dotFIT™ ThermAccel™

Goal

To accelerate or continue desired weight loss, especially when diet and exercise may be maximized based on acceptable lifestyle parameters, by supplying effectively timed doses of bioactive ingredients that have separately demonstrated favorable effects through unique targets on human body fat metabolism leading to enhanced body fat/weight loss when compared to a non-supplemented state. Daily simultaneous ingestion of these combined actives may contribute additive effects since the individual mechanisms of action related to fat oxidation, energy expenditure and appetite are distinctly unique. The formula's primary goal is to increase total daily energy expenditure/calorie burn (TDEE) by increasing resting energy expenditure (REE) and overall metabolism including daily activities.
ThermAccel's (TA) natural thermogenic blend is uniquely formulated to deliver a "better stimulant effect" when compared to currently available popular energy formulas that often lead to "burnout" and related stress, including "end of day fatigue." ThermAccel is designed to produce balanced and enhanced energy levels that may also help users increase voluntary daily activities. Through TA's thermogenic effect (boosting metabolism by wasting calories as heat), favorable fat oxidation properties and smoother daily energy boost, users may be able to avoid or overcome natural plateaus during weight reduction without having to continually "add more work."
TA's secondary endpoints are to increase fat oxidation/burning (energy/nutrient partitioning) and decrease appetite beyond TA's caffeine stimulant blend's normal effects on these targets, by incorporating two other groups of natural ingredients, Caralluma fimbriata and Sinetrol (the polyphenols naringin and neohesperidin), which work through respectively different body fat regulation pathways than the thermogenic blend. In totality, through addressing multiple body fat regulation targets thus offering potentially additive contributions, TA may help mitigate the normal stresses and struggles of dieting and weight control including helping to maintain total daily energy expenditure due to the loss of lean body mass (LBM) during weight loss when compared to a non-supplemented state, or consumer channel over the counter fat loss aids or the potentially more dangerous prescription pharmaceuticals.

Rationale

While use of a complete multivitamin and mineral supplement (including calcium as necessary) should be considered mandatory during any caloric restriction,[1] the rationale for the use of any specialty dietary supplement as part of an overall weight loss plan is to speed and/or ease the journey contributing to enhanced motivation to complete the process, at which time a specialty supplement, such as ThermAccel, should not be required to maintain the desired weight or body composition (see Introduction to Weight Loss Section).

Dieting (calorie restriction) for weight loss is overall difficult at best[2,3] and regularly frustrating based on unavoidable plateaus from normal adaptations to weight loss including lean body mass (LBM)[4] with subsequent enhanced fitness, (e.g. mitochondrial adaptations/efficiency, reduced heart rate, etc.)[5,6,7] in which both conditions can lead to a lower metabolism.[8,9] This reduction in daily expended calories causes a plateau even though the calories consumed and daily activities are the same as when weight loss was originally initiated.[4,8,10] The natural defenses the body mobilizes during weight loss causing plateaus and weight regain are, but not limited to: adaptive thermogenesis, including a reduction in thyroid hormone levels,[11] reduced energy expenditure (as described above and from weight/LBM loss)[12], increased circulation of appetite mediating hormones (e.g. ghrelin), decreased leptin (satiety hormone)[13] and potentially the relapse of old habits.[14] Exercise alone is largely ineffective at producing significant amounts of weight loss due to the volume needed to achieve and sustain a calorie deficit to induce weight loss. As such, research has consistently shown exercise by itself to not be a complete weight loss solution.[15,16,17,18,19]
To continue weight/fat loss when natural/adaptive plateaus occur, and diet is generally healthy, more deliberate work and/or fewer calories, which in turn causes increased hunger, is the only remedy unless:[4,12] 1) calories burned can be increased without adding more exercise, or the needed added work is voluntary because of increased energy levels, and/or 2) appetite can be controlled during further caloric restriction. Thermogenic blends have demonstrated the

ability to accomplish the former[20,21,22] and few natural plant extracts have had some success with the latter.[23,24,25] Theoretically these combined effects would ease the workload and mitigate hunger to allow continued weight reduction with less hardship.

Therefore, ThermAccel contains:

1) A thermogenic complex with caffeine,[26] yerba mate,*[27] guarana,*[28] green tea extract polyphenol (EGCG)[29] and capsaicin[30] that have independently and combined[20,21,22,31] demonstrated total daily energy expenditure (TDEE) enhancements and fat oxidation increases compared to placebo.
2) Sinetrol (polyphenols), which is a combination of non-stimulant polyphenols that also contributes, but through different mechanisms, to increases in fat oxidation[32] - i.e. partitioning energy usage
3) Caralluma fimbriata, a plant-based appetite suppressor has been shown to have mild effects on weight loss[25,33]

Thermogenic Complex (2-tabs) providing 270 mg EGCG, 200 mg Caffeine & 100,000 Heat Units

Caffeine (200 mg), yerba mate (20 mg),* guarana seed (20 mg),* green tea leaf extract (630 mg, 98% polyphenol with 270 mg EGCG) and cayenne fruit (17 mg standardized to produce 100K Scoville Heat Units [SHU]**) are uniquely combined to increase the user's total daily calorie burn by stimulating the central nervous system (CNS) and increasing thermogenesis. (increasing metabolism through wasting calories/fat as heat) including activation of brown adipose tissue (BAT) and by possibly inducing the desire to increase physical activity through enhanced alertness and CNS excitement.[20,34] Caffeine and caffeine-containing herbs have also demonstrated a positive effect on appetite suppression and fat oxidation.[35,36,37,38,39] Taken together, these functional ingredients have the potential to produce significant effects on metabolic targets such as satiety, thermogenesis and fat oxidation.[20,21,22,31,40,41,42,43]

*Yerba mate and guarana powder are part of the manufacturer's complete blend but in non-significant amounts and therefore will not be discussed here.

** The Scoville scale is a measurement of the pungency (spicy/heat of pepper) of chili peppers, or other spicy foods, as reported in Scoville Heat Units (SHU), a function of capsaicin concentration. Capsaicin is one of many related pungent compounds found in chili peppers, collectively called capsaicinoids. Average size cayenne pepper contains 30-50K SHUs; jalapeno peppers contain 2.5-5K SHUs

Caffeine (1, 3, 7-trimethylxanthine)

Caffeine naturally occurs in varying quantities within the structures of beans, leaves, and fruits of more than 60 plants including the cacao bean, yerba mate, guarana berry and kola nut, with roasted coffee beans and tea leaves (*Camellia sinensis*) being the world's most common sources of caffeine.[44]

Caffeine, Energy Expenditure (EE) and Fat Oxidation (FO)

Caffeine is a methylxanthine compound and is structurally related to theophylline, theobromine, and uric acid.[45] It is 100% bioavailable after oral ingestion and easily crosses the blood brain barrier thus, affecting the nervous system.[44] Caffeine is metabolized primarily in the liver producing among others, the metabolites paraxanthine, theophylline and theobromine.[46] The half-life of caffeine in healthy adults is 5-6 hours.[47] Caffeine is the primary ingredient in this formula because of its positive effects on weight loss through its ability to increase EE, lipolysis and fat oxidation (burning of fat for energy).[20,48, 49,50] As Figure 1 from Harpaz et al. depicts, caffeine in humans increases metabolic rate and fat oxidation partly through 1) sympathetic activation of the CNS[26,49] (increasing sympathetic activities is also associated with a reduction in food intake[51]); 2) inhibition of phosphodiesterase (PDE), the enzyme that degrades the intracellular 3,5-cyclic-adenosine monophosphate (cAMP), (cAMP is the signal for increasing cellular lipolysis, heat production and liver satiety signals); 3) stimulation of adenosine receptors, (a blockade that may also increase dopamine levels[52]) causing a buildup of (cAMP) leading to greater activity in cells.[26,44,53,54]

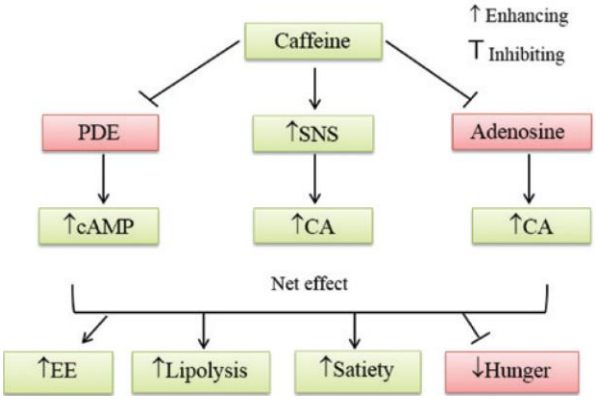


Figure 1
Caffeine Targets in Supporting Weight Loss
PDE- phosphodiesterase
SNS- sympathetic nervous system
cAMP- 3,5-cyclic-adenosine monophosphate
CA- catecholamines
EE- energy expenditure

Caffeine has been shown to increase energy expenditure (EE) approximately 3-5% in the first 2.5 hours after ingestion.[26,39,55] While comparable increases in EE have been shown with epigallocatechin gallate from green tea (EGCG) in human subjects,[53] more often EGCG supplementation alone increases resting EE less than caffeine alone but may possess an additive effect based on different mechanisms of action.[56]
Caffeine dosages (usually in combination with other ingredients) used in weight loss studies range between 1.5-2.3 mg/lb of body weight spread throughout the day but should not exceed 500 mg/d.[20,48] Valentine et al. demonstrated that ingestion of 2 mg/lb of body weight of caffeine raises 3-hr post-exercise energy expenditure (~31 kcal) probably through the increased energy cost of ventilation.[57] Schubert et al. used 1.36 mg/lb of body weight of caffeine 90 minutes before and the same dose 30 minutes after exercise which showed significantly greater EE and FO, reduced appetite, greater energy deficit, and exercise perceived as more enjoyable and less difficult when compared to placebo.[58]
Caffeine consumption has been shown to have different pharmacokinetics in lean subjects compared to their overweight counterparts with the latter group experiencing a lesser effect on fat oxidation but generally comparable changes in resting energy expenditure (REE).[38,59,60] Researchers have shown caffeine's half-life and metabolism to end products are longer or incomplete in overweight individuals leading to the potential differences in metabolic outcomes. However, caffeine shows positive effects on EE and lipolysis in both groups.[26,38,40,41,59,60]
Another suggested mechanism for caffeine's effects on EE is the stimulation of catecholamine, which binds to adipose cells leading to enhanced thermogenic gene expression and release of free fatty acids which concurrently increases the uncoupling proteins (UCPs) that produce mitochondria heat or energy wasting in brown and white adipose tissues and skeletal muscle.[61,62,63,64,65]
In a pilot study Acar-Tek N, et al. used 2.75mg/lb of caffeine from green coffee (extract for unroasted green coffee beans) to test REE on 24 females measured at 30, 60, 120- and 180-minutes post ingestion. The authors found chlorogenic acid in the green tea to be independently correlated with REE values from the green coffee caffeine, and that the former may have antihypertensive effects.[66]
Silveira et al. demonstrated caffeine administered to cyclist at 2.3 mg/LB increased time to exhaustion by 34% by increasing time maintained at VO_2max thus increasing total work completed above critical power leading the authors to conclude caffeine allows a longer maximal oxidative metabolic rate.[67]
Studies with caffeine alone or green tea with some caffeine (lesser amounts than studies using caffeine alone) generally show a ~4% increase in 24 hour metabolic rate.[39,53,68,69] Therefore, combining caffeine and EGCG together may have a synergistic effect on 24 hour EE.[20,41,70]

Caffeine and Appetite

Caffeine's effects on appetite have been mixed, primarily because most caffeine containing products targeting fat loss contain other potential appetite suppressing ingredients such as red pepper extracts, tea catechins, fibers etc. These

ingredient combination studies have been able to highlight that the addition of caffeine may amplify the anorectic effect of these other chemicals – i.e. making an additive contribution to satiety.[20,21,22,26,31,71]
Schubert et al. tested caffeine on energy intake between meals and had subjects complete four trials: placebo (PLA), decaffeinated coffee (DECAF), caffeine (CAF), and caffeine with decaffeinated coffee (COF).[72] Participants dosed twice, once at breakfast and once two hours later. Four and a half hours after breakfast, participants were given access to an ad libitum meal for determination of energy intake. The authors found no significant effect on energy intake with a slight decrease trend toward the caffeine alone group and therefore concluded that consumption of caffeine and/or coffee for regulation of energy balance over longer periods of time warrant further investigation.[72] In a follow up review on coffee and caffeine alone on appetite, Schubert et al. found that ***coffee*** administered 3-4.5 hours before a meal had minimal influence on food and macronutrient intake, while ***caffeine*** ingested 0.5-4 hours before a meal may suppress acute energy intake.[73] Furthermore, they found the evidence regarding the influence of caffeine and coffee on gastric emptying, appetite hormones, and appetite perceptions to be equivocal. Additionally, the authors surmised that "the influence of covariates such as genetics of caffeine metabolism and bitter taste phenotype remain unknown."[73,74] And finally, it has been reported often that caffeine's effects on EE or appetite are more pronounced in subjects with lower daily caffeine intakes from all sources (<330 mgs/d)[75,76]
In summary, while caffeine alone is universally considered a significantly effective performance enhancing supplement in specific athletes and activities, (which would make its own incremental contribution to total daily calories burned),[77] caffeine administered alone as a supplement for weight loss may only contribute modestly when everything else is equal. However, over time that modest contribution may be clinically significant.[26] At the same time, the addition of other potential EE enhancers and appetite suppressing ingredients that work through other mechanisms of actions from caffeine, may complement each other to produce and additive effect with more meaningful outcomes.[20,21,22,31,35,36,37,38,39,40,41]

Green Tea Extract Including 270 mg (2-tabs) of Epigallocatechin gallate (EGCG)

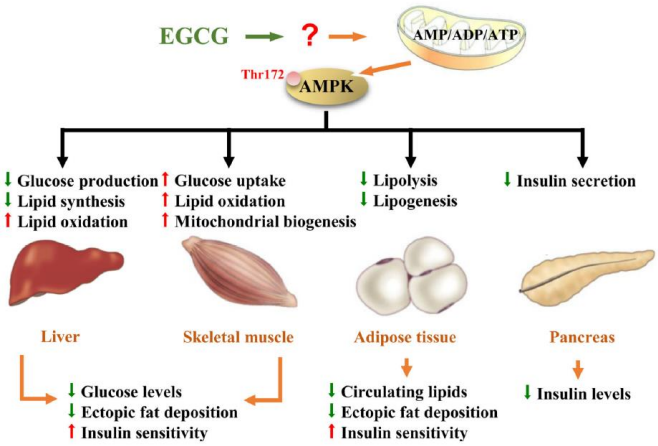
It is generally agreed that much of the positive health effects associated with green tea (GT) are mediated by its polyphenols known as catechins.[29,78,79,80,88,112] The major catechins in green tea are EGCG, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epicatechin. EGCG accounts for 50% to 80% of GT catechins amounting to ~80 to 150 mg per brewed (2.5 g tea leaves) cup of green tea and 20-50 mg of caffeine (tea processing results in wide variances).[81,88] In addition, green tea and its extracts also include some polyphenols like caffeine, theanine, theaflavin, thearubigin, quarcetin, cholorogenic acid and gallic acid.[82]
EGCG ingestion has been shown to improve lipid/fat metabolism, including reducing circulating triglycerides and LDL cholesterol;[83] enhance catabolism (breakdown) and oxidation; (energy usage/partitioning)[53,68,84] increase EE;[41,53,68] and contribute a modest but favorable influence on weight control.[29]

Mechanisms of Action

Research offers many mechanisms in which EGCG (mindful that most EGCG extracts of GT contain some caffeine, albeit relatively low amounts[40,85]) may promote weight loss and/or improve body composition and thermogenesis including total daily EE and fat metabolism: 1) EGCG directly inhibits the enzyme catechol-O-methyl-transferase (COMT),[86] that degrades epinephrine (EPI) and norepinephrine (both hormones are stimulated by caffeine), fostering higher circulating concentration of sympathetic-induced catecholamines and enhancing beta-oxidation thus fat oxidation (FO);[53,82,87] 2) may suppress gluconeogenesis and lipogenesis and enhance lipolysis through activation of AMP-activated protein kinase (AMPK),[88,89] (possibly via upregulation of sirtuin 1[90]) which has been shown to take place in muscle, liver, adipose tissue and pancreas[91,92,93] with manifestations as depicted by Yang et al. in Figure 2;[88] 3) in the gastrointestinal (GI) EGCG may decrease digestion and absorption of macronutrients: lipids by interfering with the emulsification needed for absorption and inhibiting pancreatic lipase (enzyme that breaks down fat),[94] and carbohydrates by inhibiting amylase and glucosidase;[95] 4) green tea constituents may enrich the probiotic population in the intestines, favoring a flora consistent with leaner humans;[96,97,98] in which part of this enhancement may be from

an increase production of short-chain fatty acids (SCFA) caused by EGCG (SCFA generation has recently been found capable of signaling a cascade effect in the body, activating AMPK, and inducing weight-loss;[29,88,99] 5) EGCG also works as an antioxidant (and possibly an indirect antioxidant [prooxidant] stimulating other antioxidant systems) scavenging free radicals and preventing the formation of reactive oxygen species (ROS) by chelating metal ions (more apparent in subjects under high oxidative stress, e.g. overweight/obese);[29,88,100] 6) EGCG has demonstrated an ability to destroy fat cells;[94,101,102] and 7) EE and fat oxidation may also increase via an effect of catechins on the gene expression of proteins that play a role in thermogenesis and beta-oxidation.[40]

Figure 2 - Proposed EGCG AMPK Actions on Organs



Yang et al. hypothesis on the role of AMPK in metabolic regulation by EGCG.[88]

"EGCG is proposed to active AMPK through affecting the ratios of AMP/ADP/ATP. The activated (phosphorylated) AMPK regulates metabolism in different organs toward the direction of reducing (↓) gluconeogenesis, fatty acid synthesis, insulin secretion and ectopic fat deposition in muscle and liver. These are accompanied by increased (↑) insulin sensitively and the oxidation of glucose and fatty acids". The lower part of the figure was modified from Long et al.[89]

Study Endpoints

One or a combination of any of the proposed mechanisms have produced clinical trials demonstrating that regular ingestion of the green tea catechins (GTCs), primarily EGCG at ~300 mg/d, can increase overall (EE),[75,88,103,104,105] and enhance fat oxidation,[37,41,54,88,105,106,107,108,109] both conditions often leading to favorable changes in body composition.[29,40,53,85,88,105] Other GTC supplementation findings suggest that green tea catechin consumption enhances exercise-induced changes in abdominal fat and serum triglycerides in humans[110] and in animal models.[111]
It should be noted that a study by Kumar et al. using 400 mg/d of a decaffeinated GTC (<1% caffeine) containing 50-75% EGCG, produced significant reductions in serum Prostate Specific Antigen (PSA) compared to placebo but at this dose (~200-300 mg EGCG) delivered no changes in body weight after 12 months of use suggesting at least some caffeine is important in EGCGs potential body composition benefits.[112] Other studies have found comparable results with decaffeinated GTC.[113,114]

EGCG with Naturally Occurring Caffeine

As noted above, most EGCG extracts of GT contain some natural caffeine, albeit in small amounts (generally <50 mg). However, the observation that EGCG from GT stimulates EE and fat oxidation cannot be completely attributed to its caffeine content because the thermogenic effect of GT extracts containing caffeine and catechin polyphenols is greater than that of an equivalent amount of caffeine alone (Figure 3).[53] According to Dulloo et al., fat oxidation accounted for approximately 42% of the total calories burned over the course of 24 hours in the EGCG group (270 mg) compared to the placebo (32%) and caffeine (34%) groups (Figure 4).[53] Moreover, respiratory quotient is lower in subjects who consumed decaffeinated EGCG compared to placebo during and after workloads which indicates greater fat oxidation.[68] A study conducted by J.D. Roberts and M.G. Roberts et al., using 571 mg/day of a decaffeinated GT extract (providing 400 mg/day of EGCG) for four weeks in exercisers found a 24.9% increase in fat oxidation rates, a 1.63% decrease in body fat, and a 10.9% improvement in performance distance covered (20.23 km to 22.43 km), all

compared to placebo.[115] This study strongly supports EGCG's ability alone to increase fat oxidation. Readers are referred to Hursel R, Westerterp, et al. for a thorough review on EGCG influence on total EE and fat oxidation.[41]

Figure 3: Dullo et al. showed at least a 10% increase in 24-hour EE or equivalent to 157 more calories burned in the caffeine/EGCG group (Average subject's weight was 173 lbs).[53]

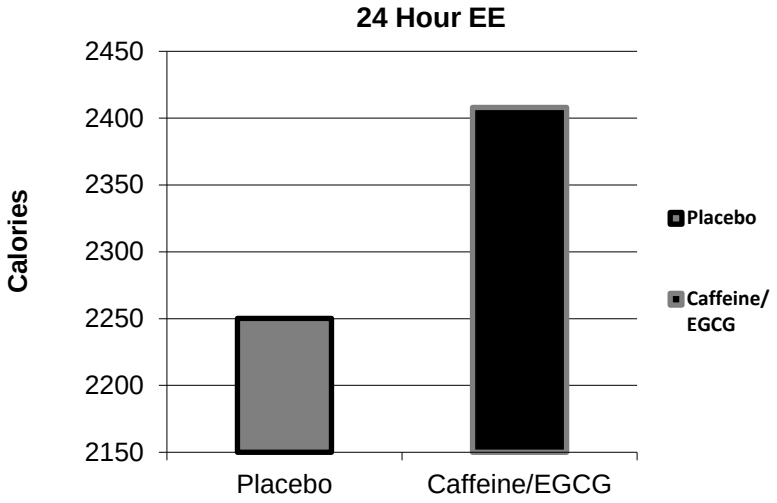
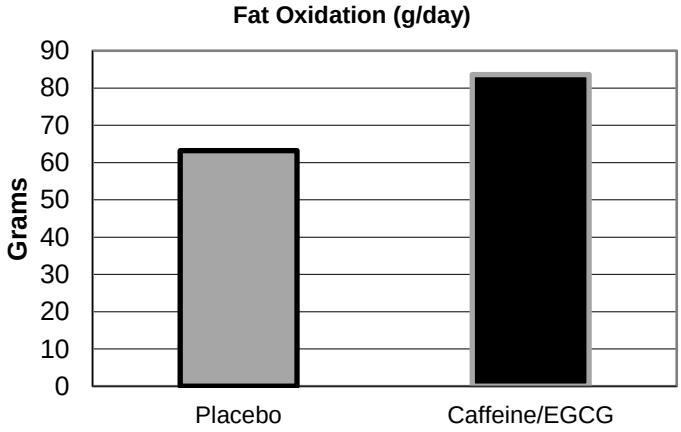


Figure 4: In the same study, approximately 20 more grams of fat was oxidized daily by the supplemented group.[53]



The Synergy

Observing the mechanisms of action of both caffeine and EGCG, we can clearly see how the potential synergies play out. As described above in "mechanisms of actions", dual effects of GTCs on EE and fat oxidation may be caused by the methylation of catechins (EGCG) directly inhibiting the enzyme catechol-O-methyl-transferase (COMT),[86] and the inhibition of phosphodiesterase by GTCs caffeine content,[26,53,54] therefore, these may be the primary mechanisms behind the stimulating properties of EGCG. This combined inhibition of the enzymes COMT (degrades epinephrine and norepinephrine while caffeine stimulates both hormones) by EGCG and PDE (the enzyme that degrades the

intracellular cAMP, which would otherwise signal for increasing cellular lipolysis and heat production) by caffeine, would improve the signaling cascade to prolong the stimulus of the sympathetic nervous system leading to potentially additive increases EE and fat oxidation.[54,105,116] This activity was demonstrated by Auvichauapat et al. after 12 weeks of catechin supplementation by showing that catecholamine metabolites in urine were modified, indicating the successful catechin stimulation of the sympathetic nervous system.[117]

Conflicting EGCG Study Outcomes

Inconsistent results on long-term weight/fat loss using green tea supplementation and its extracts may often be attributed to the extract's caffeine content, test subject's ethnicity/genetics and high or low regular caffeine and/or other related catechin intake. To be sure, in a review by Rothenberg et al.,[29] the researchers reported that "Caucasian ethnicity and high regular caffeine intake both weakened GT/EGCGs weight-loss effects when compared to Asian ethnicity and low regular caffeine intake. Enzyme activity varies with ethnicity and therefore, ethnicity is a factor due to the enzyme-related nature through which tea polyphenols induce weight loss."[29,68,75,118] Additionally, the absorption rate of catechins may affect the degree of thermogenesis.[40]

Summary and Dosage

Whatever effects are at work here from ingesting EGCG daily, the endpoint for body composition outcomes is generally measured as an enhancement of EE and fat oxidation,[53,105] which when diet and exercise are managed correctly for weight/fat loss, daily use of EGCG may deliver a better body composition result and/or lessen the burden, compared to no supplementation.[20,29,75,88,105,115]

EGCG Doses

A systematic review and meta-analysis of 8 qualified RCTs by Kapoor et al. found that EGCG alone has the potential to increase metabolic rate including respiratory quotient (RQ/FO) and EE at 300 mg/d dose and collectively, the outcome supports the findings that EGCG influences metabolic parameters. Similarly, Cisneros et al. in a systematic review of 15 qualified articles (out of 424 reviewed) on the effects of green tea and its EGCG content on body weight and fat mass, found "daily consumption of green tea with doses of EGCG between 100 and 460 mg/day demonstrated the greatest effect on body fat and weight reduction in intervention periods of ≥12 weeks. However, the use of caffeine doses between 80 and 300 mg/day was shown to be a factor in studies with the more positive results. Furthermore, results were greater in participants with lower habitual caffeine intakes (<300 mg/day) prior to the interventions.[119]

Safety

There have been reports of potential liver toxicity with regular ingestion of high dose green tea extracts.[120,121] To address these accounts, The European Food Safety Association (EFSA) prepared an 89-page report concluding: "Based on the available data on the potential adverse effects of green tea catechins on the liver, the Panel concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement statistically significantly increase serum transaminases in treated subjects compared to control."[121] Additionally, the EFSA also stated "From the clinical studies reviewed there is no evidence of hepatotoxicity below 800 mg EGCG/day up to 12 months." [121]

ThermAccel contains only 270 mgs (2-tabs) and 540 mgs (4-tabs as maximum dose) of EGCG to be taken daily, which is well below the upper limit described by the EFSA. dotFIT also states, as at the onset of this document: *use of any specialty dietary supplement, such as ThermAccel, as part of an overall weight loss plan is to speed and/or ease the journey contributing to enhanced motivation to complete the process, at which time a specialty supplement, such as ThermAccel, should not be required to maintain the desired weight or body composition.* Therefore, long-term usage is not recommended. That said, clinical trials using dosages ranging from 300-800 mg/d for up to one year have yielded no signs of liver damage.[29,75,88,112,119,122] It should be noted that regular higher doses (>800 mg) may yield a transient elevation in alanine aminotransferase (ALT) but in healthy subjects, levels should return to an individual's baseline

upon cessation.[123] Anyone with a liver disorder should consult their doctor before considering use at any dosage or simply not use any products containing EGCG extracts. The dotFIT dosage and product duration recommendation would be considered safe and effective for generally healthy adult populations.

Green Tea Extract with 270-540 mg EGCG & Combined Total of 200-400 mg Caffeine from all Sources

Based on the caffeine and EGCGs data above, including their unique and mutual metabolic targets, it appears caffeine and EGCG used together at these doses would be safe and have a greater effect on fat loss than either ingredient alone.[20,31,40,84,65,124,125,126] Therefore, the thermogenic blend in ThermAccel contains 270-540 mg of EGCG and 200-400 mg of caffeine in two and four tabs respectively from all sources.

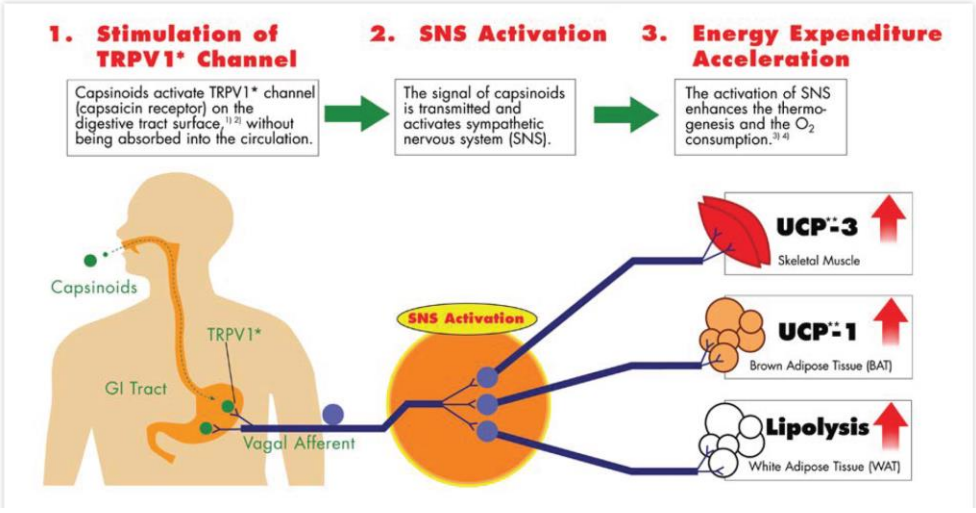
Capsaicin from Cayenne Fruit

The last functional ingredient in the thermogenic blend is capsaicin because it stimulates calorie burning differently than both caffeine and EGCG. [127] Capsaicin is a natural bioactive ingredient, and the most potent capsaicinoid found in hot peppers.[128] Capsaicin is included in this thermogenic complex because it has been shown to increase energy expenditure,[30] increase lipid oxidation, and reduce appetite through different mechanisms than caffeine or caffeine-containing herbs and EGCG.[30,34,128,129,130]

Capsaicin and Brown Adipose Tissue (BAT)

Capsaicin's primary effects on increasing energy expenditure and fat oxidation is through its ability to activate brown adipose tissue (BAT).[127,131,] BAT is a site of non-shivering thermogenesis (burning calories for heat) that is activated by cold in order to help heat the body.[132] The amount of BAT in humans decreases with age.[127,133] In this context, there is considerable research interest in increasing thermogenesis by targeting BAT, which by activation of the sympathetic nervous system (SNS) increases calorie burning to produce heat through the uncoupling of oxidative phosphorylation mediated by uncoupling protein 1 (UCP1).[134] It is known that the stimulatory effects of cold on BAT are mediated through the activation of the SNS and initiated by peripheral stimulation of transient receptor potential (TRP [TRPV1 and TRPA1]) channels in sensory neurons.[135] This pathway is also activated by capsaicin and subsequently stimulates the SNS and favorably alters lipid metabolism including lipolysis and fat oxidation.[136,137,138,139,140] As depicted in Figure 5 from Glanbia Nutritionals,[141] capsinoid stimulation of TRP channels enhances BAT thermogenesis and the upregulation of (UCP1) and connexin-43 (Cx43) molecules.[131,134,137,142]

Figure 5 - The Mechanism of Action by which Capsinoids Accelerate Energy Expenditure. Adopted from E. Drummond, 2015. [141]



Yoneshiro, et al. found that 9 mg/day of capsinoid treatment for six weeks significantly increased EE from 20 calories/day to 200 calories/day by increasing BAT activity during cold exposure,[131] demonstrating that capsaicin activation of the sympathetic nervous system promotes the secretion of catecholamines (epinephrine and norepinephrine), leading to increases in metabolic rate[143] and temperature primarily through BAT.[34,144] Josse et al. confirmed previous findings that ingestion of 10 mg of capsinoids increased adrenergic activity, energy expenditure, and resulted in a shift in substrate utilization toward lipid, thus demonstrating the thermogenic and metabolic effects of capsinoids and further highlighted its potential role as an adjunct weight loss aid, in addition to diet and exercise.[145] Zsiboras et al. in a meta-analysis of human studies found capsaicin to be effective at increasing EE ~60 calories/day and the respiratory quotient (RQ) decreased by 0.216 indicating an increase in fat oxidation. However, they also found the greatest supplement effect on subjects with a BMI >25 (increase in EE ~70 calories/day and 0.257 decrease in RQ).[140]

Besides a subject's weight or body fat being a factor, likewise, the actual increase in EE from daily capsaicin ingestion may also be dependent on the amount of BAT within the individual, which may range from 50-200 grams.[146] The more BAT, the greater capsaicin supplement effect. [127,131,134]

In agreement with Gerngross et al.,[147] in a study by Sun et al.[127] using capsaicin supplementation at 12 mg/d, described their results (quantified by 18-fluorine fluorodeoxyglucose positron emission tomography) in terms of calories and compared them to cold exposure. They found in healthy adults, the average increase in EE to be 120 kcal/d and a whopping 240 kcal/d after cold exposure for two hours, but again, the increase was greater in people with the highest BAT concentrations.[127]

White adipose tissue (WAT) includes subcutaneous fat and is the largest body fat component in humans. Because of capsaicin's known activation (agonist) of TRPV1 channels and subsequent stimulation of BAT, Baskaran et al. investigated the effect of capsaicin in WAT.[148] Their results, using mice, clearly demonstrated that capsaicin administration can up-regulate the expression of protein machinery that causes the molecular conversion of WAT to brite/beige cells (cells with the characteristics of BAT) – i.e. the browning of WAT and depicted in Figure 6 from Baskaran et al.. They found capsaicin to significantly induce the expression of brown fat thermo-genes, UCP-1 and BMP8b, a result that would lead to the browning of WAT.[148] If this action could be broadly duplicated in humans, it could develop into an effective anti-obesity strategy.

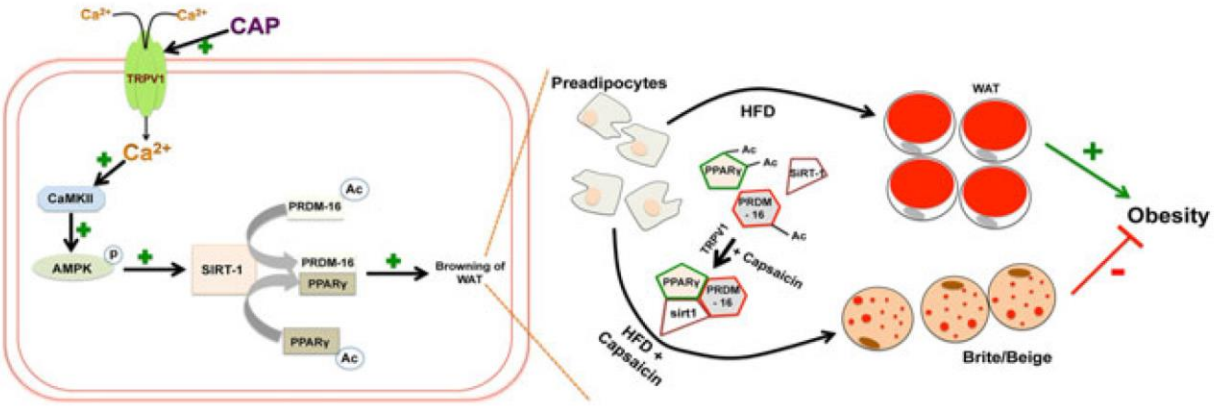


Figure 6 - Model Describing the Mechanism of Action of Capsaicin (CAP).
Intracellular Ca2+ rise via TRPV1 channels stimulated by CAP activates CaMKII/AMPK, which phosphorylate and activate SIRT-1. This causes deacetylation of PPARγ and PRDM-16 and facilitates their interaction to promote browning of WAT. Adopted from P. Baskaran et al.[148]

Capsaicin and Appetite

Capsaicin ingestion has also demonstrated efficacy in appetite suppression. Data from a 2014 meta-analysis suggested that daily consumption of a minimum dose of 2 mg of capsaicinoid prior to a meal reduced ad libitum energy intake by 74 calories during the meal. The meta-analysis findings suggest that daily consumption of capsaicinoids may contribute to weight management through reductions in energy intake.[149] Janssens et al. used doses of 2.56 mg (1.03 g of red chili pepper, 39,050 Scoville heat units) with every meal and found that while in energy balance the addition of capsaicin to the diet increases satiety and fullness, and tends to prevent overeating when food intake is free. And after dinner, capsaicin prevented the effects of the negative energy balance on the desire to eat.[150]

van Avesaat M, et al. attempted to discover capsaicin's appetite reducing mechanism by performing intraduodenal capsaicin infusions of 1.5 mg pure capsaicin in healthy volunteers and tested the effects on hunger, satiety, and gastrointestinal symptoms and the release of their related hormones, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), from enteroendocrine cells in the small intestine. The infusion significantly increased satiety compared to placebo but did not affect plasma concentrations of GLP-1 and PYY. The effect on satiety appeared related to gastrointestinal stress including bloating. Furthermore, satiety scores had a positive correlation with all gastrointestinal symptoms.[151] Along these lines, Rigamoni et al. found 2 mg of capsaicin administered before an ad libitum dinner did not alter satiety/hunger hormones nor effect energy intake or appetite following the meal compared to placebo. However, the capsaicin subjects REE was significantly increased over placebo. In fact, REE in the capsaicin went from 1957.2 calories/day to 2342.3 calories/day, while the placebo group went from 2060.1 calories/day to 2296.0 calories/d). Additionally, the pre-post meal difference in REE after capsaicin administration was significantly higher than that found after placebo (385.1 calories/day vs 235.9 calories/day.)[30] It's always a good sign for weight control measures when you can increase EE without increasing appetite.

Summary

Ingestion of capsinoids or analogs >10 mg/d facilitate cold-induced BAT recruitment and thermogenic activation, purportedly through mechanisms of ADRB3 (beta-3 adrenergic receptor located mainly in adipose tissue and involved in the regulation of lipolysis and thermogenesis) activation through TRPV1-associated SNS initiation and related hormone release (e.g. norepinephrine) as depicted in Figure 6. Additionally, high regular pepper consumption, containing capsaicin, has been associated with a 13% decrease in total mortality possibly via its effects on lipid metabolism and its carry-over to cardiovascular health indicating safe long-term use.[138] Therefore, from a practical standpoint, rather than using cold exposure to raise EE through BAT activation (capsinoids induce BAT via the same channels), and considering capsaicin's potential role in appetite,[149,150,151] prolonged safe ingestion of capsaicin may be a more practical solution for assisting in weight control.[34,127.131,140,149,152] Adding the effective respective doses of caffeine and EGCG described above, capsaicin at 17 mg (2-tabs) to 34 mg (4-tabs, maximum dose) as found in TA, may bring another significant additive effect to supporting weight loss,[153] especially since average adult weight gain is insidious by nature.[154] Meaning, 100-200 calories/day increase in EE imposed by healthy interventions, such as caffeine, EGCG combined with capsaicin and with no accompanying energy intake (EI) compensation, weight control might progress with less hardship. Notably, all the compounds named so far may also contribute to appetite control.

Sinetrol

Sinetrol is a trade name for a synergistic group of bioactive polyphenols extracted from specific varieties of sweet and blood oranges *(Citrus sinensis L.),.),* grapefruit *(Citrus paradisi Macfad.),* and guarana *(Paullinia cupana Kunth)*.[32]

Sinetrol is a proprietary polyphenolic rich fruit extract (red orange, grapefruit, sweet orange, and guarana) standardized to contain at least 90% of total polyphenols (expressed as catechin), at least 20% of total flavanones (expressed as naringin) and between 1% and 3% of natural caffeine.[32]

Naringin, a flavanone glycoside derived from naringinin primarily found in grapefruit, represents the primary active in Sinetrol. Neohesperidin, a glycoside derived from hesperidin, is the other dominate bioactive compound and due to their glycoside fractions, the bioavailability of naringin and neohesperidin is enhanced.[32,155,156]

This non-thermogenic proprietary complex has been included in the ThermAccel (TA) formula to deliver an additive complement to the thermogenic blend including the catechin polyphenol EGCG discussed above, with the goal of further increasing energy expenditure (EE) and fat oxidation.[32,155,156]

Mechanisms of Action (Figure 7)

Polyphenols, like the polyphenol catechin EGCG, are a family of phytochemicals that exist in plants and found to have profound indirect effects on human health.[157] Bioactive flavonoids, a class of polyphenolic compounds, have many subclasses with varying molecular structures and thus participate in human health in multiple areas.[157,158] Flavonoids potential health contributions have been generally attributed to their antioxidant properties.[159,160] Few flavonoids are also known as phosphodiesterase (PDE) and a protein kinase C (PKC) inhibitors acting like caffeine[26] in these pathways,[161,162] therefore more recent investigations have explored specific polyphenols (flavonoids) role in interacting with cell signaling machinery in metabolic pathways that affect lipid metabolism including adipogenesis, energy partitioning and appetite.[163,164,165]

Naringenin

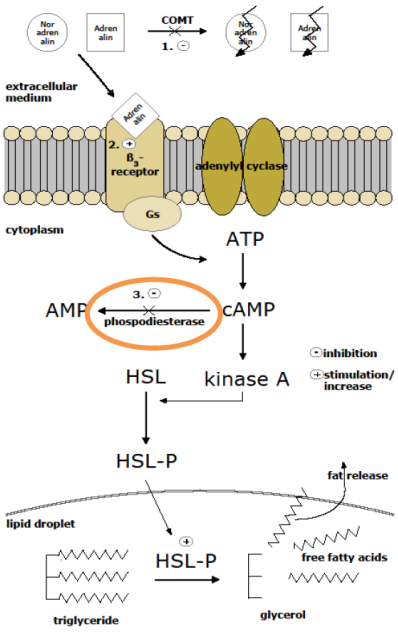
Early in vitro research demonstrated flavonoids to exert lipolytic (fat oxidation/burning) activity by inhibiting the enzyme, phosphodiesterase (PDE),[166] that degrades cyclic adenosine monophosphate (cAMP), which would otherwise decrease lipolysis because high cAMP levels help maintain fat usage for energy.[26] However, different from caffeine's pathway to decreasing PDE activity, the flavone naringenin (an aglycone of the grapefruit flavonoid naringin in Sinetrol) also containing known antioxidant properties,[165] shows the ability to induce the expression of fatty acid oxidation genes CYP4A11, ACOX, UCP1, and ApoA1[167,168] and induce apoptosis (cell death) in preadipocytes (fibroblast that can be stimulated to form fat cells).[165,169,170,171] As another potential mechanism of action, Ke et al. found the expression of genes involved in fatty acid oxidation, Cpt1α (mitochondrial) was significantly higher in mice fed a naringenin diet, which contributed to significantly less weight and caloric intake compared to contorls.[168] Furthermore, a review by Zobeiei et al. on naringenin's supplementation (using nanoparticles) concluded that naringenin demonstrates many biological actions "including the decrease of biomarkers of lipid peroxidation and protein carbonylation, increase of antioxidant defenses, scavenging of reactive oxygen species and modulation of signaling pathways related to fatty acid metabolism, which can favor the oxidation of fatty acid, lower lipid accumulation in the liver and thereby support liver health."[172]

Neohesperidin (NHP)

NHP, A bitter flavonoid glycoside, is the other major active flavone in Sinetrol and is also derived from citrus fruit peels especially specific oranges named above and works basically through the same pathways as naringenin to enhance lipid metabolism including fat oxidation.[32,173,174] Additionally, Wu H et al. found NHP to regulate lipid metabolism in vivo and in vitro via FGF21 and AMPK/SIRT1/PGC-1α signaling axis.[175]

Based on the totality of research, it appears the primary mechanism of actions for the flavones in Sinetrol are related to participating in the inhibition of PDE and stimulation of fat oxidation genes and other genes/areas shown to enhance lipid metabolism including related apoptosis and energy partitioning. Because of their different structures, thus receptors and subsequent actions, it is logical that they may be additive to the thermogenic blend.

Figure 7 - Proposed Mechanisms of Action to Enhance Overall Lipolysis and Body Compostion. Adopted from Dallas et al., 2013.[32]



Inhibition of Phosphodiesterase [PDE-4]

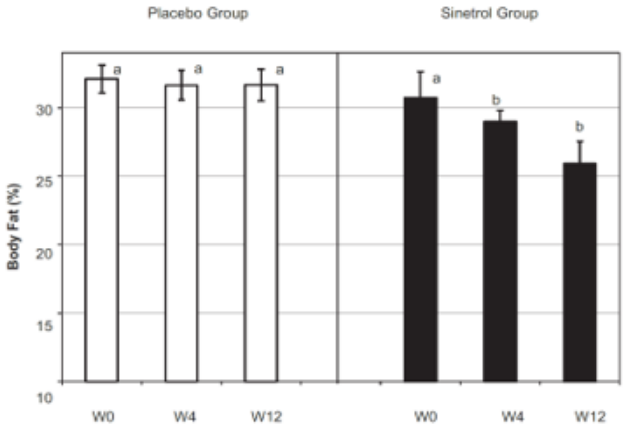
→ Catabolism of triglycerides into Free fatty acids (FFA) + Glycerol

→ Release of FFA + Glycerol in the bloodstream

→ **Direct fat burning action**

Sinetrol Alone Studies

The first Sinetrol trial compared two groups of 10 overweight subjects during 4 and 12 weeks with 1.4 g/day of Sinetrol and placebo supplementation.[155] Measuring free fatty acid release from adipocytes, the researchers found that SINETROL significantly stimulated lipolytic activity via the polyphenols inhibition actions on cAMP-phosphodiesterase (PDE) in a range of six fold greater than the placebo. As shown in Table 1 and the figures below, compared to placebo the treatment subjects' body fat significantly decreased with a difference of 2.53% and 5.6% after 4 and 12 weeks, respectively. Additionally, the body weight decreased with a significant difference of 6.6 lb and 12.3 lb after 4 and 12 weeks, respectively. [155]



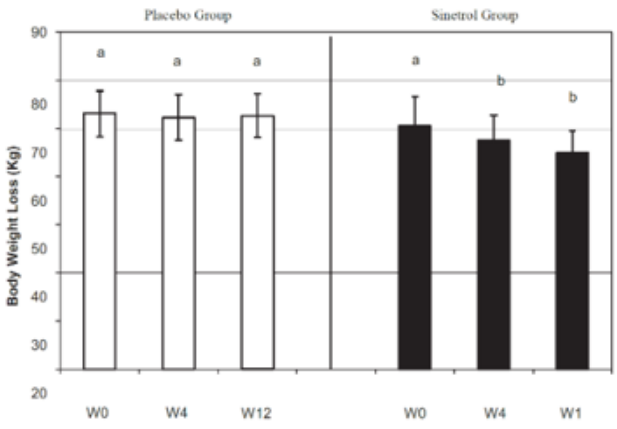


Table 1. Effect of Placebo and Sinetrol on BMI, Body Weight & Body Fat in 20 Volunteers after 4 & 12 Weeks of Treatment[155]

Groups	BMI		Body weight evolution (kg)			Body fat evolution (%)		
	Initial	Variation (%) after 12 weeks	Initial 0 weeks (W0)	After 4 weeks (W4)	After 12 weeks (W12)	Intial 0 weeks (W0)	After 4 weeks (W4)	After 12 weeks (W12)
Placebo	28.570.7[a]	−0.270.5[a]	73.074.8[a]	72.274.7[a]	72.674.5[a]	32.071.0[a]	31.671.0[a]	31.671.0[a]
SINETROL[S]	28.172.45[a]	−2.270.9 [b]	70.576.0[a]	67.575.2[b]	64.974.5[b]	30.771.9[a]	29.070.8[b]	25.971.0[b]

Values are mean7SE, *n* ¼ 10, for each placebo and SINETROL[S] tested group.
Means within rows followed by the same superscript are not significantly different (*p*o0.05).

The second Sinetrol trial included 95 overweight subjects and went deeper into health parameters.[32] In a 12-week, randomized, double-blind, placebo-controlled trial, Sinetrol was given to overweight subjects twice daily with meals versus a placebo. Participants took 450 mg at breakfast and 450 mg at lunch for a total of 900 mg/d or placebo. All women were told to consume 1800-2000 calories/day and men 2000-2500 calories/day and were instructed to limit physical activity to 30 minutes/week (three 10-minute walks). Although total body weight loss was not impressive, the results were clearly metabolically favorable including fat mass loss (Table 2).
Waist and hip circumference and abdominal fat were significantly decreased in the Sinetrol group as compared with placebo group (-5.71% vs -1.56% for waist, -4.71% vs -1.35% for hip and -9.73% vs -3.18% for fat). Inflammatory markers were reduced significantly more in the treatment group (C-reactive protein: -22.87% vs +61%; fibrinogen: -19.93% vs -1.61%). Oxidative stress was lowered as seen by the reduction of malondialdehyde (-14.03% vs +2.76%) and the increase in superoxide dismutase and glutathione (17.38% vs 2.19% and 4.63% vs -2.36%, respectively). [32]

Table 2. Percent Change For BMI, Weight, Body Fat, and Waist and Hip Size After 12 Week of Treatment with Placebo or Sinetrol in Overweight Adults

	Placebo			Sinetrol-XPur		
	Baseline	W12	% change	Baseline	W12	% change
BMI (kg/m^2)	27.27 ± 0.14	26.12 ± 0.35[a]	−4.23 ± 1.12	27.58 ± 0.16	26.39 ± 0.33[a]	−4.31 ± 1.02, NS
Body weight (kg)	77.39 ± 1.23	75.78 ± 1.23	−2.09 ± 0.17	78.14 ± 1.35	75.52 ± 1.25	−3.28 ± 0.24***
Body fat (%)	36.87 ± 1.48	35.85 ± 1.51	−3.18 ± 0.33	37.97 ± 1.59	34.36 ± 1.49	−9.73 ± 0.54***
Waist (cm)	88.44 ± 1.09	87.02 ± 1.02	−1.56 ± 0.20	88.68 ± 1.05	83.53 ± 0.87[a]	−5.71 ± 0.35***
Hip (cm)	109.90 ± 0.96	108.47 ± 0.99	−1.35 ± 0.19	110.08 ± 1.21	104.91 ± 1.23[a]	−4.71 ± 0.29***
Waist/hip	0.809 ± 0.113	0.808 ± 0.101	−0.23 ± 1.69	0.813 ± 0.113	0.784 ± 0.155	−1.01 ± 2.28, NS

This study supports the polyphenols' ability to increase fat oxidation and partitioning the energy usage by drawing more required energy from fat stores than from glycogen or protein, and fortuitously drawing from the abdominal region.

Third Trial – Company White Paper (Unpublished) Available at https://www.sinetrol.com/
The third Sinetrol study used the same diet, exercise and dosage strategy as the second study described above and was a 12-week randomized double-blind parallel pilot trial of Sinetrol on body weight, abdominal fat, waist circumference, and muscle metabolism in overweight men.[156] The results were consistent with the second trial in that body fat and other anthropometric measurements were reduced significantly more in the treatment group than placebo (Table 3) and taking place in visceral areas important to improving health as seen in the quantified metabolic parameters in Tables 4 and 5. Additionally, the increase in body weight loss vs placebo in this pilot was significant. Because the overall metabolic and anthropometric results are not trivial, they are all posted below in the Tables 4 and 5 from Cases et al.[156]

These results speak to the value the polyphenols contained in Sinetrol offer beyond diet and exercise, especially in overall health and body composition (body fat: -9.7% vs -4.8% in the placebo group and -7.5% vs -2.1% in the placebo group for waist reduction). The authors also quantified a threefold greater release in fatty acids in the Sinetrol subjects demonstrating the ingredients' ability to increase lipolysis involving the inhibition of cAMP-PDE. Also, of note in Table 5, the C-reactive protein (CRP) was significantly reduced in the Sinetrol subjects. Beyond a direct health implication, CRP reduction may be important because research has shown that the appetite hormone leptin serves as a regulator of body fat storage by modulating satiation, glycemic control and metabolism, and that reduction in serum leptin correlates with lower regional body fat and total body fat.[176] Overweight people become resistant to the effects of leptin, causing them to produce more as their receptors become resistant. One reason for this may be that weight gain elevates levels of CRP, which inhibits leptin's role in controlling appetite by binding to leptin, thus disallowing it to penetrate the blood brain barrier to signal satiety.[177,178]

Table 3 - Weight, Abdominal Fat, Waist Size and Hip Circumference and % Change (Δ) at Baseline (W0) and After 12 Weeks (W12) of Treatment with *Placebo* or Sinetrol in Healthy Overweight Male Adults.

	Placebo			Sinetrol® XPur		
	W0	W12	Δ (%)	W0	W12	Δ (%)
Body weight (kg)	86.4±4.7	84.9±4.7[a]	-1.76±0.61	89.3±6.1	85.9±5.6[a]	-3.75±0.81**
Abdominal fat (%)	26.7±3.3	25.4±2.8[a]	-4.81±1.74	26.9±3.4	24.3±3.3	-9.74±3.84**
Waist (cm)	98.5±3.6	96.4±3.4[a]	-2.11±0.48	98.8±3.3	91.4±3.5[a]	-7.50±2.00**
Hip (cm)	105.5±4.0	103.5±4.0[a]	-1.89±1.24	104.7±4.5	99.1±4.5[a]	-5.33±1.68**
Waist/hip ratio	0.93±0.02	0.93±0.02	-0.20±1.53	0.95±0.04	0.92±0.04[a]	-2.27±2.42*

Values are means ± SD, *n*=13 (*placebo*) or *n*=12 (Sinetrol® XPur). Δ (%): % difference W12 – W0. [a]an intragroup difference between W0 and W12 at p<0.05. *p<0.05 and **p<0.001 indicate Δ differences between *placebo* and Sinetrol® Xpur.

Table 4 - Blood Metabolic Parameters at Baseline (W0) and After 12 Weeks (W12)

	Placebo		Sinetrol® XPur	
Normal range	W0	W12	W0	W12
Glycemia (mmol/L) <5.6	6.1±0.5	6.1±0.3	5.9±0.6	5.1±0.5[a]*
NEFAs (µmol/L) <720	154.6±25.3	186.2±36.8[a]	155.6±19.3	581.3±115.6[a]*
Apo A1 (µmol/L) 37-77	48.2±8.0	46.6±3.5	50.2±9.4	52.9±3.0*

Table 5 - Muscle Metabolism and Kidney Function at Baseline (W0) and after 12 Weeks (W12)

	Placebo		Sinetrol® XPur	
Normal range	W0	W12	W0	W12
Muscle metabolism				
Creatinine (mg/L) 9-14	12.1±2.4	14.0±1.9[a]	12.4±1.7	13.3±2.2
Inflammation				
hs-CRP (mg/L) <5	2.4±1.4	2.8±1.2[a]	3.0±1.7	1.6±0.7[a]
Fibrinogen (g/L) 1.5-3	3.5±0.7	3.5±0.7	3.4±0.8	2.9±0.5[a]*
Oxidative stress				
MDA (µmol/L) <2.8	2.7±0.3	3.1±0.3[a]	3.2±0.4	2.9±0.5
Uric acid (mg/L) 40-60	56.5±10.0	58.8±5.2	58.3±6.4	47.9±4.1[a]**
Kidney function				
Na (mmol/l) 135-145	134.6±3.3	135.4±4.6	136.2±2.4	135.6±2.7
K (mmol/L) 3.6-5.2	4.0±0.3	3.9±0.2	4.3±0.3	4.5±0.4**
Urea (g/L) 0.18-0.45	0.44±0.05	0.45±0.05	0.36±0.12	0.41±0.08

Values are means ± SD, *n*=13 (*placebo*) or *n*=12 (Sinetrol® XPur). [a]an intragroup difference between W0 and W12 at p<0.05. *p<0.05 and **p<0.001 indicate a difference between *placebo* and Sinetrol® Xpur.

Sinetrol Summary

The non-thermogenic polyphenol blend consumed at 900 mg/day split in two 450 mg doses has been found to be safe and to significantly improve body composition and metabolic parameters compared to placebo including preferentially reducing abdominal/ectopic fat stores shown in the tables above. The primary proposed mechanisms of action are the ingredients' ability to improve overall lipolytic activity via inhibiting cAMP-PDE (maintaining higher levels of cAMP) and enhancing fat oxidation and related gene expression (favorable energy partitioning and drawing from areas most important to health).

With the combined ingredients in the thermogenic blend and the addition of Sinetrol, the evidence points to synergistic and additive contributions based on the unique and mutual mechanisms of action, with the caveat that one ingredient's actions could overwhelm another's ability to perform its action that has been demonstrated in studies using ingredients in isolation. Meaning the truth is in the pudding (empirical evidence from use in our orbit). Certainly, the clinical outcomes of individual ingredient or blends, have been positive by themselves.

Caralluma Fimbriata Extract (CFE)

CFE is a natural extract from an edible succulent cactus that is a well-known famine food that works as an appetite suppressant and grows wild in India.[179] Indian tribes chewed chunks of Caralluma (CF) to suppress hunger during prolonged hunts, giving the CFE its allure for use as an appetite suppressant today. Based on its history of use, it has established more empirical evidence than clinical. But rationale for CFE's inclusion in ThermAccel is the plant's historical use (i.e. surviving the test of time for suppressing hunger)[180] and its purported chemical targets (mechanism of action) following ingestion. To be sure, the extract has been safely tested with some success.[23,24,25,181]

Mechanism of Action

CFE contains pregnane glycosides (PG) that are known to exert appetite suppressant effects through enhanced satiety hypothalamic signaling.[182,183] Therefore, CFE's proposed mechanisms of actions for reducing food intake include: 1) direct intervention in appetite control at the level of the hypothalamus where the PG act;[182,183] 2) PG may act directly on adipose tissue by inhibiting adipocyte proliferation and differentiation;[184,185,186] 3) CFE may down regulate ghrelin synthesis (hunger hormone) in the stomach and subsequently neuropeptide-Y in the hypothalamus,[33] with ultimately has the same effect of suppressing appetite;[187,188,189] 4) dose dependent ability to inhibit the activity of enzymes involved in carbohydrate digestion/absorption, alpha-amylase, and alpha-glucosidase;[190] 5) CFE's PG may have selective serotonin reuptake inhibitor (SSRI)-like activity[191] (reduced serotonin [5-hydroxytryptamine; 5-HT] mediated signaling may lead to decreased signaling of satiety in the brain).[192]

Studies

In human studies using CFE, Kuriyan et al. demonstrated that by using 1 g/day for 60 days, CFE users appeared to have a suppressed appetite and reduced waist circumference when compared to placebo.[181]

While not controlling for diet and exercise, Ekta Arora et al. found that 1 g/day of CFE did not statistically effect weight loss or appetite compared to placebo.[193]

A pilot study with 43 overweight adults using 1 g/day of CFE for 12 weeks while controlling diet and exercise found significant reductions in body weight, BMI, waist circumference (2.6 inches vs 1.0 inches with placebo) appetite (palatability of test meal), blood pressure, and triglyceride levels compared to placebo suggesting CFE may be helpful when combined with diet and exercise.[194]

Griggs, et al. tested CFE on children with Prader-Willi syndrome (PWS), a genetic defect that leads to uncontrollable overeating.[25] The researchers found CFE to ease the hyperphagic behavior (abnormal appetite) in the child subjects after four weeks of treatment. A significant decrease in the category of behavior (stress related to food) was recorded by the parents along with a decrease in hyperphagia after four weeks of CFE administration at the highest dose (1,000 mg/day CFE), which is an adult recommended dose, hinting that dosage might need to be adjusted according to body weight. This pilot study supports the theory that CFE may partially act by way of a selective serotonin reuptake inhibitor (SSRI).[25,191,195,196]

Animal studies have shown CFE efficacy for appetite suppression and subsequent weight loss may be dose dependent, with a possible ideal dose of 22 mg/day per pound of body weight. This would translate to 3,300 mg/day for a 150 lb person if it was linear by species.[33,197,198] All above studies have demonstrated safety even in very high doses.[199]

In summary, based on CFEs potential appetite support through hypothalamic/nootropic actions at ~1000 mg/day, the extract may additively (beyond TA's other ingredients) support diet induced weight loss – i.e. help to ease common diet-associated struggles.

L-Theanine

L-Theanine (LT) is the major amino acid found in green tea with one cup containing ~25 mg and is often credited for green tea's (GT) calming effects, although GT also contains caffeine (35-50 mg/cup).[200,201] Green tea contains one to three percent theanine,[202] and easily crosses the blood brain barrier (BBB) and reaches peak concentrations in 30-120 minutes following ingestion.[203] LT is added to ThermAccel to maintain an LT/caffeine ratio closer to the natural ratio in GT to help preserve the anti-stress effects.[204] L-theanine has historically been used for its relaxing and anti-anxiety effects whether alone or in combination with other generally stimulatory ingredients.[200,201] (Note: L-theanine supplementation's functional absorption has been shown to be equal, based on quantity, to GT derived LT).[205]

Mechanism of Action

L-theanine (-glutamylethylamide) is an amino acid structurally similar to glutamate thus LT can bind to glutamate receptor subtypes,[206] and potentially inhibit glutamate reuptake reducing glutamate related stimulated excitation.[207,208] Other proposed mechanisms for LT's anti-stress and anxiolytic effects are L-theanine's ability to increase levels of gamma-aminobutyric acid (GABA) through its action on the glutamine (Gln) transporter inhibiting

the incorporation of extracellular Gln into neurons (in the brain, Glu is the main excitatory neurotransmitter while GABA is the main inhibitory neurotransmitter).[212] Glutamine converts to glutamic acid (Glu) via glutaminase, and Glu can be decarboxylated into γ-amino butyric acid (GABA) in neurons indicating that theanine modulates GABA production from Glu[212] and playing a principle role in reducing neuronal excitability throughout the nervous system. LT has also been shown to modulate serotonin (chemical responsible for maintaining mood balance; a deficit can lead to depression) levels in the brain.[209] Prolonged LT administration has shown additional actions, such as facilitating an increase in brain-derived neurotrophic factor (BDNF) expression in the hippocampus,[210,211] offering cognitive structural support.[206,208,212] Finally, LT may dampen stress or caffeine related stimulation increases.[213]

Theanine, Caffeine and EGCG in Combination

The balance between theanine, caffeine and catechins has been assumed to be critical for green tea to express its anti-stress effect.[214,215] Additionally, L-theanine may interact with caffeine to enhance performance in terms of attention switching and the ability to ignore distraction, which is probably a reflection of higher level cognitive activity and balancing caffeine's effects related to overstimulation including lessening caffeine's common "jitteriness" effect, especially in caffeine-containing supplements.[216,217] A systematic review and meta-analysis was conducted on 11 randomized trials involving L-theanine and EGCG alone or in combination with caffeine on cognitive function and mood. Results showed caffeine in combination with L-theanine had the greatest positive effect on outcome measures.[218] Regardless of the combination of theanine and caffeine's purported cognitive performance results, LT is contained in this product to help balance any potential over stimulation based on an individual's physiology, while preserving caffeine's favorable energy expenditure and fat oxidation actions.

Studies testing the effects of caffeine and L-theanine on cognitive functions and/or mood demonstrating positive outcomes used L-theanine doses ranging from 50-200 mg/day and therefore ThermAccel contains 100 mg in two tabs (200 mg in the maximum dose).[218,219,220,221,222] Likewise, the 100 mg of LT and 200 mg of caffeine (anhydrous only, as the EGCG extracts contains <10 mgs in two tabs of (200 and 400 mg in four tabs) ThermAccel is also consistent with the caffeine to LT relationship in standard green tea.

Product Summary

The above data demonstrates that the combined ingredients of ThermAccel enhance overall lipolytic activities, showing the ability to significantly increase metabolic rate, fat oxidation (favorable energy partitioning) and potentially daily activities (total calorie burn) while balancing the stimulatory effects of caffeine, and suppress appetite through multiple mechanisms.

Thermogenic Blend (maximum daily dose of two tabs, twice daily)

Two (2) tabs:

- ***Caffeine (200mg)***: increases metabolic rate and fat oxidation through: 1) sympathetic activation of the CNS; 2) inhibition of phosphodiesterase (PDE) to maintain higher cAMP leading to increase lipolysis, heat production and liver satiety signals; 3) stimulation of adenosine receptors, (a blockade that may also increase dopamine levels) causing a buildup of cAMP with increased cell activities
- ***Green tea extract (270 mg EGCG):*** Increases EE and fat oxidation via inhibiting the enzyme COMT (degrades epinephrine and norepinephrine while caffeine stimulates both); 2) activation of AMPK through affecting the ratios of AMP/ADP/ATP (suppressing gluconeogenesis and lipogenesis and enhancing lipolysis) and signaling the gene expression of proteins that play a role in thermogenesis and beta-oxidation
- ***Capsaicin (17 mg):*** increases EE and lipid oxidation, and reduces appetite by increasing thermogenesis through 1) stimulation of TRP channels enhancing BAT, which by activation of the SNS increases calorie burning to produce heat through the uncoupling of oxidative phosphorylation mediated by UCP1, and 2) improves lipid metabolism
- ***Sinetrol (600 mg):*** improves overall lipolytic activity via inhibiting cAMP-PDE (maintaining higher levels of cAMP) and enhancing fat oxidation and related gene expression (favorable energy partitioning)

- ***Caralluma Fimbriata (500 mg):*** appetite support through 1) hypothalamic/nootropic actions including SSRI activity and 2) ability to inhibit activity of enzymes involved in carbohydrate digestion/absorption
- ***L-Theanine (100mg):*** increases GABA levels to deliver anti-stress effects including balancing caffeine stimulation

Based on the individual ingredients unique and synergistic mechanisms of action including multiple metabolic targets, this combination may allow the user to avoid or overcome typical plateaus related to early weight loss without the normal obligatory increase in activity or decrease in food intake required to continue desired weight/fat reduction. With weight loss prescription drugs being shown to have many negative side effects (including being pulled off the market[223]) with minimal results,[15,224,225] there is high interest in products like ThermAccel and other natural sources for assisting in weight management.[15,124,129,149,152 ,226,227,228]
Note: while many of the positive weight control studies cited here were supplement usage without diet and exercise, dotFIT considers diet, exercise and evidence-based supplementation all integral components of a weight/fat loss solution, where the role of supplementation is to accelerate and ease the journey, thus enhancing motivation to continue until the goal is reached – i.e. weight control with less hardship, mindful that the small contributions that properly formulated supplements make, whether it be burning an extra 100-200 calories daily, controlling appetite and/or preserving lean body mass (all compared to a non-supplemented state) can be a very large contribution in the long-term big picture.

Typical Use

- Anyone without adverse events to stimulants and seeking to accelerate weight loss, avoid plateaus and ease the journey, including helping control appetite
- People who need a serious multiple pronged approach to weight control including a strong stimulatory effect to help increase metabolism
- Do not use if taking heart medications
- Do not use with other stimulants. Keep a minimum of four (4) hours between other stimulants including caffeine
- Discontinue after reaching body fat reduction goal or when lifestyle is under control to continue to the desired body composition goal without assistance
- Maximum dose: take four (4) tablets daily, two (2) at breakfast and two (2) with lunch with at least eight (8) ounces of fluids.
    - If sensitive to caffeine, start with two (2) tabs daily in one (1) tab doses and move to two (2) tabs max dose twice daily if comfortable

Precautions

- ThermAccel™ contains moderate amounts of central nervous system (CNS) stimulants and should be avoided by those sensitive to caffeine or who are contraindicated for caffeine-containing supplements or adverse to any other ingredient in ThermAccel. Do not mix with other stimulants, especially bitter orange[229] or ephedra.[230]
- Caffeine has no significant effect on hydration, fluid balance or electrolytes and therefore no contraindication related to hydration and exercise[231]
- If using blood thinners consult a qualified physician before use (you may submit this document) [232]

Contraindications

- ThermAccel is contraindicated for pregnant and lactating women and for those under the age of 18 due to lack of data on this population.

- Caffeine is contraindicated in hypertension, anxiety and thyroid disease. Caffeine can interfere with some medications such as lithium and MAO inhibitors. Caffeine is also contraindicated in those with cardiac arrhythmias, other forms of heart disease and peptic ulcers.
- Should not mix excessive caffeine with beta-agonists. Theoretically, concomitant use of large amounts of caffeine might increase cardiac inotropic effects of beta-agonists.[233]
- Do not mix with diuretic drugs. Theoretically excessive amounts of caffeine in combination with diuretics may increase the risk of hypokalemia. [234]
- Anyone with a liver disorder should consult their doctor before considering use at any dosage or simply not use any products containing EGCG extracts.[121,122] The EFSA report stated "From the clinical studies reviewed there is no evidence of hepatotoxicity below 800 mg EGCG/day up to 12 months." [121]
- In vitro studies suggest that capsicum may increase the effects of antiplatelet drugs.[232] Additionally, there are some self-reported incidents regarding capsicum use being associated with an increased risk of bleeding in patients taking warfarin.[235] However, clinical research shows that taking capsaicin at 400-800 mcg orally in combination with aspirin 500 mg does not decrease platelet aggregation compared with taking aspirin 500 mg alone[236]

Adverse Reactions

- **Caffeine** use may result in diuresis (increased water loss, usually in non-users) and insomnia when taken late in the day. Numerous studies on the safety of caffeine exist.[237] Caffeine abuse can cause tension, anxiety, excitability and restlessness at doses over 400 mg at one time. Doses over 1,000 mg at one time can elicit toxicity symptoms.[238,239] Because ThermAccel has 200 mg/serving, adverse effects may occur in sensitive individuals. Taking ThermAccel with other stimulants is not advised.
- **Caralluma fimbriata** is safe at the amounts found in ThermAccel with no known adverse events.[181,199]
- **Sinetrol** has no known adverse reaction at the dose in ThermAccel[32]
- **EGCG**: typical doses range from one to 10 cups of green tea per day without any adverse events.[240] Very high intake of green tea may cause nausea, abdominal bloating and pain, flatulence, and diarrhea. It can also cause central nervous system stimulation and adverse effects such as dizziness, insomnia, fatigue, agitation, tremors, restlessness, and confusion. These effects are more common with higher doses of green tea or green tea extract, equivalent to 5-6 liters of tea per day.[241]
- **Capsaicin:** very high doses may cause gastrointestinal stress including bloating.[151] There are no known adverse reactions to capsaicin in the dosage found in ThermAccel.[148,149,152]

Upper Limit/Toxicity

- None of the compounds in ThermAccel have an established upper limit or approach toxic levels.

Summary

Purpose

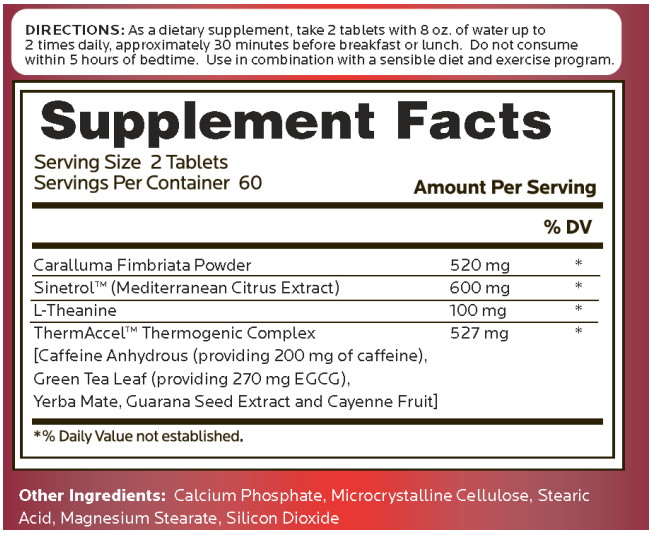
- Accelerate fat loss by increasing exercise and non-exercise induced calorie burning including daily activities through a balanced stimulant effect and contribute to appetite support during energy restriction.
- Reduce the typical hardships associated with weight/fat reduction including avoiding or breaking through plateaus. Maximum dose of four (4) tabs/day is an aggressive adjunct to diet induced weight/fat loss.

Unique Features

- Formula and recommendations have no competitor based on its multiple body fat reduction targets, which are designed to aggressively attack the body's natural defenses against weight loss.

- The thermogenic blend delivers a superior but balanced stimulatory effect thus eliminating the end of day "burnout" associated with other thermogenic products.
- ThermAccel™ contains Sinetrol™ by Fytexia, whom was awarded Best Natural Wellness Product Provider
- ThermAccel will deliver all the ingredients by means of a two-stage technology involving microspheres and macrospheres, providing immediate and prolonged activity throughout the day.
- Can be used alone or as part of the dotFIT 90 Day Weight Loss Solution (aka LeanPak90)
- Manufactured in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC.

Supplement Facts



DIRECTIONS: As a dietary supplement, take 2 tablets with 8 oz. of water up to 2 times daily, approximately 30 minutes before breakfast or lunch. Do not consume within 5 hours of bedtime. Use in combination with a sensible diet and exercise program.

Supplement Facts

Serving Size 2 Tablets
Servings Per Container 60

	Amount Per Serving	% DV
Caralluma Fimbriata Powder	520 mg	*
Sinetrol™ (Mediterranean Citrus Extract)	600 mg	*
L-Theanine	100 mg	*
ThermAccel™ Thermogenic Complex [Caffeine Anhydrous (providing 200 mg of caffeine), Green Tea Leaf (providing 270 mg EGCG), Yerba Mate, Guarana Seed Extract and Cayenne Fruit]	527 mg	*

*% Daily Value not established.

Other Ingredients: Calcium Phosphate, Microcrystalline Cellulose, Stearic Acid, Magnesium Stearate, Silicon Dioxide

References

[1] Matthew G. Engel, Hua J. Kern, J. Thomas Brenna and Susan H. Mitmesser. Micronutrient Gaps in Three commercial Weight-Loss Diet Plans. Nutrients 2018, 10, 108; doi:10.3390/nu10010108

[2] Kraschnewski JL, Boan J, Esposito J et al. Long-term weight loss maintenance in the United States. Int J bes (Lond) 2010; 34: 1644–1654

[3] Pedersen S, Sniehotta FF, Sainsbury K, Evans EH, Marques MM, Stubbs RJ, Heitmann BL, Lähteenmäki L. The complexity of self-regulating food intake in weight loss maintenance. A qualitative study among short- and long-term weight loss maintainers. Soc Sci Med. 2018 May 6;208:18-24. doi: 10.1016/j.socscimed.2018.05.016. [Epub ahead of print]

[4] Juen Guo, Danielle C Brager, and Kevin D Hall. Simulating long-term human weight-loss dynamics in response to calorie restriction. Am J Clin Nutr 2018;107:558–565. Printed in USA

[5] Jastroch M, Divakaruni AS, Mookerjee S, Treberg JR, Brand MD: Mitochondrial proton and electron leaks. Essays Biochem 2010, 47:53–67.

[6] Rolfe DF, Brand MD: Contribution of mitochondrial proton leak to skeletal muscle respiration and to standard metabolic rate. Am J Physiol 1996, 271:C1380–1389.

[7] Herman Pontzer, et al. Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans. Current Biology 26, 410–417, February 8, 2016

[8] Thomas DM , Ivanescu AE , Martin CK , Heymsfield SB , Marshall K , Bodrato VE , Williamson DA , Anton SD , Sacks FM , Ryan D , Bray GA. Predicting successful long-term weight loss from short-term weight-loss outcomes: new insights from a dynamic energy balance model (the POUNDS Lost study). Am J Clin Nutr. 2015 Mar;101(3):449-54. doi: 10.3945/ajcn.114.091520. Epub 2014 Dec 24

[9] Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. Am J Physiol Endocrinol Metab. 2010; 298(3): E449-66.

[10] Heymsfield SB, Thomas D, Nguyen AM, Peng JZ, Martin C, Shen W, et al. Voluntary weight loss: systematic review of early phase body composition changes. Obes Rev. 2010

[11] Kim B: Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid 2008, 18:141–144.

[12] Andrew Pardue, Eric T. Trexler, and Lisa K. Sprod. Case Study: Unfavorable But Transient Physiological Changes During Contest Preparation in a Drug-Free Male Bodybuilder. International Journal of Sport Nutrition and Exercise Metabolism, 2017, 27, 550 -559

[13] Strohacker K, McCaffery JM, Maclean PS, Wing RR: Adaptations of leptin, ghrelin or insulin during weight loss as predictors of weight regain: a review of current literature. Int J Obes 2013:1–9. http://www.nature.com/ijo/journal/vaop/ncurrent/full/ijo2013118a.html.

[14] Eric T Trexler1, Abbie E Smith-Ryan1* and Layne E Norton . Metabolic adaptation to weight loss: implications for the athlete. Trexler et al. Journal of the International Society of Sports Nutrition 2014, 11:7 http://www.jissn.com/content/11/1/7

[15] Kari Johansson, Martin Neovius, and Erik Hemmingsson Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014;99:14–23. Printed in USA. _ 2014 American Society for Nutrition

[16] I-Min Lee, MBBS, ScD; Luc Djoussé, MD, DSc; Howard D. Sesso, ScD; Lu Wang, MD, PhD; Julie E. Buring, ScD. Physical Activity and Weight Gain Prevention JAMA. 2010;303(12):1173-1179. doi:10.1001/jama.2010.312

[17] Fredrik Bertz, Hilde K Brekke, Lars Ellegård, Kathleen M Rasmussen, Margareta Wennergren, and Anna Winkvist. Diet and exercise weight-loss trial in lactating overweight and obese women. Am J Clin Nutr 2012;96:698–705. Printed in USA. _ 2012 American Society for Nutrition

[18] A Malhotra,T Noakes, S Phinney. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. Br J Sports Med 2015;0:1–2. doi:10.1136/bjsports-2015-094911

[19] Lukas Schwingshackl, Sofia Dias, Georg Hoffmann. Impact of long-term lifestyle programmes on weight loss and cardiovascular risk factors in overweight/obese participants: a systematic review and network meta-analysis. Syst Rev. 2014; 3: 130 Published online 2014 Oct 30. doi: 10.1186/2046-4053-3-130

[20] Roger A. Vaughan, Carole A. Conn, and Christine M. Mermier. Effects of Commercially Available Dietary Supplements on Resting Energy Expenditure: A Brief Report. ISRN Nutrition Volume 2014, Article ID 650264, 7 pages http://dx.doi.org/10.1155/2014/650264

[21] Mahdieh Golzarand, Karamollah Toolabi, Mohadeseh Aghasia. Effect of green tea, caffeine and capsaicin supplements on the anthropometric indices: A meta-analysis of randomized clinical trials. Journal of Functional Foods Volume 46, July 2018, Pages 320–328
[22] Sidney J. Stohs and Vladimir Badmaev. A Review of Natural Stimulant and Non-stimulant Thermogenic Agents. PHYTOTHERAPY RESEARCH. Phytother. Res. 30: 732–740 (2016) Published online 9 February 2016 in Wiley Online Library
[23] Astell KJ , Mathai ML, Su XQ. A review on botanical species and chemical compounds with appetite suppressing properties for body weight control. Plant Foods Hum Nutr. 2013 Sep;68(3):213-21. doi: 10.1007/s11130-013-0361-1.
[24] Astell KJ , Mathai ML, Su XQ. Plant extracts with appetite suppressing properties for body weight control: a systematic review of double blind randomized controlled clinical trials. Complement Ther Med. 2013 Aug;21(4):407-16. doi: 10.1016/j.ctim.2013.05.007. Epub 2013 Jun 24.
[25] Joanne L. Griggs, Xiao Q. Su, and Michael L. Mathai. Caralluma Fimbriata Supplementation Improves the Appetite Behavior of Children and Adolescents with Prader-Willi Syndrome. N Am J Med Sci. 2015 Nov; 7(11): 509–516. doi: 10.4103/1947-2714.170611
[26] Eynav Harpaz, Snait Tamir, Ayelet Weinstein and Yitzhak Weinstein. The effect of caffeine on energy balance DOI 10.1515/jbcpp-2016-0090. Received June 13, 2016; accepted October 11, 2016; previously published online November 8, 2016
[27] Sun-Young Kim, Mi-Ra Oh, Min-Gul Kim, Han-Jeoung Chae, et al. Anti-obesity effects of Yerba Mate (Ilex Paraguariensis): a randomized, double-blind, placebo-controlled clinical trial. BMC Complementary and Alternative Medicine (2015) 15:338 DOI 10.1186/s12906-015-0859-1
[28] Natália da Silva Lima et al. Guarana (Paullinia cupana) Stimulates Mitochondrial Biogenesis in Mice Fed High-Fat Diet. Nutrients 2018, 10, 165; doi:10.3390/nu10020165
[29] Dylan O'Neill Rothenberg 1, Caibi Zhou 2 and Lingyun Zhang. A Review on the Weight-Loss Effects of Oxidized Tea Polyphenols. Molecules 2018, 23, 1176; doi:10.3390/molecules23051176
[30] Rigamonti AE, Casnici C, Marelli O, De Col A, et al. Acute administration of capsaicin increases resting energy expenditure in young obese subjects without affecting energy intake, appetite, and circulating levels of orexigenic/anorexigenic peptides. Nutr Res. 2018 Apr;52:71-79. doi: 10.1016/j.nutres.2018.02.002. Epub 2018 Feb 10.
[31] Ahmad Alkhatib, Marcos Seijo, Eneko Larumbe and Fernando Naclerio. Acute effectiveness of a "fat-loss" product on substrate utilization, perception of hunger, mood state and rate of perceived exertion at rest and during exercise. Journal of the International Society of Sports Nutrition (2015) 12:44 DOI 10.1186/s12970-015-0105-8
[32] Constantin Dallas, Alain Gerbi, Yves Elbez, Philippe Caillard, Nicolas Zamaria and Maurice Cloarec. Clinical Study to Assess the Efficacy and Safety of a Citrus Polyphenolic Extract of Red Orange, Grapefruit, and Orange (Sinetrol-XPur) on Weight Management and Metabolic Parameters in Healthy Overweight Individuals. PHYTOTHERAPY RESEARCH Phytother. Res. (2013) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ptr.4981
[33] Vitalone A, Di Sotto A, Mammola CL, et al. Phytochemical analysis and effects on ingestive behaviour of a Caralluma fimbriata extract. Food Chem Toxicol. 2017 Oct;108(Pt A):63-73. doi: 10.1016/j.fct.2017.07.027. Epub 2017 Jul 13.
[34] Meshail Okla, et al. Dietary Factors Promoting Brown and Beige Fat Development and Thermogenesis. Adv Nutr 2017;8:473–83; doi:10.3945/an.116.014332
[35] Acheson KJ, Gremaud G, Meirim I, et al. Metabolic effects of caffeine in humans: lipid oxidation or futile cycling? Am J Clin Nutr 2004;79:40-6
[36] Koot P, Deurenberg P. Comparison of changes in energy expenditure and body temperatures after caffeine consumption. Ann Nutr Metab. 1995;39(3):135-42.
[37] Diepvens K, Westerterp KR, Westerterp-Plantenga MS. Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin and green tea. Am J Physiol Regul Integr Comp Physiol. 2006 Jul 13; [Epub ahead of print]
[38] Bracco D, Ferrarra JM, Arnaud MJ, Jequier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. Am J Physiol. 1995 Oct;269(4 Pt 1):E671-8.
[39] Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and post obese human volunteers. Am J Clin Nutr. 1989 Jan;49(1):44-50.
[40] Rick Hursel and Margriet S Westerterp-Plantenga. Catechin- and caffeine-rich teas for control of body weight in humans. Am J Clin Nutr 2013;98(suppl):1682S–93S
[41] Hursel R, Westerterp-Plantenga MS. Thermogenic ingredients and body weight regulation. Int J Obes (Lond). 2010 Apr;34(4):659-69. Epub 2010 Feb 9. Review.

[42] Campbell et al. Journal of the International Society of Sports Nutrition (2016) 13:13 DOI 10.1186/s12970-016-0123-1
[43] Ziegenfuss TN, et al. Effect of a Multi-Nutrient Over-the-Counter Supplement on Changes in Metabolic Rate and Markers of Lipolysis. J Diet Suppl. 2017 May 4;14(3):288-302. Epub 2016 Sep 9
[44] Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7- trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci 2010;75:R77–87.
[45] Suleman A, Siddiqui NH. Haemodynamic and cardiovascular effects of caffeine. Medicine On Line Int J Medicine 2000. www.priory.com/pharmol/caffeine
[46] Sinclair CJ, Geiger JD. Caffeine use in sports. A pharmacological review. J Sports Med Phys Fitness 2000;40:71-9
[47] Haller CA, Jacob P 3rd, Benowitz NL. Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use. Clin Pharmacol Ther 2002;71:421-32
[48] Sayed Hossein Davoodi, Seyed Javad Hajimiresmaiel, Marjan Ajami, et al. Caffeine Treatment Prevented from Weight Regain after Calorie Shifting Diet Induced Weight Loss. Iranian Journal of Pharmaceutical Research (2014), 13 (2): 707-718. Copyright © 2014 by School of Pharmacy
[49] Bracco D, Ferrarra JM, Arnaud MJ, Jequier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. Am J Physiol 1995;269:E671–8.
[50] Vandenberghe C , St-Pierre, et al. Caffeine intake increases plasma ketones: an acute metabolic study in humans. Can J Physiol Pharmacol. 2017 Apr;95(4):455-458. doi: 10.1139/cjpp-2016-0338. Epub 2016 Nov 25
[51] Messina G, De Luca V, Viggiano A, Ascione A, Iannaccone T, Chieffi S, et al. Autonomic nervous system in the control of energy balance and body weight: personal contributions. Neurol Res Int 2013:1–5.
[52] Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. Eur J Clin Nutr 1999;53:831-9
[53] Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. Am J Clin Nutr. 1999 Dec;70(6):1040-5.
[54] Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J. Green tea and thermogenesis: interactions between catechinpolyphenols, caffeine and sympathetic activity. Int J Obes Relat Metab Disord. 2000 Feb;24(2):252-8.
[55] Diepvens K, Westerterp KR, Westerterp-Plantenga MS. Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin, and green tea. Am J Physiol Regul Integr Comp Physiol. 2007 Jan;292(1):R77-85. Epub 2006 Jul 13. Review.
[56] Janssens PL, Hursel R, Westerterp-Plantenga MS Long-Term Green Tea Extract Supplementation Does Not Affect Fat Absorption, Resting Energy Expenditure, and Body Composition in Adults. J Nutr. 2015 Mar 4. pii: jn.114.207829. [Epub ahead of print]
[57] Valentín E. Fernández-Elías, Juan Del Coso, Nassim Hamouti, et al. Ingestion of a Moderately High Caffeine Dose Before Exercise Increases Postexercise Energy Expenditure. International Journal of Sport Nutrition and Exercise Metabolism, 2015, 25, 46 -53 http://dx.doi.org/10.1123/ijsnem.2014-0037
[58] Schubert MM , Hall S , Leveritt M , Grant G , Sabapathy S , Desbrow B . Caffeine consumption around an exercise bout: effects on energy expenditure, energy intake, and exercise enjoyment. J Appl Physiol (1985). 2014 Oct 1;117(7):745-54. doi: 10.1152/japplphysiol.00570.2014. Epub 2014 Aug 14.
[59] Acheson KJ, Zahorska-Markiewicz B, Pittet P, Anantharaman K, Jequier E. Caffeine and coffee: their influence on metabolic rate and substrate utilization in normal weight and obese individuals. Am J Clin Nutr 1980;33:989–97
[60] Kamimori GH, Somani SM, Knowlton RG, Perkins RM. The effects of obesity and exercise on the pharmacokinetics of caffeine in lean and obese volunteers. Eur J Clin Pharmacol 1987;31:595–600
[61] Silva JE. Thermogenic mechanisms and their hormonal regulation. Physiol Rev 2006;86:435–64.
[62] Peirce V, Carobbio S, Vidal-Puig A. The different shades of fat. Nature 2014;510:76–83
[63] Kogure A, Sakane N, Takakura Y, Umekawa T, Yoshioka K, Nishino H, et al. Effects of caffeine on the uncoupling protein family in obese yellow KK mice. Clin Expert Pharmacol Physiol 2002;29:391–4
[64] Matteis R, Arch J, Petroni M, Ferrari D, Cinti S, Stock M. Immunohistochemical identification of the β3-adrenoceptor in intact human adipocytes and ventricular myocardium effect of obesity and treatment with ephedrine and caffeine. Int J Obesity 2002;26:1442–50.
[65] Yoneshiro T, Matsushita M, Hibi M, et al. Tea catechin and caffeine activate brown adipose tissue and increase cold-induced thermogenic capacity in humans. Am J Clin Nutr. 2017 Apr;105(4):873-881. doi: 10.3945/ajcn.116.144972. Epub 2017 Mar 8

[66] Acar-Tek N, Ağagündüz D, Ayhan B. Effect of Green Coffee Consumption on Resting Energy Expenditure, Blood Pressure, and Body Temperature in Healthy Women: A Pilot Study. J Am Coll Nutr. 2018 May 3:1-10. doi: 10.1080/07315724.2018.1461147. [Epub ahead of print]
[67] Silveira R, Andrade-Souza VA, et al. Caffeine Increases Work Done above Critical Power, but Not Anaerobic Work. Med Sci Sports Exerc. 2018 Jan;50(1):131-140. doi: 10.1249/MSS.0000000000001408
[68] R. Hursel,W. Viechtbauer, A.G. Dulloo et al., "The effects of catechin rich teas and caffeine on energy expenditure and fat oxidation: a meta-analysis," Obesity Reviews, vol. 12,no. 7, pp. e573– e581, 2011.
[69] A. G. Dulloo, "The search for compounds that stimulate thermogenesis in obesity management: from pharmaceuticals to functional food ingredients," Obesity Reviews, vol. 12, no. 10, pp. 866–883, 2011
[70] Bérubé-Parent S, Pelletier C, Doré J, Tremblay A. Effects of encapsulated green tea and Guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men. Br J Nutr. 2005 Sep;94(3):432-6.
[71] Carter BE, Drewnowski A. Beverages containing soluble fiber, caffeine, and green tea catechins suppress hunger and lead to less energy consumption at the next meal. Appetite 2012;59:755–61
[72] Schubert MM, Grant G, Horner K, et al. Coffee for morning hunger pangs. An examination of coffee and caffeine on appetite, gastric emptying, and energy intake. Appetite. 2014 Dec;83:317-26. doi: 10.1016/j.appet.2014.09.006. Epub 2014 Sep 16
[73] Schubert MM, Irwin C, Seay RF, Clarke HE. Caffeine, coffee, and appetite control: a review. Int J Food Sci Nutr. 2017 Dec;68(8):901-912. doi: 10.1080/09637486.2017.1320537. Epub 2017 Apr 27
[74] Womack et al. The influence of a CYP1A2 polymorphism on the ergogenic effects of caffeine. Journal of the International Society of Sports Nutrition 2012, 9:7
[75] Duygu Türközü & Nilüfer Acar Tek (2015): A Minireview of Effects of Green Tea on Energy Expenditure, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2014.986672
[76] Westerterp-Plantenga, M.S., Lejeune, M.P., Kovacs, E.M. (2005). Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obes Res
13(7): 1195-204
[77] Peter Peeling and Martyn J. Binnie, et al. Evidence-Based Supplements for the Enhancement of Athletic Performance. International Journal of Sport Nutrition and Exercise Metabolism, 2018, 28, 178-187
[78] Brahma N. Singh1, Sharmila Shankar2, and Rakesh K. Srivastava. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol. 2011 December 15; 82(12): 1807–1821. doi:10.1016/j.bcp.2011.07.093
[79] Jane J. Y. Kim,1 Yi Tan,1 Linda Xiao,1 Ya-Li Sun,2 and Xianqin Qu1. Green Tea Polyphenol Epigallocatechin-3-Gallate Enhance Glycogen Synthesis and Inhibit Lipogenesis in Hepatocytes. BioMed Research International Volume 2013, Article ID 920128, 8 pages http://dx.doi.org/10.1155/2013/920128
[80] Mi Y, Qi G, Fan R. et. al. EGCG ameliorates high-fat- and high-fructose-induced cognitive defects by regulating the IRS/AKT and ERK/CREB/BDNF signaling pathways in the CNS. FASEB J. 2017 Nov;31(11):4998-5011. doi: 10.1096/fj.201700400RR. Epub 2017 Jul 24
[81] Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. Cancer research. 2006; 66:2500–5. [PubMed: 16510563]
[82] Rains, TM, Agarwal, S, and Maki, KC. Antiobesity effects of green tea catechins: A mechanistic review. J Nutr Biochem 22: 1–7, 2011
[83] Samavat H, Newman AR, et al. Effects of green tea catechin extract on serum lipids in postmenopausal women: a randomized, placebo-controlled clinical trial. Am J Clin Nutr. 2016 Dec;104(6):1671-1682. Epub 2016 Nov 2.
[84] Edward Jo, Kiana L. Lewis, et al. Dietary Caffeine and Polyphenol Supplementation Enhances Overall Metabolic Rate and Lipid Oxidation at Rest and After a Bout of Sprint Interval Exercise. Journal of Strength and Conditioning Research. 30(7)/1871–1879, Volume 30, 7, July 2016
[85] Jurgens TM, Whelan AM, Killian L, Doucette S, Kirk S, Foy E. Green tea for weight loss and weight maintenance in overweight or obese adults. Cochrane Database Syst Rev. 2012; 12:CD008650
[86] Chen D, Wang CY, Lambert JD, Ai N, et al. Inhibition of human liver catechol-O-methyltransferase by tea catechins and their metabolites: structure-activity relationship and molecular-modeling studies. Biochem Pharmacol. 2005; 69:1523–1531. [PubMed: 15857617]
[87] Murase, T, Misawa, K, Haramizu, S, and Hase, T. Catechin-induced activation of the LKB1/AMP-activated protein kinase pathway. Biochem Pharmacol 78: 78–84, 2009

[88] Chung S. Yang, Jinsong Zhang, et al. Mechanisms of Body Weight Reduction and Metabolic Syndrome Alleviation by Tea. Mol Nutr Food Res. 2016 January; 60(1): 160–174. doi:10.1002/mnfr.201500428
[89] Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. J Clin Invest. 2006; 116:1776–1783. [PubMed: 16823475]
[90] Bae UJ, Park J, et al. Epigallocatechin-3-Gallate-Rich Green Tea Extract Ameliorates Fatty Liver and Weight Gain in Mice Fed a High Fat Diet by Activating the Sirtuin 1 and AMP Activating Protein Kinase Pathway. Am J Chin Med. 2018;46(3):617-632. doi: 10.1142/S0192415X18500325. Epub 2018 Mar 29
[91]Murase T, Misawa K, Haramizu S, Hase T. Catechin-induced activation of the LKB1/AMP-activated protein kinase pathway. Biochem Pharmacol. 2009; 78:78–84. [PubMed: 19447226]
[92] Zhou J, Farah BL, Sinha RA, Wu Y, et al. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, stimulates hepatic autophagy and lipid clearance. PLoS One. 2014; 9:e87161. [PubMed: 24489859
[93] Kim HS, Quon MJ, Kim JA. New insights into the mechanisms of polyphenols beyond antioxidant properties, lessons from the green tea polyphenol, epigallocatechin 3-gallate. Redox Biol. 2014; 2:187–195. [PubMed: 24494192]
[94] Huang J, Wang Y, Xie Z, Zhou Y, et al. The anti-obesity effects of green tea in human intervention and basic molecular studies. Eur J Clin Nutr. 2014; 68:1075–1087. [PubMed: 25074392
[95] Yang, X.; Kong, F. Effects of tea polyphenols and different teas on pancreatic _-amylase activity in vitro. LWT-Food Sci. Technol. 2016, 66, 232–238
[96] Jin JS, Touyama M, Hisada T, Benno Y. Effects of green tea consumption on human fecal microbiota with special reference to Bifidobacterium species. Microbiol Immunol. 2012; 56:729–739. [PubMed: 22924537
[97] Reiner Jumpertz, Duc Son Le, Peter J Turnbaugh, Cathy Trinidad, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr 2011;94:58–65. Printed in USA. _ 2011 American Society for Nutrition
[98] Angelakis E, Armougom F, Million M, Raoult D. The relationship between gut microbiota and weight gain in humans. Future Microbiol 2012; 7: 91-109 [PMID: 22191449 DOI:10.2217/fmb.11.142]
[99] Besten, G.D.; Bleeker, A.; Gerding, A.; Eunen, K.V.; Havinga, R.; Dijk, T.H.; Bakker, B.M. Short-chain fatty acids protect against high-fat diet–Induced obesity via a PPAR -dependent switch from lipogenesis to fat oxidation. Diabetes 2015, 64, 2398–2408
[100] Sae-Tan, S.; Grove, K.A.; Kennett, M.J.; Lambert, J.D. (?)-Epigallocatechin-3-gallate increases the expression of genes related to fat oxidation in the skeletal muscle of high fat-fed mice. Food Funct. 2011, 2, 111–116
[101] Lin J, Della-Fera MA, Baile CA. Green tea polyphenol epigallocatechin gallate inhibits adipogenesis and induces apoptosis in 3T3-L1 adipocytes. Obes Res. 2005 Jun;13(6):982-90.
[102] Welker, T.L.; Wan, X.; Zhou, Y.; Yang, Y.; Overturf, K.; Barrows, F.; Liu, K. Effect of dietary green tea supplementation on growth, fat content, and muscle fatty acid profile of rainbow trout (Oncorhynchus mykiss). Aquac. Int. 2016, 25, 1073–1094
[103] Murase T, Nagasawa A, Suzuki J, Hase T, Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. Int J Obes Relat Metab Disord. 2002 Nov;26(11):1459-64.
[104] Hursel R, Viechtbauer W, Westerterp-Plantenga MS. The effects of green tea on weight loss and weight maintenance: a meta-analysis. Int J Obes (Lond). 2009 Sep;33(9):956-61. doi: 10.1038/ijo.2009.135. Epub 2009 Jul 14
[105] Kapoor MP , Sugita M , Fukuzawa Y , Okubo T. Physiological effects of epigallocatechin-3-gallate (EGCG) on energy expenditure for prospective fat oxidation in humans: A systematic review and meta-analysis. J Nutr Biochem. 2017 May;43:1-10. doi: 10.1016/j.jnutbio.2016.10.013. Epub 2016 Nov 2
[106] Berube-Parent S, Pelletier C, Dore J, Tremblay A. Effects of encapsulated green tea and Guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men. Br J Nutr. 2005 Sep;94(3):432- 6.
[107] Nagao T, Meguro S, Soga S, Otsuka A, Tomonobu K, Fumoto S, Chikama A, Mori K, Yuzawa M, Watanabe H, Hase T, Tanaka Y, Tokimitsu I, Shimasaki H, Itakura H. Tea catechins suppress accumulation of body fat in humans. J Oleo Sci 2001; 50: 717– 728.
[108] Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. Am J Clin Nutr. 1999 Dec;70(6):1040-5.
[109] Zheng G, Sayama K, Okubo T, Juneja LR, Oguni I. Anti-obesity effects of three major components of green tea, catechins, caffeine and theanine, in mice. In Vivo. 2004 Jan-Feb;18(1):55-62.
[110] Maki KC, Reeves MS, Farmer M, Yasunaga K, Matsuo N, Katsuragi Y, Komikado M, Tokimitsu I, Wilder D, Jones F, Blumberg JB, Cartwright Y. Green tea catechin consumption enhances exercise-induced abdominal fat loss in overweight and obese adults. J Nutr. 2009 Feb;139(2):264-70. Epub 2008 Dec 11.

[111] Sae-Tan S, Rogers CJ, Lambert JD. Voluntary exercise and green tea enhance the expression of genes related to energy utilization and attenuate metabolic syndrome in high fat fed mice. Mol Nutr Food Res. 2014 May;58(5):1156-9. doi: 10.1002/mnfr.201300621. Epub 2013 Dec 27
[112] Nagi B. Kumar, Roshni Patel, et al. Long-term supplementation of decaffeinated green tea extract does not modify body weight or abdominal obesity in a randomized trial of men at high risk for prostate cancer. Oncotarget, 2017, Vol. 8, (No. 58), pp: 99093-99103
[113] Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr. 2010; 91:73
[114] Baladia E, Basulto J, Manera M , Martínez R , Calbet D. [Effect of green tea or green tea extract consumption on body weight and body composition; systematic review and meta-analysis]. Nutr Hosp. 2014 Mar 1;29(3):479-90. doi: 10.3305/nh.2014.29.3.7118
[115] Justin D Roberts, Michael G Roberts, Michael D Tarpey, Jack C Weekes, and Clare H Thomas. The effect of a decaffeinated green tea extract formula on fat oxidation, body composition and exercise performance. Roberts et al. Journal of the International Society of Sports Nutrition (2015) 12:1. DOI 10.1186/s12970-014-0062-7
[116] Shixian Q, VanCrey B, Shi J, Kakuda Y, Jiang Y. Green tea extract thermogenesis-induced weight loss by epigallocatechin gallate inhibition of catechol-O-methyltransferase. J Med Food 2006;9:451–8.
[117] Auvichayapat P, Prapochanung M, Tunkamnerdthai O, Sripanidkulchai BO, Auvichayapat N, Thinkhamrop B, Kunhasura S, Wongpratoom S, Sinawat S, Hongprapas P. Effectiveness of green tea on weight reduction in obese Thais: a randomized, controlled trial. Physiol Behav 2008;93:486–91
[118] Hodgson, J.M.,Puddey, I.B., Burke, V., Croft, K.D. (2006). Is reversal of endothelial dysfunction by tea related to flavonoid metabolism? Br J Nutr 95(1): 14-7
[119] Lucía Cristina Vázquez Cisneros, Patricia López-Uriarte, et al. Effects of green tea and its epigallocatechin (EGCG) content on body weight and fat mass in humans: a systematic review. Nutr Hosp. 2017; 34(3):731-737 ISSN 0212-1611 - CODEN NUHOEQ S.V.R. 318
[120] Yates AA, Erdman JW Jr, Shao A, Dolan LC, Griffiths JC. Bioactive nutrients - Time for tolerable upper intake levels to address safety. Regul Toxicol Pharmacol. 2017;84:94-101
[121] Younes M, Aggett P, Aguilar F, et al. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Scientific opinion on the safety of green tea catechins. EFSA Journal 2018;16(4):5239
[122] Mielgo-Ayuso, et al. Effects of dietary supplementation with epigallocatechin-3-gallate on weight loss, energy homeostasis, cardiometabolic risk factors and liver function in obese women: randomised, double-blind, placebo-controlled clinical trial. Br J Nutr. 2014 Apr 14;111(7):1263-71. doi: 0.1017/S0007114513003784. Epub 2013 Dec 3.
[123] Dostal AM, et al. The safety of green tea extract supplementation in postmenopausal women at risk for breast cancer: results of the Minnesota Green Tea Trial. Food Chem Toxicol. 2015 Sep;83:26-35. doi: 10.1016/j.fct.2015.05.019. Epub 2015 Jun 5.
[124] Jordan Outlaw, Colin Wilborn, Abbie Smith, et al. Effects of ingestion of a commercially available thermogenic dietary supplement on resting energy expenditure, mood state and cardiovascular measures. Journal of the International Society of Sports Nutrition 2013, 10:25 Page 2 of 8 http://www.jissn.com/content/10/1/25
[125] Jeukendrup AE , Randell R. Fat burners: nutrition supplements that increase fat metabolism. Obes Rev. 2011 Oct;12(10):841-51. doi: 10.1111/j.1467-789X.2011.00908.x.
[126] Smith AE, Lockwood CM, Moon JR, Kendall KL, Fukuda DH, Tobkin SE, Cramer JT, Stout JR. Physiological effects of caffeine, epigallocatechin-3-gallate, and exercise in overweight and obese women. Appl Physiol Nutr Metab. 2010 Oct;35(5):607-16. doi: 10.1139/H10-056.
[127] Lijuan Sun, et al. Capsinoids activate brown adipose tissue (BAT) with increased energy expenditure associated with subthreshold 18-fluorine fluorodeoxyglucose uptake in BAT-positive humans confirmed by positron emission tomography scan. Am J Clin Nutr 2018;107:62–70. Printed in USA
[128] Ludy MJ, Moore GE, Mattes RD. The effects of capsaicin and capsiate on energy balance: critical review and meta-analyses of studies in humans. Chem Senses 2012;37:103–21
[129] Yoneshiro T, Aita S, Kawai Y, Iwanaga T, Saito M. Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. Am J Clin Nutr 2012;95:845–50.
[130] Whiting S, Derbyshire E, Tiwari BK. Capsaicinoids and capsinoids. A potential role for weight management? A systematic review of the evidence. Appetite. 2012 Oct;59(2):341-8. doi: 10.1016/j.appet.2012.05.015. Epub 2012 May 22

[131] Takeshi Yoneshiro,1 Sayuri Aita,2 Mami Matsushita, et al. Recruited brown adipose tissue as an anti-obesity agent in humans. J Clin Invest. 2013;123(8):3404–3408. doi:10.1172/JCI67803
[132] van Marken Lichtenbelt WD Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009;360:1500–8
[133] Cypess AM, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509–1517.
[134] Abdul G. Dulloo. Translational issues in targeting brown adipose tissue thermogenesis for human obesity management. Ann. N.Y. Acad. Sci. ISSN 0077-8923
[135] Nakamura K. Central circuitries for body temperature regulation and fever. Am J Physiol Regul Integr Comp Physiol. 2011;301(5):R1207–R1228.
[136] Shintaku K, et al. Activation of transient receptor potential A1 by a non-pungent capsaicin like compound, capsiate. Br J Pharmacol. 2011; 165(5):1476–1486.
[137] Chen J, Li L, Li Y, Liang X, Sun Q, Yu H, Zhong J, Ni Y, Chen J, Zhao Z, Gao P, Wang B, Liu D, Zhu Z, Yan Z. Activation of TRPV1 channel by dietary capsaicin improves visceral fat remodeling through connexin43-mediated Ca2+ Influx. Cardiovasc Diabetol. 2015 Feb 13;14:22. doi: 10.1186/s12933-015-0183-6
[138] Chopan M, Littenberg B (2017) The Association of Hot Red Chili Pepper Consumption and Mortality: A Large Population-Based Cohort Study. PLoS ONE 12(1): e0169876. doi:10.1371/journal.pone.0169876
[139] Zsombok A. Vanilloid receptorsÐdo they have a role in whole body metabolism? Evidence from TRPV1. Journal of diabetes and its complications. 2013; 27(3):287±92. Epub 2013/01/22. doi: 10.1016/j.jdiacomp.2012.11.006
[140] Zsiborás C, et al. Capsaicin and capsiate could be appropriate agents for treatment of obesity: A meta-analysis of human studies. Crit Rev Food Sci Nutr. 2018 Jun 13;58(9):1419-1427. doi: 10.1080/10408398.2016.1262324. Epub 2017 Jun 12.
[141] Elaine Drummond, Ph.D. Capsinoids as Natural Energy Regulators for Enhanced Athletic Endurance & Weight Management. Glanbia Nutritionals. CapsiAtra® White Paper August 2015
[142] Snitker S, Fujishima Y, Shen H, Ott S, Pi-Sunyer X, Furuhata Y, Sato H, Takahashi M. Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. Am J Clin Nutr. 2009 Jan;89(1):45-50. Epub 2008 Dec 3.
[143] Westerterp-Plantenga M, Diepvens K, Joosen AM, Bérubé-Parent S, Tremblay A. Metabolic effects of spices, teas, and caffeine. Physiol Behav. 2006 Aug 30;89(1):85-91. Epub 2006 Mar 30. Review.
[144] Belza A, Jessen AB. Bioactive food stimulants of sympathetic activity: effect on 24-h energy expenditure and fat oxidation. Eur J Clin Nutr. 2005 Jun;59(6):733-41.
[145] Josse AR, Sherriffs SS, Holwerda AM, Andrews R, Staples AW, Phillips SM. Effects of capsinoid ingestion on energy expenditure and lipid oxidation at rest and during exercise. Nutr Metab (Lond). 2010 Aug 3;7:65.
[146] Virtanen, K.A. et al. 2009. Functional brown adipose tissue in healthy adults.N. Engl. J. Med. 360: 1518–1525.
[147] Gerngross C, Schretter J, Klingenspor M, Schwaiger M, Fromme T. Active brown fat during 18FDG-PET/CT imaging defines a patient
group with characteristic traits and an increased probability of brown fat redetection. J Nucl Med 2017;58:1104–110
[148] Padmamalini Baskaran, et al. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. British Journal of Pharmacology (2016) 173 2369–2389 2369
[149] Whiting S, Derbyshire EJ , Tiwari B. Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. Appetite. 2014 Feb;73:183-8. doi: 0.1016/j.appet.2013.11.005. Epub 2013 Nov 15.
[150] Janssens PL, Hursel R , Westerterp-Plantenga MS. Capsaicin increases sensation of fullness in energy balance, and decreases desire to eat after dinner in negative energy balance. Appetite. 2014 Jun;77:44-9. doi: 10.1016/j.appet.2014.02.018. Epub 2014 Mar 12
[151] van Avesaat M, et al. Capsaicin-induced satiety is associated with gastrointestinal distress but not with the release of satiety hormones. Am J Clin Nutr. 2016 Feb;103(2):305-13. doi: 10.3945/ajcn.115.123414. Epub 2015 Dec 30
[152] Saito M, Yoneshiro T. Capsinoids and related food ingredients activating brown fat Thermogenesis and reducing body fat in humans. Curr Opin Lipidol. 2013 Feb;24(1):71-7. doi: 10.1097/MOL.0b013e32835a4f40.
[153] Taghizadeh M, et al. The Effect of Dietary Supplements Containing Green Tea, Capsaicin and Ginger Extracts on Weight Loss and Metabolic Profiles in Overweight Women: A Randomized Double-Blind Placebo-Controlled Clinical Trial. Ann Nutr Metab. 2017;70(4):277-285. doi: 10.1159/000471889. Epub 2017 Jun 9
[154] Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003;299:853–5.

[155] Constantin Dallas, et al. Lipolytic effect of a polyphenolic citrus dry extract of red orange, grapefruit, orange (SINETROL) in human body fat adipocytes. Mechanism of action by inhibition of cAMP-phosphodiesterase (PDE). Phytomedicine 15 (2008) 783–792. Elsevier Press
[156] Julien Cases, et al. A 12-week randomized double-blind parallel pilot trial of Sinetrol® XPur on body weight, abdominal fat, waist circumference, and muscle metabolism in overweight men. ISSN: 0963-7486 (print), 1465-3478 (electronic) Int J Food Sci Nutr, Early Online: 1–7. 2015 Informa UK Ltd. DOI:10.3109/09637486.2015.1042847
[157] Zhang PY Polyphenols in Health and Disease. Cell Biochem Biophys. 2015 Dec;73(3):649-64. doi: 10.1007/s12013-015-0558-z.
[158] Rodrigo R, Libuy M, Feliu F, Hasson. Polyphenols in disease: from diet to supplements. Curr Pharm Biotechnol. 2014;15(4):304-17
[159] Goetz ME, Judd SE, et al. Dietary flavonoid intake and incident coronary heart disease: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Am J Clin Nutr. 2016 Nov;104(5):1236-1244. Epub 2016 Sep 21.
[160] Hwang SL, Shih PH, Yen GC. Neuroprotective effects of citrus flavonoids. J Agric Food Chem. 2012 Feb 1;60(4):877-85. doi: 10.1021/jf204452y. Epub 2012 Jan 23.
[161] Orallo F, Camiña M, Alvarez E, Basaran H, Lugnier C. Implication of cyclic nucleotide phosphodiesterase inhibition in the vasorelaxant activity of the citrus-fruits flavonoid (+/-)-naringenin. Planta Med. 2005 Feb;71(2):99-107
[162] Rezaeizadeh, et al. A systematic review of the uterine relaxant effect of herbal sources. Curr Pharm Biotechnol. 2016 Apr 25. [Epub ahead of print]
[163] Xiaohui Guo, et al. Polyphenol Levels Are Inversely Correlated with Body Weight and Obesity in an Elderly Population after 5 Years of Follow Up (The Randomised PREDIMED Study). Nutrients 2017, 9(5), 452; doi:10.3390/nu9050452
[164] Assini JM, Mulvihill EE, Huff MW. Citrus flavonoids and lipid metabolism. Curr Opin Lipidol. 2013 Feb;24(1):34-40. doi: 10.1097/MOL.0b013e32835c07fd.
[165] Erika Hernández-Aquino, Pablo Muriel. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. World J Gastroenterol 2018 April 28; 24(16): 1679-1707 ISSN 1007-9327 (print) ISSN 2219-2840 (online)
[166] Dallas C, Gerbi A, Tenca G, Juchaux F, Bernard FX. 2008. Lipolytic effect of a polyphenolic citrus dry extract of red orange, grapefruit, orange (SINETROL) in human body fat adipocytes. Mechanism of action by inhibition of cAMP-phosphodiesterase (PDE). Phytomedicine 15: 783–792.
[167] Goldwasser J, Cohen PY, Yang E, Balaguer P, Yarmush ML, Nahmias Y. 2010. Transcriptional regulation of human and rat hepatic lipid metabolism by the grapefruit flavonoid naringenin: role of PPARalpha, PPARgamma and LXRalpha. PLoS One 5(8): e12399
[168] Ke JY et al. The flavonoid, naringenin, decreases adipose tissue mass and attenuates ovariectomy-associated metabolic disturbances in mice. Nutr Metab (Lond). 2015 Jan 13;12:1. doi: 10.1186/1743-7075-12-1. eCollection 2015.
[169] Chin-Lin Hsu, et al. Inhibitory Effect of Phenolic Acids on the Proliferation of 3T3-L1 Preadipocytes in Relation to Their Antioxidant Activity. J. Agric. Food Chem., 2006, 54 (12), pp 4191–4197. DOI: 10.1021/jf0609882
[170] Allison J. Richard, Zhaleh Amini-Vaughan, et al. Naringenin Inhibits Adipogenesis and Reduces Insulin Sensitivity and Adiponectin Expression in Adipocytes. Evidence-Based Complementary and Alternative Medicine Volume 2013, Article ID 549750, 10 pages http://dx.doi.org/10.1155/2013/549750
[171] Alam MA, Subhan N, Rahman MM, Uddin SJ, Reza HM, Sarker SD. Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. Adv Nutr. 2014;5:404–417. doi: 10.3945/an.113.005603
[172] Zobeiri M, et al. Naringenin and its nano-formulations for fatty liver: cellular modes of action and clinical perspective. Curr Pharm Biotechnol. 2018 May 14. doi: 10.2174/1389201019666180514170122. [Epub ahead of print]
[173] Banjerdpongchai R, et al. Hesperidin from Citrus seed induces human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways. Tumour Biol. 2016 Jan;37(1):227-37. doi: 10.1007/s13277-015-3774-7. Epub 2015 Jul 21.
[174] Mahmoud AM, et al. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. J Diabetes Complications. 2012 Nov-Dec;26(6):483-90. doi: 10.1016/j.jdiacomp.2012.06.001. Epub 2012 Jul 17.
[175] Wu H, et al. Neohesperidin Exerts Lipid-Regulating Effects in vitro and in vivo via Fibroblast Growth Factor 21 and AMP-Activated Protein Kinase/Sirtuin Type 1/Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α Signaling Axis. Pharmacology. 2017;100(3-4):115-126. doi: 10.1159/000452492. Epub 2017 May 30.
[176] Klok MD, Jakobsdottir S, Drent ML: The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007, 8:21-34.

[177] Zamboni M, Di Francesco V, Garbin U, Fratta Passini A, Mazzali G, Stranieri C, Zoico E, Fantin F, Bosello O, Cominacini L: Adiponectin gene expression and adipocyte NF-kappaB transcriptional activity in elderly overweight and obese women: inter-relationships with fat distribution, hs-CRP, leptin and insulin resistance. Int J Obes (Lond) 2007, 31:1104-1109.
[178] Chen K, Li F, Li J, Cai H, Strom S, Bisello A, Kelley DE, Friedman-Einat M, Skibinski GA, McCrory MA, Szalai AJ, Zhao AZ: Induction of leptin resistance through direct interaction of C-reactive protein with leptin. Nat Med 2006, 12:425-432.
[179] Caralluma fimbriata – Caralluma-Flowers of India. [Last assessed on 2013 Oct 12]. Available from: http://www.flowersofindia.net/catalog/slides/Caralluma.html .
[180] O. Kunert, V. G. Rao, G. S. Babu et al., "Pregnane glycosides from Caralluma adscendens var. fimbriata," Chemistry and Biodiversity, vol. 5, no. 2, pp. 239–250, 2008.
[181] Kuriyan R, Raj T, Srinivas SK, Vaz M, Rajendran R, Kurpad AV. ct of Caralluma fimbriata extract on appetite, food intake and anthropometry in adult Indian men and women. Appetite. 2007 May;48(3):338-44. Epub 2006 Nov 13.
[182] D. B. MacLean and L.-G. Luo, "Increased ATP content/production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside," Brain Research, vol. 1020, no. 1- 2, pp. 1–11, 2004.
[183] Dutt HC , Singh S, Avula B, Khan IA, Bedi YS. Pharmacological review of Caralluma R.Br. with special reference to appetite suppression and anti-obesity. J Med Food. 2012 Feb;15(2):108-19. doi: 10.1089/jmf.2010.1555. Epub 2011 Dec 22
[184] A. Plaza, A. Perrone, M. L. Balestrieri et al., "New unusual pregnane glycosides with antiproliferative activity from Solenostemma argel," Steroids, vol. 70, no. 9, pp. 594–603, 2005.
[185] M. De Leo, N. De Tommasi, R. Sanogo et al., "New pregnane glycosides from Caralluma dalzielii," Steroids, vol. 70, no. 9, pp. 573–585, 2005.
[186] G. Cioffi, R. Sanogo, A. Vassallo et al., "Pregnane glycosides from Leptadenia pyrotechnica," Journal of Natural Products, vol. 69, no. 4, pp. 625–635, 2006
[187] T. Shibasaki,T. Oda, T. Imaki,N. Ling, andH. Demura, "Injection of anti-neuropeptide Y γ-globulin into the hypothalamic paraventricular nucleus decreases food intake in rats," Brain Research, vol. 601, no. 1-2, pp. 313–316, 1993.
[188] M.G.Hulsey, C. M. Pless,B.D.White, and R. J.Martin, "ICV administration of anti-NPY antisense oligonucleotide: effects on feeding behavior, body weight, peptide content and peptide release," Regulatory Peptides, vol. 59, no. 2, pp. 207–214, 1995.
[189] J. V. Gardiner, W. M. Kong, H. Ward, K. G. Murphy, W. S. Dhillo, and S. R. Bloom, "AAV mediated expression of antisense neuropeptide Y cRNA in the arcuate nucleus of rats results in decreased weight gain and food intake," Biochemical and biophysical Research Communications, vol. 327, no. 4, pp. 1088–1093, 2005.
[190] Shenai Ashwini and Roy Anitha. Antihyperglycemic Activity of Caralluma fimbriata: An In vitro Approach. Pharmacogn Mag. 2017 Oct; 13(Suppl 3): S499–S504. Published online 2017 Oct 11. doi: 10.4103/pm.pm_59_17
[191] Kunert O, Rao VG, Babu GS, Sujatha P, Sivagamy M, Anuradha S, et al. Pregnane glycosides from Caralluma adscendens var. fimbriata. Chem Biodivers. 2008;5:239–50. [PubMed: 18293437
[192] El-Merahbi R, Löffler M, Mayer A, Sumara G. The roles of peripheral serotonin in metabolic homeostasis. FEBS Lett. 2015 Jul 8;589(15):1728-34. doi:10.1016/j.febslet.2015.05.054. Epub 2015 Jun 9
[193] Ekta Arora, Vijay Khajuria, Vishal R. Tandon, Atul Sharma, Annil Mahajan, Zahid H. Gillani, and Naiyma Choudhary. To evaluate efficacy and safety of Caralluma fimbriata in overweight and obese patients: A randomized, single blinded, placebo control trial. Perspect Clin Res. 2015 Jan-Mar; 6(1): 39–44. doi: 10.4103/2229-3485.148812
[194] Astell KJ , Mathai ML, McAinch AJ, Stathis CG, Su XQ. A pilot study investigating the effect of Caralluma fimbriata extract on the risk factors of metabolic syndrome in overweight and obese subjects: a randomised controlled clinical trial. Complement Ther Med. 2013 Jun;21(3):180-9. doi: 10.1016/j.ctim.2013.01.004. Epub 2013 Feb 23.
[195] Dimitropoulos A, Feurer ID, Roof E, Stone W, Butler MG, Sutcliffe J, et al. Appetitive behavior, compulsivity, and neurochemistry in Prader-Willi syndrome. Ment Retard Dev Disabil Res Rev. 2000;6:125–30. [PubMed: 10899805]
[196] Rajendran R, Ambikar D, Khandare R, Sannapuri V, Clayton P, Vyawahare N. Nootropic activity of Caralluma fimbriata extract in mice. FNS. 2014;5:147–52
[197] Rajendran R, Ambikar D, Khandare R, Sannapuri V, Clayton P, Vyawahare N. Nootropic activity of Caralluma fimbriata extract in mice. FNS. 2014;5:147–52.
[198] Gujjala S, et al. Preventive effect of Caralluma fimbriata vs. Metformin against high-fat diet-induced alterations in lipid metabolism in Wistar rats. Biomed Pharmacother. 2016 Dec;84:215-223. doi: 10.1016/j.biopha.2016.09.029. Epub 2016 Sep 19
[199] Odendaal AY , Deshmukh NS, Marx TK, Schauss AG, Endres JR, Clewell AE. Safety assessment of a hydroethanolic extract of Caralluma fimbriata. Int J Toxicol. 2013 Sep-Oct;32(5):385-94. doi: 10.1177/1091581813492827. Epub 2013 Jun 14

[200] Haskell CF, Kennedy DO, Milne AL, Wesnes KA, Scholey AB. The effects of L-theanine, caffeine and their combination on cognition and mood. Biol Psychol. 2008 Feb;77(2):113-22. Epub 2007 Sep 26.
[201] Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine. 2017 Oct 15;34:26-37. doi: 10.1016/j.phymed.2017.07.008. Epub 2017 Jul 27.
[202] Sadzuka Y, Sugiyama T, Sonobe T. Efficacies of tea components on doxorubicin induced antitumor activity and reversal of multidrug resistance. Toxicol Lett 2000;114:155-62.
[203] Van der Pijla, P.; Chenb, L.; Muldera, T. Human disposition of L-theanine in tea or aqueous solution. J. Funct. Foods 2010, 2, 239–244
[204] David J. White, et al. Anti-Stress, Behavioural and Magnetoencephalography Effects of an L-Theanine-Based Nutrient Drink: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial. Nutrients 2016, 8, 53; doi:10.3390/nu8010053
[205] Scheid L, et al. Kinetics of L-theanine uptake and metabolism in healthy participants are comparable after ingestion of L-theanine via capsules and green tea. J Nutr. 2012 Dec;142(12):2091-6. doi: 10.3945/jn.112.166371. Epub 2012 Oct 24
[206] Kakuda, T.; Nozawa, A.; Sugimoto, A.; Niino, H. Inhibition by theanine of binding of [3H] AMPA, [3H] kainate, and [3H] MDL 105,519 to glutamate receptors. Biosci. Biotechnol. Biochem. 2002, 66, 2683–2686.
[207] Sugiyama, T.; Sadzuka, Y.; Tanaka, K.; Sonobe, T. Inhibition of glutamate transporter by theanine enhances the therapeutic efficacy of doxorubicin. Toxicol. Lett. 2001, 121, 89–96.
[208] Di, X.; Yan, J.; Zhao, Y.; Zhang, J.; Shi, Z.; Chang, Y.; Zhao, B. L-theanine protects the APP (Swedish mutation) transgenic SH-SY5Y cell against glutamate-induced excitotoxicity via inhibition of the NMDA receptor pathway. Neuroscience 2010, 168, 778–786
[209] Lu K, Gray MA, Oliver C, et al. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. Hum Psychopharmacol 2004;19:457-65
[210] Wakabayashi, C.; Numakawa, T.; Ninomiya, M.; Chiba, S.; Kunugi, H. Behavioral and molecular evidence for psychotropic effects in L-theanine. Psychopharmacology 2012, 219, 1099–1109
[211] Tamano, H.; Fukura, K.; Suzuki, M.; Sakamoto, K.; Yokogoshi, H.; Takeda, A. Advantageous effect of theanine intake on cognition. Nutr. Neurosci. 2014, 17, 279–283
[212] Kakuda, T. Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction. Pharmacol. Res. 2011, 64, 162–168
[213] Yoto et al. Journal of Physiological Anthropology 2012, 31:28 http://www.jphysiolanthropol.com/content/31/1/28
[214] Unno, K.; Hara, A.; Nakagawa, A.; Iguchi, K.; Ohshio, M.; Morita, A.; Nakamura, Y. Anti-stress effects of drinking green tea with lowered caffeine and enriched theanine, epigallocatechin and arginine. Phytomedicine 2015, 23, 1365–1374
[215] Keiko Unno, et al. Reduced Stress and Improved Sleep Quality Caused by Green Tea Are Associated with a Reduced Caffeine Content. Nutrients 2017, 9, 777; doi:10.3390/nu9070777
[216] Bryan J. Psychological effects of dietary components of tea: caffeine and L-theanine. Nutr Rev. 2008 Feb;66(2):82-90. Review.
[217] Rogers PJ, Smith JE, Heatherley SV, Pleydell-Pearce CW. Time for tea: mood, blood pressure and cognitive performance effects of caffeine and theanine administered alone and together. Psychopharmacology (Berl). 2008 Jan;195(4):569-77. Epub 2007 Sep 23.
[218] Camfield DA , Stough C, Farrimond J, Scholey AB. Acute effects of tea constituents L-theanine, caffeine, and epigallocatechin gallate on cognitive function and mood: a systematic review and meta-analysis. Nutr Rev. 2014 Aug;72(8):507-22. doi: 10.1111/nure.12120. Epub 2014 Jun 19
[219] Giesbrecht T , Rycroft JA, Rowson MJ, De Bruin EA. The combination of L-theanine and caffeine improves cognitive performance and increases subjective alertness. Nutr Neurosci. 2010 Dec;13(6):283-90. doi: 10.1179/147683010X12611460764840.
[220] Dodd FL , Kennedy DO, Riby LM, Haskell-Ramsay CF. A double-blind, placebo-controlled study evaluating the effects of caffeine and L-theanine both alone and in combination on cerebral blood flow, cognition and mood. Psychopharmacology (Berl). 2015 Mar 13. [Epub ahead of print]
[221] Owen GN , Parnell H, De Bruin EA, Rycroft JA. The combined effects of L-theanine and caffeine on cognitive performance and mood. Nutr Neurosci. 2008 Aug;11(4):193-8. doi: 10.1179/147683008X301513
[222] Einöther SJ, Martens VE, Rycroft JA, De Bruin EA. L-theanine and caffeine improve task switching but not inter sensory attention or subjective alertness. Appetite. 2010 Apr;54(2):406-9. Epub 2010 Jan 15.
[223] Williams G. Withdrawal of sibutramine in Europe. Br J Med 2010;340:c824.
[224] Rodgers RJ, Tsch€op MH, Wilding JPH. Anti-obesity drugs: past present and future. Dis Model Mech 2012;5:621–626

[225] Khera, Rohan et al. "Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-Analysis." JAMA 315.22 (2016): 2424–2434. PMC. Web. 9 July 2018.
[226] Yun JW. Possible anti-odbesity therapeutics from nature—A review. Phytochemistry 2010;71:1625–1641
[227] Akhlaghi M, Ghobadi S, et al. Flavanols are potential anti-obesity agents, a systematic review and meta-analysis of controlled clinical trials. Nutr Metab Cardiovasc Dis. 2018 Jul;28(7):675-690. doi: 10.1016/j.numecd.2018.04.001. Epub 2018 Apr 13
[228] CD Coleman, JR Kiel, AH Mitola and LM Arterburn. Comparative effectiveness of a portion-controlled meal -replacement program for weight loss in adults with and without diabetes/high blood sugar. Nutrition & Diabetes (2017) 7, e284; doi:10.1038/nutd.2017.32
[229] Haller CA, Benowitz NL, Jacob P 3rd. Hemodynamic effects of ephedra-free weight-loss supplements in humans. Am J Med 2005;118:998-1003.
[230] Kockler DR, McCarthy MW, Lawson CL. Seizure activity and unresponsiveness after hydroxycut ingestion. Pharmacotherapy 2001;21:647-51
[231] Erica R Goldstein,Tim Ziegenfuss, Doug Kalman, Richard Kreider, Bill Campbell, Colin Wilborn, et al. International society of sports nutrition position stand: caffeine and performance. Goldstein et al. Journal of the International Society of Sports Nutrition 2010, 7:5 http://www.jissn.com/content/7/1/5
[232] Hogaboam CM, Wallace JL. Inhibition of platelet aggregation by capsaicin. An effect unrelated to actions on sensory afferent neurons. Eur J Pharmacol 1991;202:129-3
[233] McEvoy GK, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 1998
[234] Rigato, I., Blarasin, L., and Kette, F. Severe hypokalemia in 2 young bicycle riders due to massive caffeine intake. Clin J Sport Med. 2010;20(2):128-130
[235] Shalansky S, Lynd L, Richardson K, et al. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. Pharmacotherapy. 2007;27:1237-47
[236] Sandor B, Papp J, Mozsik G, et al. Orally given gastroprotective capsaicin does not modify aspirin-induced platelet aggregation in healthy male volunteers (human phase I examination). Acta Physiol Hung. 2014 Dec;101(4):429-37
[237] Robin Poole et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017; 359: j5024. Published online 2017 Nov 21. doi: 10.1136/bmj.j5024
[238] Institute of Medicine. Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations. Washington, DC: National Academy Press, 2001. Available at: http://books.nap.edu/books/0309082587/html/index.html
[239] Hardman JG, Limvird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, editors. Goodman & Gilman's The pharmacological basis of therapeutics. 9th Ed. New York: McGraw-Hill; 1996. p 1274, 1275, 1426; 1903p.
[240] Nemecz G. Green tea. US Pharm 2000;May:67-70.
[241] Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. Cancer 2003;97:1442-6