Management of Obesity and Diabetes by targeting thermogenesis and fat oxidation:

From Pharmaceuticals to Nutraceuticals

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What are Nutraceuticals?

Nutraceuticals are pharmaceutical forms (pills, powders, capsules, vials, etc.) containing food ingredients as active principles, (bioactive food ingredients)

Phytochemicals: several groups of polyphenols (anthocyanins, proanthocyanidins, flavanones, isoflavones, resveratrol and ellagic acid) are currently used in the nutraceutical industry.
What are bioactive food ingredients?

Bioactive constituents of:

Plants
fruits/seeds
Vegetables
Herbs
Spices
Animal products
Bacterial, algae & fungal products
(oils rich in AA or DHA)

Phytochemicals
Methyloxanthines (caffeine, theobromine)
Antioxidant polyphenols from
black tea, green tea, Cocoa
Grape seeds, Citrus species
Flaxseed lignans, Olive oil
Soy bean phytoestrogens
Capsaicinoids from red pepper & chillies

Animal products
Milk bioactive peptides, whey protein
Dairy calcium, alpha-lipoic acid
Specific aminoacids: leucine, arginine

Specific fatty acids:
MCT, n6 PUFA, AA, Conjugated Linoleic
Acid, marine n3 PUFAs (EPA,DHA)

Nutraceuticals & Functional food ingredients
Functional foods in the management of obesity and type 2 diabetes

Foods (& food ingredients) can be regarded as *functional*
if proven to affect beneficially one or more target functions in the body,
*be**yond adequate nutritional effects*, in a way relevant to improved state of health and well-being, reduction of risk of diseases, or both.

Are functional foods redefining nutritional requirements?

Jones PJ, Varady KA.
1. **What** are bioactive food ingredients?

2. **Why** interest in this search?: 
   
   *physiological rationales for obesity management*

3. **How** are we searching?
   
   *past, present & future*
Physiological rationale for stimulating thermogenesis

- Low BMR is a risk factor for later obesity
  \cite{Griffiths1990, Ravussin1993}

- Low capacity to increase thermogenesis in response to energy surplus enhances susceptibility to obesity
  \cite{Levin1999, Stock1999}

- Formerly obese (post-obese) patients have a 5-fold higher risk of having a low BMR than the never obese
  \cite{Astrup1996}
Reduced postprandial thermogenesis in response to a mixed meal (300 kcal) in young women.

Energy Expenditure (kcal/day)

- 20 Kg weight

Thermogenesis
BMR

Obligatory Mass
Behavioral Activity
Regulatory Thermogenesis

500-800 kcal/day

From Dulloo Nutrition (1993)
Counter-acting factors

Spontaneous weight setting

Constraint

enforced -ve energy balance

Relaxing or Escape

Evolution of body weight in the ‘treated’ obese

Guy-Grand, 1988

New weight setting

Maintenance

Rebound

Restoration

Counter-acting factors

(metabolic and psychological)
The past: Pre-1980 Classification of thermogenic compounds

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Synthetics</th>
<th>Foods</th>
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<tbody>
<tr>
<td>Thyroid extracts</td>
<td>Uncouplers (DNP)</td>
<td>Amino acids</td>
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<tr>
<td>Oestrogens</td>
<td>Anti-inflammatory</td>
<td>Liebig extract</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Vasodilators</td>
<td>Citrus extract</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Ouabain</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>Isocitrate</td>
<td>Caffeine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Alcohol)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Nicotine)</td>
</tr>
</tbody>
</table>

* Thermogenic drugs of everyday life

Derek Miller (QEC, London University)
1980’s: Neurohormonal control of thermogenesis

Central controller

Brain

SNS /Thyroid

Peripheral tissues/organs

Efferent

Adr NA T3

β-ARs

Peripheral tissues/organs

Effectors

Organ/molecular

Energy Intake

Fat stores

Regulated variable

1980’s: Neurohormonal control of thermogenesis

Central controller

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Energy Intake

Fat stores

Regulated variable
1980’s

Rationale underlying systematic search for anti-obesity sympathomimetics

Sympathetic Nervous System (SNS)

Noradrenaline (NA)

Thermogenesis

Etiology
Susceptibility to obesity

Treatment
Counteract efficacy of hypocaloric regimens
Synergistic interactions between methylxanthines (Mx) and stimuli of the SNS on thermogenesis in humans

Increase above Basal metabolic rate (BMR)

The Do-Do pill
- Ephedrine: 22 mg
- Caffeine: 50mg
- Theophylline: 30mg


Cold exposure

Exercise

Concept of Accelerators and Brakes

Adenosine Prostaglandin
(-) (+) (+)
cAMP

Phosphodiesterase
(-) Adenylate cyclase

Thermogenesis Fat oxidation

Ephedrine

Xanthines
Caffeine Theophylline Theobromine

(+)

COMT

β₁ β₂

Adenosine

Prostaglandin

NA

Greater efficacy of E+C than E or C in inducing weight loss on a hypocaloric regimen

Weight loss (kg) vs. Duration of treatment (weeks)

Astrup et al. IJO (1992)
Side-effects: mild and transient

Number of adverse events

Dizziness
Tremor
Headache
Anxiety
Insomnia

From F. Greenway
*Obesity reviews* (2001)
Ephedrine + Caffeine
as thermogenic anti-obesity drug cocktail?

• Issues of patentability for putting these ‘old’ drugs to a new purpose,

• Risks for hypertension, tachycardia and tremor associated with drugs that could be acting on classical (α1, β1 and β2) adrenoceptors among a broad spectrum of the population, many of whom may have unrecognized risk factors

• Belief that more selective, safer and more efficacious novel sympathomimetics in development by pharmaceutical companies would soon become available.
The pharmaceutical approach (1984-2000)

\( \beta_3 \)-agonists: where are we?

- Very effective thermogenic anti-obesity and anti-diabetic agents in rodents

- In humans, failure to produce a compound with good efficacy, selectivity and pharmacokinetic properties suitable for the stimulation of the small numbers of \( \beta_3 \)-adrenoceptor

A vacuum filled by potential thermogenic dietary food ingredients
Potential ‘thermogenic’ dietary/herbal ingredients

MA HUANG
(Ephedra sinica)
ephrine + isomers

Coffee & Guarana
Caffeine

Coleus forskohlii
forskoline:

Bark of Willow
Aspirin

Coconut oil: MCT

Green tea
Adenosine Prostaglandin COMT

(-) (+) (+) (-)

Adenosine

Prostaglandin

Adenylate cyclase

cAMP

Phosphodiesterase

Fat oxidation

Thermogenesis

MCT

Ephedrine

(-) (+) (-) (-)

Polyphenols Catechins

Xanthines Caffeine

PG-Inhibitors

Aspirin (Salicylate)

Capsaicinoids Piperine; Gingerols Allyl isothiocyanate

Increased energy expenditure (EE) in humans consuming high-fat diets richer in MCT (substituting LCT)

+ 5% daily EE associated with increased 24h urinary noradrenaline excretion

sympathetic activation of thermogenesis

Thé vert et polyphénols

CAMELLIA SINENSIS
(GREEN TEA EXTRACT)

Catechins (catechin-polyphenols)

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<tr>
<th></th>
<th>( R_1 )</th>
<th>( R_2 )</th>
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<tbody>
<tr>
<td>Epigallocatechin gallate</td>
<td>EGCG</td>
<td>Gallate</td>
</tr>
<tr>
<td>Epigallocatechin</td>
<td>EGC</td>
<td>H</td>
</tr>
<tr>
<td>Epicatechin gallate</td>
<td>ECG</td>
<td>Gallate</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>EC</td>
<td>H</td>
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</table>

\( OH \)
Total Flavonoids in Tea

Green Tea

Black Tea

<table>
<thead>
<tr>
<th>Catechins</th>
<th>Theaflavins &amp; Thearubigins</th>
<th>Flavonols</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>R₁</th>
<th>R₂</th>
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<td>Gallate</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>EC</td>
<td>H</td>
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</tbody>
</table>
Measurements in a room respirometer

24h energy expenditure, substrate oxidation
urinary catecholamines

in 10 healthy men (normal weight to overweight)
in response to ingestion (3 x a day) of capsules containing either:

- Placebo
- A Green tea extract (50 mg caffeine & 90 mg catechin polyphenols)
- 50 mg caffeine

Daily doses: 150 mg caffeine and 270 mg catechins
Elevated 24h energy expenditure (kJ) in response to green tea extract but not to caffeine alone.

**EE (KJ/d)**

- Placebo
- Caffeine
- Green tea (+4%, **: P<0.01)**
Elevated 24h lipid oxidation in response to green tea extract but not to caffeine alone
Elevated 24h urinary noradrenaline in response to green tea extract but not to caffeine alone.
The effects of catechins and caffeine on fat oxidation: a meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Catechins</th>
<th>Caffeine</th>
<th>Mean Difference (95% CI)</th>
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<tbody>
<tr>
<td>Dulloo et al., 1999</td>
<td>270mg</td>
<td>150mg</td>
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<tr>
<td>Dulloo et al., 1999</td>
<td>0mg</td>
<td>150mg</td>
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<tr>
<td>Bérubé-Parent et al., 2005</td>
<td>270mg</td>
<td>200mg</td>
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<tr>
<td>Bérubé-Parent et al., 2005</td>
<td>600mg</td>
<td>200mg</td>
<td></td>
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<tr>
<td>Bérubé-Parent et al., 2005</td>
<td>900mg</td>
<td>200mg</td>
<td></td>
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<tr>
<td>Bérubé-Parent et al., 2005</td>
<td>1200mg</td>
<td>200mg</td>
<td></td>
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<tr>
<td>Rudelle et al., 2007</td>
<td>282mg</td>
<td>300mg</td>
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<tr>
<td>Rumpler et al., 2001</td>
<td>244mg</td>
<td>270mg</td>
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<td>135mg</td>
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<tr>
<td>Bracco et al., 1995, lean subjects</td>
<td>0mg</td>
<td>1248mg</td>
<td></td>
</tr>
<tr>
<td>Bracco et al., 1995, obese subjects</td>
<td>0mg</td>
<td>1604mg</td>
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</table>

Hursel, Viechtbauer, Dulloo, Tremblay, Tappy, Rumpler, Westerterp-Plantenga
*Obesity Reviews* (2011, in press)
Long-term consumption of green tea rich in catechins is associated with altered body composition and lower abdominal (visceral) fat.

Green tea extract ingestion, fat oxidation & glucose tolerance in healthy humans


Green tea extract (GTE) (○)
Mechanisms of action at organ/tissue level

catechins and caffeine interact with sympathetically-released NA

stimulate thermogenesis?

Ex-vivo studies in highly sympathetically innervated rat interscapular brown adipose tissue fragments
WAT & BAT
UCP-1 mitochondrial protein - brown

Cinti S: The adipose organ. 1999. Editrice Kurtis, Milano, Italy
Respiration rates (MO2) of rat brown adipose tissue


*P<0.05; **P<0.01; ***P<0.001.
Synergistic interactions between EGCG and caffeine on brown adipose tissue thermogenesis in vitro

EGCG, in its own rights, had no effects or trivial effects on BAT thermogenesis

Unexpected evidence for active brown adipose tissue in adult humans

Jan Nedergaard, Tore Bengtsson, and Barbara Cannon

2-[18F]fluoro-2-deoxy-glucose (FDG) uptake in brown fat cells

Sites of FDG uptake corresponding to brown adipose tissue in adult humans

Stained with Hematoxylin and eosin

Stained with anti-serum against UCP1

www.med.harvard.edu/JPNM/chetan/normals/brown_fat/case.html
Functional brown adipose tissue in adult humans

**Cold-Activated Brown Adipose Tissue in Healthy Men**

**Identification and Importance of Brown Adipose Tissue in Adult Humans**

**Functional Brown Adipose Tissue in Healthy Adults**

**The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue.**

**High Incidence of Metabolically Active Brown Adipose Tissue in Healthy Adult Humans: Effects of Cold Exposure and Adiposity.**
Brown adipose tissue:
The safest target for weight control in adult humans!

But β3-agonists are ineffective in humans

Need to bypass adrenoceptor system!
<table>
<thead>
<tr>
<th>Category</th>
<th>Classes</th>
<th>Major Food Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolic acids</td>
<td>• Ferulic acid</td>
<td>Dietary fiber – hemicelluloses</td>
</tr>
<tr>
<td></td>
<td>• Caffeic acid (Chlorogenic acid)</td>
<td>Many fruits and vegetables, coffee</td>
</tr>
<tr>
<td></td>
<td>• Condensed tannins</td>
<td>Mango fruit</td>
</tr>
<tr>
<td></td>
<td>• Hydrolyzable tannins:</td>
<td>Blackberries, raspberries, strawberries, wine, brandy aged in oak barrels</td>
</tr>
<tr>
<td></td>
<td>(Gallotannins, Ellagittannins)</td>
<td></td>
</tr>
<tr>
<td>Flavonoids</td>
<td>• Flavones</td>
<td>Sweet red pepper, celery</td>
</tr>
<tr>
<td></td>
<td>• Flavonols (Quercetin)</td>
<td>Tea, onions, many fruits &amp; vegetables</td>
</tr>
<tr>
<td></td>
<td>• Flavanols: (Catechins)</td>
<td>Green tea, chocolate, cocoa</td>
</tr>
<tr>
<td></td>
<td>• Flavanones (Hesperetin)</td>
<td>Oranges, citrus fruits</td>
</tr>
<tr>
<td></td>
<td>• Isoflavones (Genistein)</td>
<td>Soybeans, soy protein-containing foods</td>
</tr>
<tr>
<td></td>
<td>• Anthocyanins (Cyanidin)</td>
<td>Red fruits: cherries, plums, strawberries, raspberries, blackberries, grapes, red</td>
</tr>
<tr>
<td></td>
<td>• Proanthocyanidins</td>
<td>and black currants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apples, pears, grapes, red wine, tea</td>
</tr>
<tr>
<td>Lignans</td>
<td>• Enterodiol</td>
<td>Flaxseed, flaxseed oil</td>
</tr>
<tr>
<td>Stilbenes</td>
<td>• Resveratrol</td>
<td>Red wine</td>
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Adapted from: Scalbert and Williamson, 200
Acknowledgements

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