini, le uova, il pesce e la carne. È un precursore della serotonina è un neurotrasmettitore che gioca un ruolo cruciale negli stati affettivi.



# Griffonia Simplicifolia

Phytomedicine. 2011 Aug 15;18(11):947-52.

**Influence of Griffonia simplicifolia on male sexual behavior in rats: behavioral and neurochemical study.**

Carnevale G, Di Viesti V, Zavatti M, Benelli A, Zanoli P.

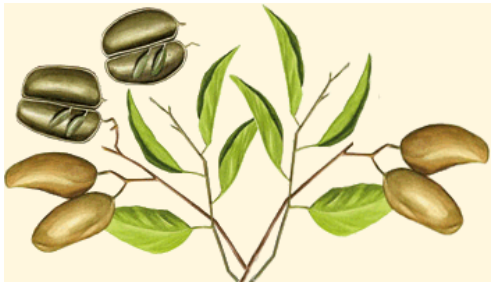
**Source**

Department of Biomedical Sciences, University of Modena and Reggio Emilia, Via Campi 287, I-41100 Modena, Italy.

**Abstract**

The seeds of Griffonia simplicifolia Baill. are rich in 5-HTP (5-hydroxytryptophan), a direct precursor of the neurotransmitter serotonin. In the present study we investigated the influence of the plant extract on male sexual behavior. The seed extract was orally administered to Sprague-Dawley male rats at three dose levels (25, 50 and 100 mg/kg) both acutely and subchronically (daily for 9 days). Mating test with receptive female rats was performed 60 min after the acute treatment or the last dose when repetitively administered. Mount, intromission and ejaculation latencies and post-ejaculatory interval were recorded. Food intake and body weight were measured over the 9-day period of treatment. Microdialysis technique was used to detect the extracellular levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in rat brain following the acute administration of the extract dosed at 100mg/kg. The acute treatment significantly increased mount latency (at any dosage), intromission and ejaculation latencies (at 100 mg/kg) and post-ejaculatory interval (at 50 and 100 mg/kg). On the contrary the subchronic treatment failed to exert a significant influence on copulatory behavior. The daily administration of the extract dosed at 50 and 100 mg/kg for 9 days significantly reduced food intake and body weight. Finally in the microdialysis experiments we found a dramatic increase in 5-HT and its metabolite 5-HIAA.

# Griffonia Simplicifolia



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The Journal of Nutrition. First published ahead of print June 15, 2011 as doi: 10.3945/jn.111.139840.

The Journal of Nutrition
Nutrient Requirements and Optimal Nutrition

# Whey Protein but Not Soy Protein Supplementation Alters Body Weight and Composition in Free-Living Overweight and Obese Adults[1,2]

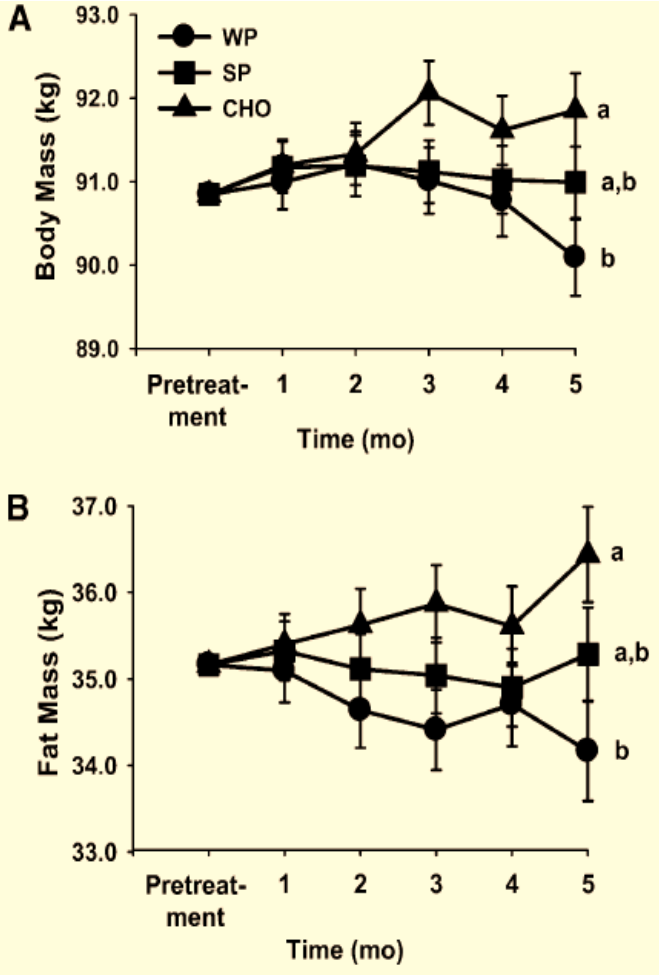
David J. Baer,* Kim S. Stote, David R. Paul, G. Keith Harris, William V. Rumpler, and Beverly A. Clevidence

Beltsville Human Nutrition Research Center, Agricultural Research Service, USDA, Beltsville, MD 20705

**TABLE 1** Chemical composition of the carbohydrate (CHO), whey protein (WP), and soy protein (SP) treatment supplements[1,2]

| | CHO | WP | SP |
|---|---|---|---|
| | | *g/packet* | |
| Weight | 52 | 51 | 52 |
| Protein | 0.6 | 27.5 | 28.1 |
| Moisture | 1.7 | 2.2 | 1.8 |
| Fat, acid hydrolysis | 0.7 | 1.5 | 2.0 |
| Ash | 1.0 | 1.4 | 2.7 |
| Total carbohydrate | 48.0 | 18.4 | 17.4 |
| Calcium | 0.20 | 0.22 | 0.25 |
| para-Aminobenzoic acid | 0.2 | 0.2 | 0.2 |
| | | *mg/packet* | |
| L-Aspartic acid | 36.4 | 3060 | 3200 |
| L-Threonine | 18.2 | 1850 | 945 |
| L-Serine | 23.4 | 1570 | 1480 |
| L-Glutamic acid | 62.4 | 4860 | 5340 |
| L-Proline | 26.0 | 1690 | 1000 |
| L-Glycine | 18.2 | 541 | 1150 |
| L-Alanine | 15.6 | 1370 | 1150 |
| L-Cystine | 10.4 | 694 | 319 |
| L-Valine | 20.8 | 1590 | 1310 |
| L-Methionine | 10.4 | 592 | 354 |
| L-Isoleucine | 13.0 | 1730 | 1310 |
| L-Leucine | 26.0 | 3060 | 2190 |
| L-Tyrosine | 26.0 | 820 | 997 |
| L-Phenylalanine | 18.2 | 918 | 1440 |
| L-Histidine | 10.4 | 530 | 716 |
| L-Lysine | 15.6 | 2470 | 1690 |
| L-Arginine | 26.0 | 726 | 2070 |
| L-Tryptophan | 10.4 | 607 | 400 |

[1] Participants consumed 2 treatment packets/d, 1 with breakfast and the evening meal, along with their typical diet.
[2] Chemical composition was determined by Covance Laboratories.

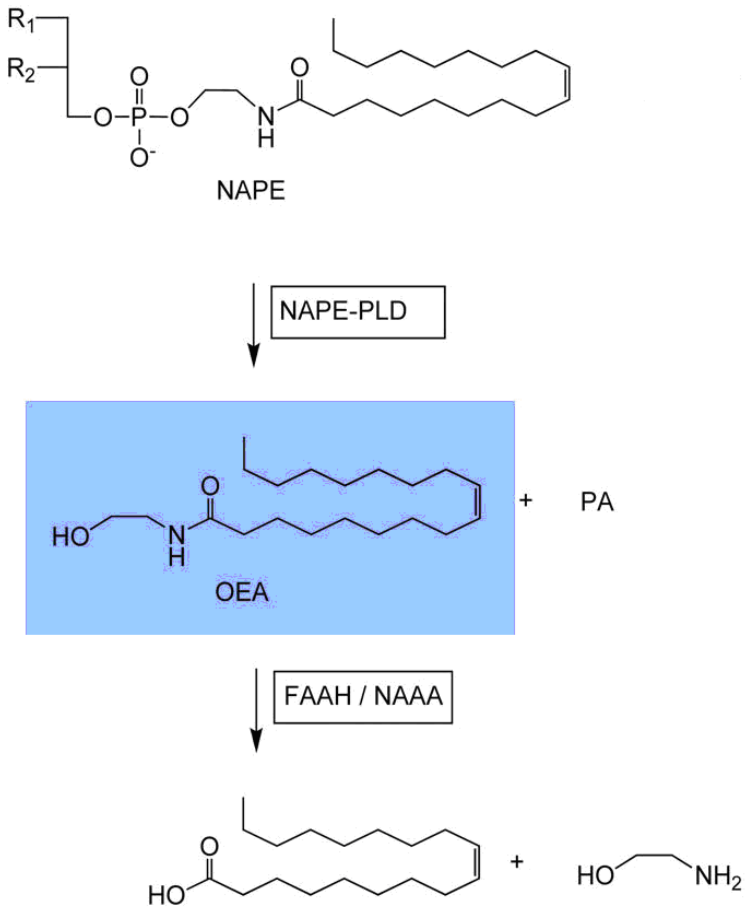


# Conclusioni

- Questo studio evidenzia che questo integratore può essere di aiuto nell'indurre calo ponderale anche in quei pazienti con sovrappeso o obesità di primo grado non responsivi alla sola dieta e alle modifiche dello stile di vita. Alle dosi consigliate nello studio non si sono osservati effetti avversi particolari.

# N-Oleil-Fosfatidil-Etanolamina (NOPE)

- è un fosfolipide presente nelle membrane cellulari
- ha origine sia endogena che esogena
- è presente in diversi alimenti



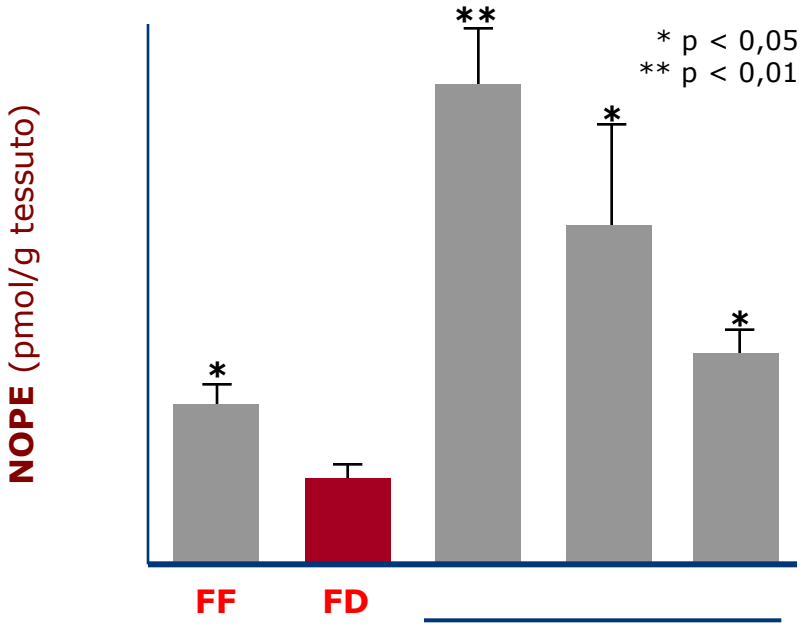

**NAPE: N-acilfosfatidil etanolamina**
**PLD: fosfolipasi D**
**FAAH: *Fatty Acid Amide Hydrolase***
**NAAA: *N-Acylethanolamine-Hydrolyzing Acid Amidase***

# NOPE e NOE

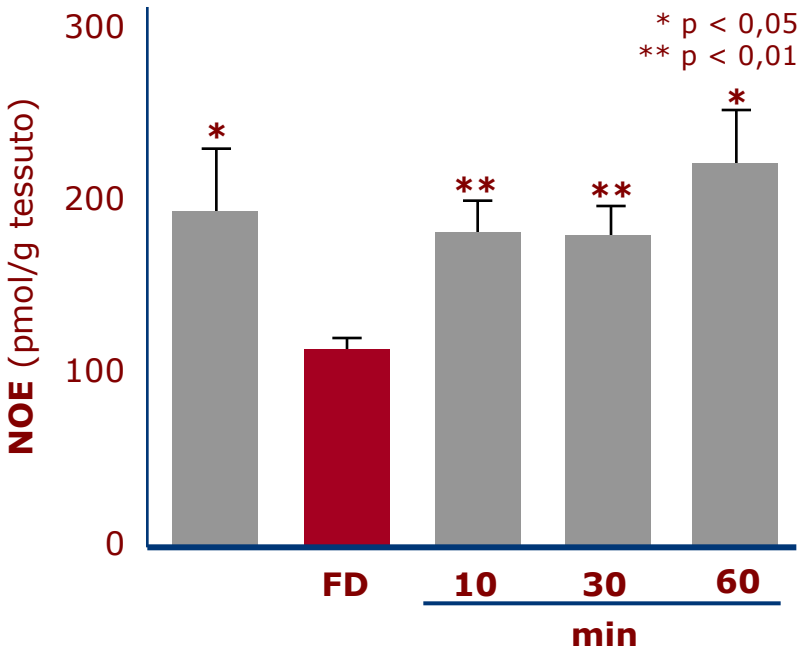
Evidenze sull'animale

Dopo i pasti si ha un aumento della Noe intestinale

**Livelli di NOPE nel tessuto intestinale 10, 30 e 60 minuti dopo il pasto**




**Livelli di NOE nel tessuto intestinale 10, 30 e 60 minuti dopo il pasto**

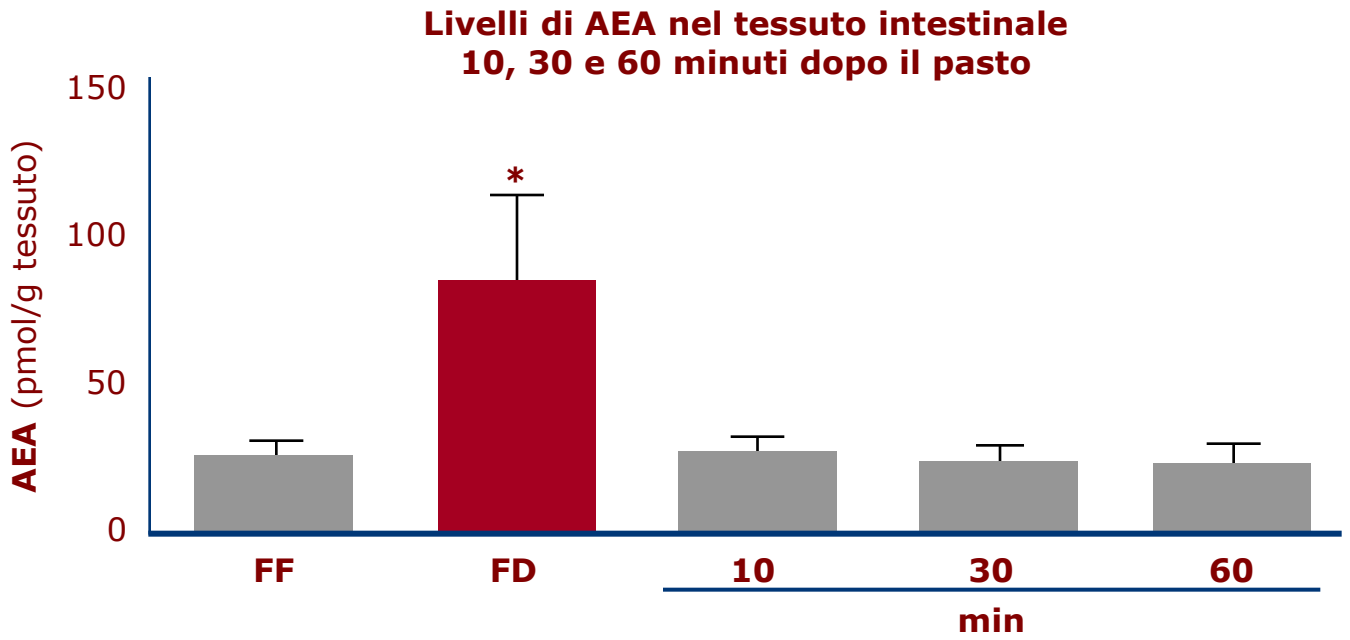



FF: *free-feeding* (alimentazione libera); FD: *food-deprivation and refeeding* (digiuno e rialimentazione) nello stesso gruppo di animali

# NOPE e NOE

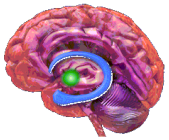
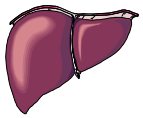
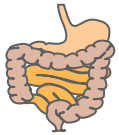
Evidenze sull'animale

Un composto analogo, l'endocannabinoide anandamide (AEA), ad azione oressizzante, regola i suoi livelli nella mucosa intestinale in modo speculare alla NOE




FF: *free-feeding* (alimentazione libera); FD: *food-deprivation and refeeding* (digiuno e rialimentazione) nello stesso gruppo di animali

# Sites of $CB_1$ receptor and effects of $CB_1$ blockade

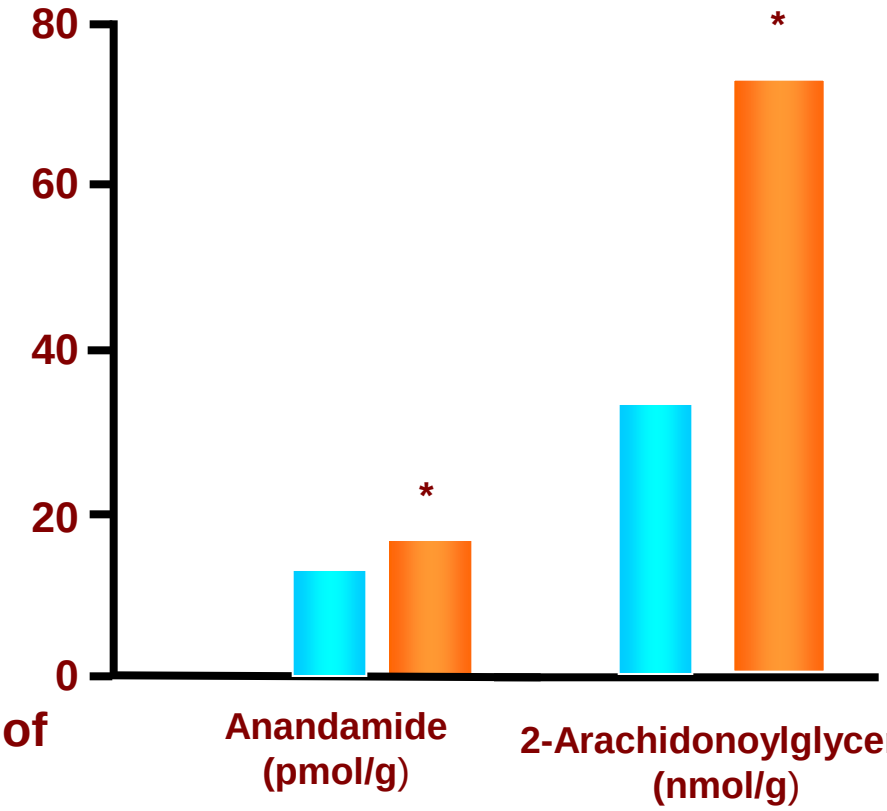
| | Site of Action | Mechanism(s) | Addresses |
|---|---|---|---|
|  | Hypothalamus / Nucleus accumbens | ↓ Food intake | Body weight<br>Intra abdominal adiposity |
|  | Adipose tissue | ↕ Adiponectin<br>↕ Lipogenesis | Dyslipidemia<br>Insulin resistance |
|  | Muscle | ↑ Glucose uptake | Insulin resistance |
|  | Liver | ↓ Lipogenesis | Dyslipidemia<br>Insulin resistance |
|  | GI tract | ↑ Satiety signals | Body weight<br>Intra abdominal adiposity |

**DiMarzo 2001; Ravinet Trillou et al 2003; Cota et al 2003; Pagotto et al 2005; Van Gaal et al 2005; Liu et al 2005; Osei-Hyiaman et al 2005**

# In Obese Hyperphagic Mice, the EC System is Overactivated, as Evidenced by Elevated Hypothalamic Endocannabinoid Levels

**db/db mice**

**(with defective leptin receptor)**




**Hypothalamic levels of**

**Lean (wild-type)**

**Obese (db/db)**

*p<0.05

*Di Marzo et al 2001*

# NOE: attivazione dei recettori GPR119

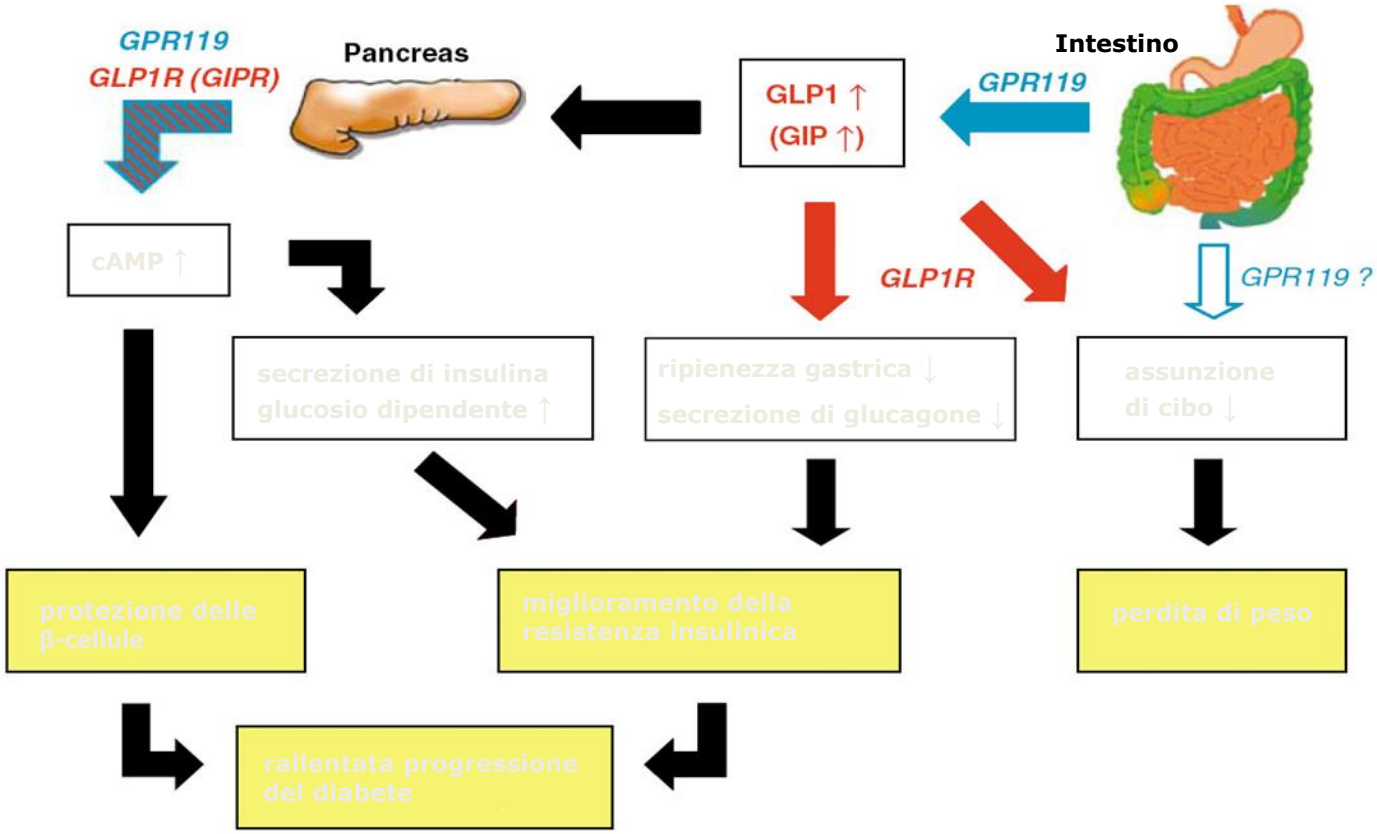
- Un studio del 2007 pubblicato sul *British Journal of Pharmacology*, ha dimostrato che la NOE è in grado di stimolare i recettori GPR119 (*G-Protein-coupled Receptor*).

- I recettori GPR119 sono in grado di trasmettere segnali all'interno delle cellule attivandole. Sono espressi prevalentemente a livello del fegato, pancreas (cellule β) e lungo il tratto gastrointestinale, in particolare nel duodeno e nel digiuno (cellule endocrine, secernenti peptidi glucoregolatori quali ad esempio GLP1 ).

- La NOE agisce stimolando i recettori GPR119 che aumentano la produzione di GLP1 con conseguente modulazione della secrezione di insulina, protezione delle β cellule, minore produzione di glucagone e aumento di sazietà → miglioramento della tolleranza glucidica

# NOE: attivazione dei recettori GPR119

Possibile meccanismo d'azione dei recettori GPR119




British Journal of Pharmacology, 2007, November, 1-6

ORIGINAL ARTICLE

# GPR119 Is Essential for Oleoylethanolamide-Induced Glucagon-Like Peptide-1 Secretion From the Intestinal Enteroendocrine L-Cell

Lina M. Lauffer,[1] Roman Iakoubov,[1] and Patricia L. Brubaker[1,2]

**OBJECTIVE**—Intestinal L-cells secrete the incretin glucagon-like peptide-1 (GLP-1) in response to ingestion of nutrients, especially long-chain fatty acids. The Gαs-coupled receptor GPR119 binds the long-chain fatty acid derivate oleoylethanolamide (OEA), and GPR119 agonists enhance GLP-1 secretion. We therefore hypothesized that OEA stimulates GLP-1 release through a GPR119-dependent mechanism.

**CONCLUSIONS**—The results of these studies demonstrate, for the first time, that OEA increases GLP-1 secretion from intestinal L-cells through activation of the novel GPR119 fatty acid derivate receptor in vitro and in vivo. *Diabetes* 58:1058–1066, 2009

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GPR119 AND GLP-1 SECRETION

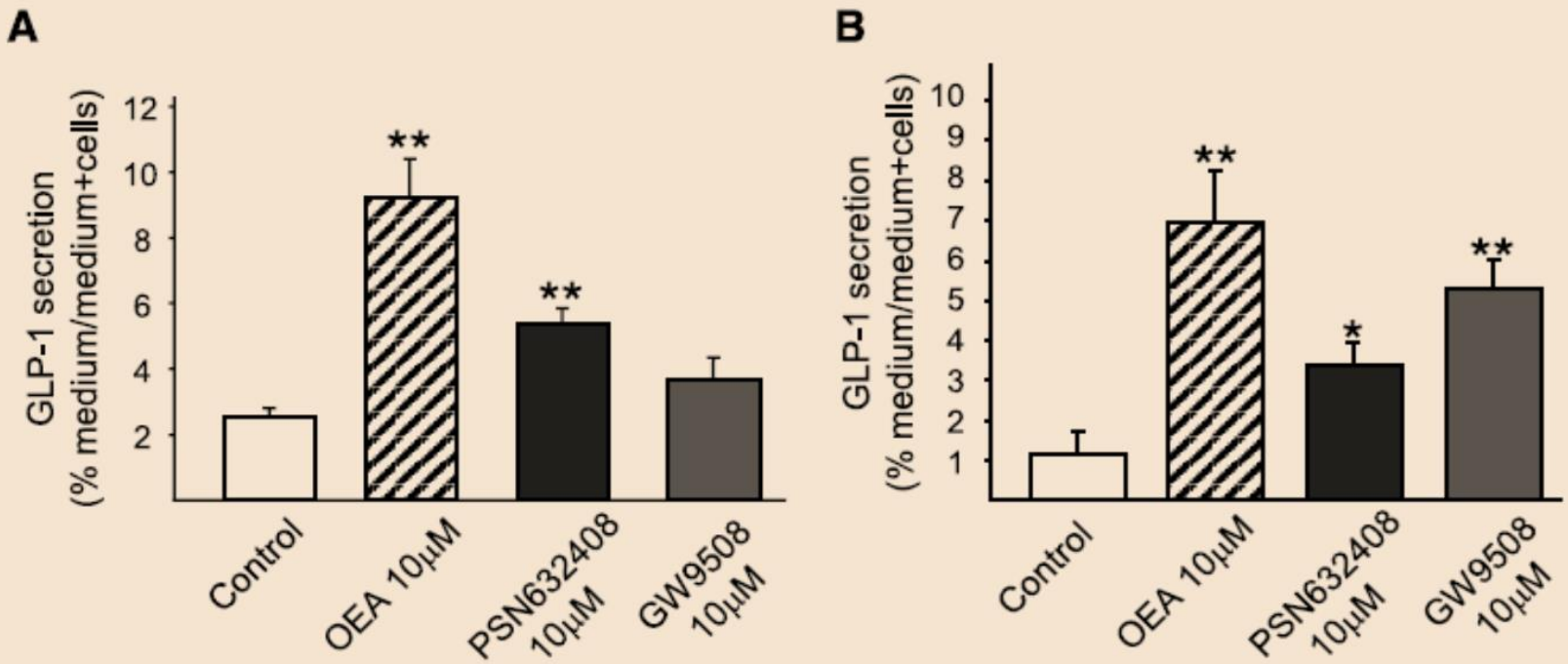


FIG. 3. Effects of GPR119 and GPR40/120 agonists on GLP-1 secretion. mGLUTag ($n = 4$) (*A*) and hNCI-H716 ($n = 4$) (*B*) cells were incubated with medium alone (1% DMSO, negative control), OEA (10 μmol/l), the GPR119 agonist PSN632408 (10 μmol/l), or the combined GPR40/GPR120 agonist GW9508 (10 μmol/l) for 2 h. GLP-1 content of media and cells was determined by RIA. $^*P < 0.05$; $^{**}P < 0.01$ vs. control.

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Hindawi

*Research Article*

# Oleoylethanolamide: A Novel Potential Pharmacological Alternative to Cannabinoid Antagonists for the Control of Appetite

Adele Romano,[1] Roberto Coccurello,[2] Giacomo Giacovazzo,[2] Gaurav Bedse,[1] Anna Moles,[2,3] and Silvana Gaetani[1]

The initial pharmaceutical interest for the endocannabinoid system as a target for antiobesity therapies has been restricted by the severe adverse effects of the CB1 antagonist rimonabant. This study points at oleoylethanolamide (OEA), a monounsaturated analogue, and functional antagonist of anandamide, as a potential and safer antiobesity alternative to CB1 antagonism. Mice treated with equal doses (5 or 10 mg/kg, i.p.) of OEA or rimonabant were analyzed for the progressive expression of spontaneous behaviors (eating, grooming, rearing, locomotion, and resting) occurring during the development of satiety, according to the paradigm called behavioral satiety sequence (BSS). Both drugs reduced food (wet mash) intake to a similar extent. OEA treatment decreased eating activity within the first 30 min and caused a temporary increase of resting time that was not accompanied by any decline of horizontal, vertical and total motor activity. Besides decreasing eating activity, rimonabant caused a marked increase of the time spent grooming and decreased horizontal motor activity, alterations that might be indicative of aversive nonmotivational effects on feeding. These results support the idea that OEA suppresses appetite by stimulating satiety and that its profile of action might be predictive of safer effects in humans as a novel antiobesity treatment.

# Oleoylethanolamide: A Novel Potential Pharmacological Alternative to Cannabinoid Antagonists for the Control of Appetite



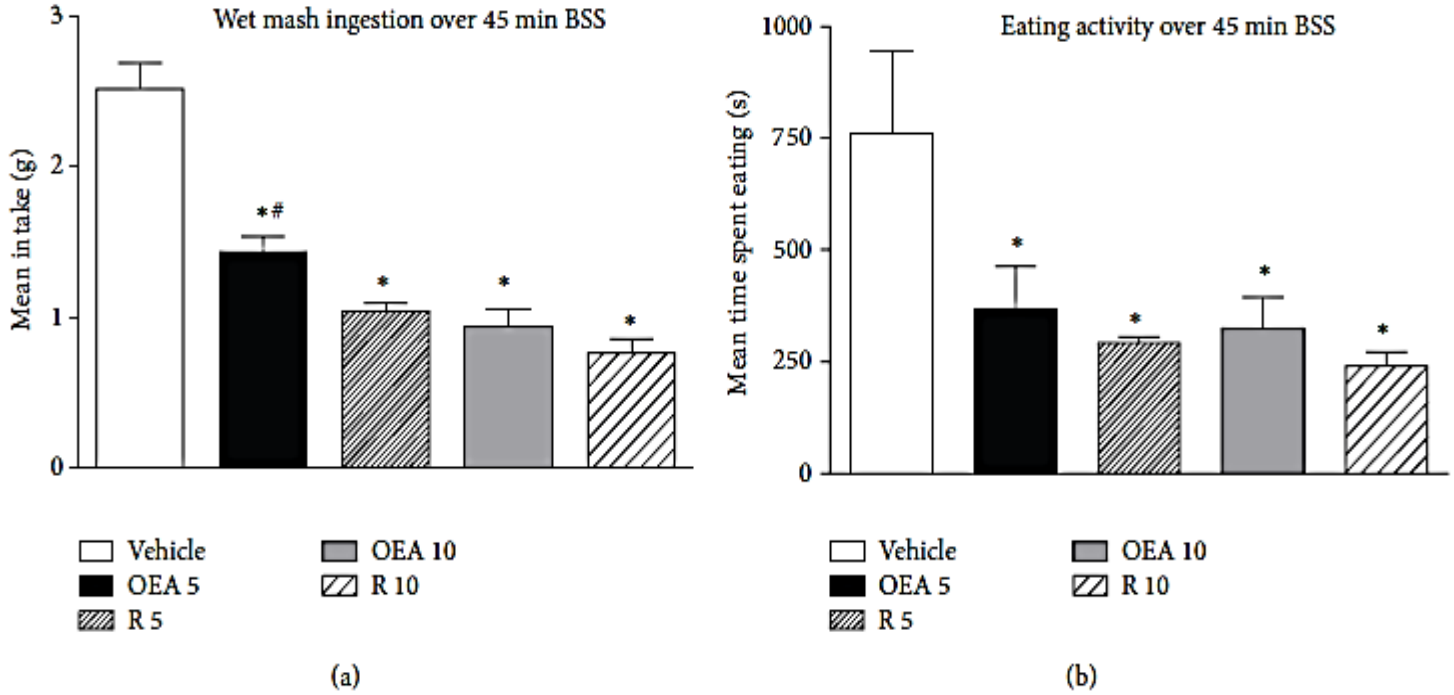


FIGURE 1: (a) and (b) show, respectively, mean cumulative wet mash intake (±S.E.M) and mean time spent in eating activity (±S.E.M) by mice treated with vehicle, OEA 5 mg/kg i.p. (OEA 5), rimonabant 5 mg/kg i.p. (R 5), OEA 10 mg/kg i.p. (OEA 10), and rimonabant 10 mg/kg, i.p. (R 10) over the 45 min BSS, ($n = 6$ vehicle group and $n = 8$ both doses of rimonabant and OEA-treated mice). $^{*}P < 0.05$ versus vehicle; $^{\#}P < 0.05$ versus OEA 5 (Tukey HSD test).

# Grazie