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REVIEW

A Review of Natural Stimulant and Non-stimulant Thermogenic Agents

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Obesity and overweight are major health issues. Exercise and calorie intake control are recognized as the primary mechanisms for addressing excess body weight. Naturally occurring thermogenic plant constituents offer adjunct means for assisting in weight management. The controlling mechanisms for thermogenesis offer many intervention points. Thermogenic agents can act through stimulation of the central nervous system with associated adverse cardiovascular effects and through metabolic mechanisms that are non-stimulatory or a combination thereof. Examples of stimulatory thermogenic agents that will be discussed include ephedrine and caffeine. Examples of non-stimulatory thermogenic agents include *p*-synephrine (bitter orange extract), capsaicin, forskolin (*Coleus* root extract), and chlorogenic acid (green coffee bean extract). Green tea is an example of a thermogenic with the potential to produce mild but clinically insignificant undesirable stimulatory effects. The use of the aforementioned thermogenic agents in combination with other extracts such as those derived from *Salacia reticulata*, *Sesamum indicum*, *Lagerstroemia speciosa*, *Cissus quadrangularis*, and *Moringa olifera*, as well as the use of the carotenoids as lutein and fucoxanthin, and flavonoids as naringin and hesperidin can further facilitate energy metabolism and weight management as well as sports performance without adverse side effects.

Keywords: thermogenesis; stimulant; non-stimulant; caffeine; ephedra; chlorogenic acid; *p*-synephrine; forskolin; green tea; capsaicin; flavonoids; carotenoids.

INTRODUCTION

Thermogenesis is a process of converting nutrient calories into the heat energy essential for body homeostasis, that is, thermoregulation, maintaining healthy metabolism, and body weight control. Total energy expenditure includes energy required to perform cellular and organ functions, energy expenditure induced by diet or cold exposure, and energy expenditure induced by physical activity. Twenty-four-hour energy expenditure (TEE) is the sum of resting energy expenditure (cardiorespiratory work and the work of maintaining transmembrane ion gradients at rest; approximately 60% of TEE), the thermic effect of feeding (the work of digestion; approximately 5–10% of TEE), and non-resting energy expenditure (energy expended in physical activity above resting; approximately 30–40% of TEE).

Alterations in energy expenditure caused by diet or cold exposure are often referred to as 'adaptive thermogenesis'. Most models of obesity indicate defects in adaptive thermogenesis and its regulation as an important mechanism in maintaining healthy body composition and weight (Celi *et al.*, 2015). Adaptive thermogenesis can be modified by food and food supplements. Potentiation of thermogenesis can be accomplished by substances that act as stimulants in addition to promoting thermogenesis or via mechanisms that do not involve central nervous system (CNS) stimulation.

Stimulants by definition are substances or agents that produce a temporary increase in the functional activity or efficiency of an organism or any of its parts. Some stimulants not only activate the CNS but may also increase thermogenesis and are therefore referred as stimulant thermogenics. Common indicators of CNS stimulatory activity are increases in heart rate and diastolic and systolic blood pressure (Kassis *et al.*, 2013). Non-stimulant thermogenic agents enhance thermogenesis but do not produce significant stimulation of the CNS and do not produce cardiovascular effects.

In general, vasoconstriction and an increase in blood pressure occur when ligands activate the noradrenergic system or directly bind to α-1 adrenergic receptors resulting in smooth muscle contraction in blood vessels, while activation of α-2 adrenergic receptors in the CNS results in reduced sympathomimetic activity. Activation of β-1 adrenergic receptors in the heart results in increased cardiovascular contractility and increased heart rate, as well as an increase in ghrelin secretion from the stomach, a hormone that promotes feeding mode. Binding to β-2 adrenergic receptors produces smooth muscle relaxation and is associated with bronchodilation. Binding of agonists to β-3 adrenergic receptors triggers thermogenesis and results in the oxidation of fatty acids and production of energy (Inchiosa, 2011; Mund and Fishman, 2013).

Stimulatory thermogenic agents as ephedrine exhibit multiple mechanisms of action consisting of an indirect effect, which involves the release of norepinephrine

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and epinephrine as well as a direct effect on adrenergic receptors. Through the indirect effect, norepinephrine and epinephrine act on α-, β-1, and β-2 adrenergic receptors to product the cardiovascular affects, while interacting with β-3 adrenergic receptors to promote thermogenesis (Mund and Frishman, 2013). Ephedrine also acts directly on all these adrenergic receptors to produce thermogenesis and the associated undesirable cardiovascular effects (Andraws *et al*., 2005; Diepvens *et al*., 2007; Inchiosa, 2011).

Sympathomimetic agents vary broadly in their abilities to activate or inhibit various adrenergic receptors, and therefore, it should not be assumed that substances with some structural similarity will have similar effects (Westfall and Westfall, 2014). For example, *p*-synephrine, which is structurally similar to epinephrine, exhibits relatively little activation of α-, β-1, and β-2 adrenergic receptors or upregulation of norepinephrine and epinephrine, while exhibiting greater selective binding to β-3 adrenergic receptors, thus promoting thermogenesis without the unwanted cardiovascular effects (Stohs *et al*., 2011a). As a consequence, *p*-synephrine is an example of a non-stimulatory thermogenic, which preferentially activates β-3 adrenergic receptors directly.

The mechanisms involved in thermogenesis have many potential intervention and regulating points (Clapham, 2012). β-3 Adrenergic stimulation activates cellular adenylyl cyclase, which leads to the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), activation of protein kinase A, and phosphorylation and activation of triacylglycerol lipase. The phosphorylated lipase converts triacylglycerols (white storage fat) into free fatty acids, which act to release uncoupling protein 1 (UCP1) by overriding the inhibition caused by purine nucleotides (adenosine diphosphate (ADP), guanosine diphosphate (GDP), and adenosine triphosphate (ATP)) (Oelkrug *et al*., 2015). The UCP1-mediated uncoupling of the respiratory chain in mitochondria ultimately produces the metabolic heat or thermogenesis (Fedorenko *et al*., 2012). How various thermogenic substances interact with this chain of metabolic events will be described in the succeeding discussion.

Uncoupling of the respiratory chain in mitochondria is recognized as the main event leading to thermogenesis and as such is targeted in pharmacologic and nutritional intervention to upregulate thermogenesis. The role of the respiratory chain is to carry electrons with the increasing oxidation potentials, ultimately reducing molecular oxygen to water. The energy generated in that process is used to pump protons from the mitochondrial matrix into the intermembrane space, creating an electrochemical gradient known as the proton motive force, which activates the ATP synthase and drives the conversion of ADP and inorganic phosphate (coupling reaction) to ATP (Rosenbaum and Leibel, 2010).

Opposite to coupling, the activation of β-3 receptors by stimulant or non-stimulant thermogenic agents results in activation of UCP1. Incidentally, the superoxide or peroxidation products generated in the respiratory chain can also activate (unlock) the UCP1. Subsequently, the activated UCP1 uncouples the respiratory chain, allowing rapid fatty acid oxidation with a low rate of ATP production and high ATP utilization and heat energy release, hence, thermogenesis.

At the termination of thermogenesis, the mitochondria oxidize the residual fatty acids, UCP1 is inactivated, and the cell resumes its normal energy-conserving mode storing ATP. UCP1 is an integral part of the inner mitochondria membrane and dissipates energy as heat – an opposite mechanism to the ATP synthase, which couples the energy inherent in the proton gradient to synthesis of ATP. The process of hydrolysis and re-synthesis of cellular ATP is a continuous process facilitating thermogenesis or generating and storage of ATP (Rosenbaum and Leibel, 2010).

In the process of generating metabolic heat, as in adaptive thermogenesis, there are quantitative and qualitative differences between the function of stimulant and non-stimulant thermogenic supplements, with the former usually burdened with cardiovascular and CNS side effects while the latter exert heat energy expenditure without the untoward biological effects. The difference between stimulant and non-stimulant thermogenic action can be exemplified by the physiological role of insulin-mediated sympathetic stimulation in dietary thermogenesis. The physiological insulin increase with food intake leads to physiological sympathetic stimulation, increased metabolic rate, the uncoupling mechanism, and physiological thermogenesis. However, the association of hyperinsulinemia with hypertension in the obese led to the hypothesis that insulin-mediated excessive sympathetic stimulation may lead to thermogenesis as well as the unintended consequence of increasing blood pressure. The physiological reaction to food-induced thermogenesis may exemplify non-stimulant thermogenic action, whereas persistent hyperinsulinemia leading to high blood pressure may exemplify a stimulant thermogenic action (Landsberg, 1996).

The UCP1 expression and thermogenesis may be increased by non-stimulant nutritional thermogenics such as carotenoids, isoflavones, polyphenols, and flavonoids, which are discussed in the succeeding paragraphs. The non-stimulant thermogenic compounds may safely address the ineffectual response in humans related to the low number of β-3 adrenergic receptors and/or inducible brown adipocytes in human white fat (Poekes *et al*., 2015). These compounds, which do not overstimulate sympathetic receptors, may effectively assist in weight management and weight loss when used in conjunction with exercise and calorie intake control.

Various natural stimulant and non-stimulant thermogenic substances are described in the succeeding paragraphs with emphasis being placed on their mechanisms of action. A detailed discussion of studies assessing efficacy of each of the substances described is beyond the scope of this review. The botanicals in this review were selected based on available literature data indicating their potential as thermogenic compounds. The purpose of the review is to highlight botanicals that have peer review data indicating thermogenic activity.

EXAMPLES OF NATURAL THERMOGENIC AGENTS

Ephedrine

Ephedrine is a phenylpropylamine protoalkaloid derived from the shrub *Ephedra sinica*. It is a sympathomimetic agent that acts both as a stimulant and a thermogenic. The ability of ephedrine to enhance

energy expenditure and promote weight loss has been demonstrated in a number of human studies (Astrup, 2000; Diepvens *et al*., 2007). Ephedrine mediates these effects by several mechanisms. It enhances the sympathetic neuronal release of norepinephrine and epinephrine with subsequent excitatory effects on the cardiovascular system via α-1, α-2, and β-1 adrenergic receptor stimulation (Diepvens *et al*., 2007). Abuse of ephedra and ephedrine by the use of indiscriminately high doses resulting in cardiovascular adverse events as an increase in blood pressure, tachycardia, insomnia, and restlessness has resulted in the removal of these products from the market. An effective thermogenic dose of ephedrine is about 20 mg twice daily with a low probability of adverse events (Hackman *et al*., 2006).

Ephedrine is believed to stimulate thermogenesis via interaction with β-3 adrenergic receptors, resulting in the breakdown of fats and modulation of glucose metabolism (Liu *et al*., 1995; De Matteis *et al*., 2002; Carey *et al*., 2015) as well as an indirect mechanism involving the release of norepinephrine and epinephrine from synaptic nerve endings, which interact with adrenergic receptors (Inchiosa, 2011). Ephedrine also inhibits monoamine oxidase and thus slows the degradation of norepinephrine. Some of the thermogenic effects may also be mediated by interaction of ephedrine with β-1 and β-2 adrenergic receptors (Liu *et al*., 1995). The thermogenic effect of ephedrine can be potentiated by the concurrent use of caffeine as the result of complementary mechanisms (Astrup, 2000; Ray *et al*., 2005; Hackman *et al*., 2006; Diepvens *et al*., 2007).

Caffeine

Caffeine is the world's most widely consumed stimulant and has various effects and mechanisms of action. In vascular smooth muscle cells, caffeine acts predominantly as a competitive inhibitor of the enzyme phosphodiesterase, which is responsible for the breakdown of 3 ,5 -cAMP. cAMP is one of the most important second messengers in mammalian cells and is responsible for diverse signaling responses including those responsible for energetic status (AMP/ATP ratio) and the effects of caffeine and coffee (Montoya *et al*., 2014; Nunes *et al*., 2014).

A second mechanism of action of caffeine is based on its binding to and inhibiting adenosine A1 and A2a receptors (Benowitz, 1990; Donovan and DeVane, 2001; Nawrot *et al*., 2003). Inhibition of the A1 receptor by caffeine results in activation of adenylate cyclase with a subsequent increase in cAMP and in the activity of protein kinase A, the latter being associated with stimulation of the CNS.

The resultant downstream pharmacological effects include an increase in energy metabolism, decrease in smooth muscle contraction, vasodilatation, and in neurotransmitter release resulting in CNS stimulation, positive inotropic (and possibly weak chronotropic) effects on the heart, vasoconstriction, and increased blood pressure. Some people experience insomnia in response to caffeine. In addition, in the kidney, caffeine induces diuresis, vasodilatation and sodium reabsorption in response to an increased glomerular filtration rate because of increased blood pressure (Benowitz, 1990; Donovan and DeVane, 2001; Nawrot *et al*., 2003). Typical doses of caffeine are in the range of 100–150 mg two to three times daily, with daily doses up to 400 mg being considered safe and without serious adverse effects (European Food Safety Authority, 2015).

p-Synephrine

p-Synephrine is a phenylethylamine derivative obtained from the dried immature fruits of *Citrus aurantium* (bitter orange) and is also present in other citrus species as mandarin oranges, clementine, and Marrs sweet oranges. The patented extract of bitter orange, which is standardized to *p*-synephrine, is known as Advantra Z® or Kinetiq™. *p*-Synephrine has some structural similarities to ephedrine, norepinephrine, and epinephrine. However, because of the structural differences, *p*-synephrine exhibits markedly different adrenergic receptor binding properties. Because *p*-synephrine exhibits little or no binding to α-1, α-2, β-1, and β-2 adrenergic receptors as opposed to ephedrine (Stohs *et al*., 2011a), cardiovascular effects as an increase in heart rate and blood pressure are not observed at commonly used doses (Stohs and Preuss, 2011; Stohs *et al*., 2011b, 2012a, 2012b; Stohs and Shara, 2013). Therefore, *p*-synephrine cannot be classified as a stimulant.

p-Synephrine exerts its effects through multiple biochemical mechanisms. It enhances thermogenesis by binding to β-3 adrenergic receptors, resulting in an increase in the body's ability to breakdown fats, which are further metabolized to produce energy (Carpene' *et al*., 1999, 2014; Mercader *et al*., 2011). *p*-Synephrine also enhances carbohydrate metabolism (Hong *et al*., 2012; Peixoto *et al*., 2012; de Oliveira *et al*., 2014). *p*-Synephrine facilitates cellular uptake of glucose in muscle cells, as well as glycogenolysis, gluconeogenesis, glycolysis, and oxygen uptake. The involvement of both calcium ion and cAMP along with adrenergic receptors were demonstrated to be involved in these biochemical processes (de Oliveira *et al*., 2014), indicating the involvement of multiple mechanisms.

Typical doses of *p*-synephrine (as Advantra Z and Kinetiq™) are in the range of 30–50 mg two to three times daily (Kaats *et al*., 2013). In summary, *p*-synephrine is an example of a non-stimulant thermogenic agent. No serious adverse events have been directly attributed to *p*-synephrine or bitter orange extract (Stohs and Preuss, 2011; Stohs *et al*., 2011b, 2012b; Stohs and Shara, 2013).

The citrus-derived bioflavonoids naringen and/or hesperidin or their aglycones have been shown in various animal experiments to improve insulin sensitivity and glucose tolerance, prevent biosynthesis and accumulation of triglycerides, inhibit cholesterol biosynthesis, and serve as antioxidants and anti-inflammatory agents with a decrease in inflammatory markers (Mulvihill *et al*., 2009; Goldwasser *et al*., 2010). A study has shown that the combination of *p*-synephrine with these two bioflavonoids enhances thermogenesis without adverse cardiovascular effects (Stohs *et al*., 2011c). A single dose of *p*-synephrine (50 mg) in human subjects exhibited a 65 kcal increase in resting metabolic rate (RMR) relative to the placebo group (24 h energy expenditure). In the group receiving *p*-synephrine plus naringin and hesperidin, the RMR increased by

183 kcal, an increase that was statistically significant with respect to the placebo control. Thus, the combination of *p*-synephrine with the bioflavonoids offers multiple mechanisms for increasing energy expenditure without adverse stimulant effects.

Capsaicin and capsiate

Hot red peppers (*Capsicum* species) contain pungent compounds called capsaicinoids with capsaicin being the major pungent principle. Capsiate is a non-pungent analog of capsaicin derived from a 'sweet' pepper, which has been demonstrated to have thermogenic properties similar to those of capsaicin (Ludy *et al*., 2012). Capsiate may prove to be of greater utility with respect to thermogenesis and weight management because it can be given at effective doses without the pungent, burning characteristics of capsaicin, and therefore may exert fewer adverse effects. Typical human doses of capsaicin are in the range of 30–150 mg per day (Ludy *et al*., 2012). To date, most studies regarding thermogenesis have been conducted with capsaicin.

Multiple mechanisms exist with respect to the actions of capsaicin, which may account for the observations that it acts as a thermogenic agent without causing stimulant and adverse cardiovascular effects (Ludy *et al*., 2012; Janssens *et al*., 2013; Yoneshiro and Saito, 2013; McCarty *et al*., 2015). Capsaicin has been shown to stimulate the release of the catacholamines norepinephrine and epinephrine from the adrenal medulla (Reinbach *et al*., 2010; Ludy *et al*., 2012), which in turn promote thermogenesis through their actions on adrenergic receptors.

However, capsaicinoids also have the potential to modulate metabolism through their activation of transient receptor potential vanilloid 1 receptors where they are also believed to be able to increase energy expenditure and decrease body fat by enhancing catabolic processes in adipose tissues (Yoneshiro and Saito, 2013; McCarty *et al*., 2015). Activation of these vanilloid receptors also causes vasodilatory responses believed to occur through activation of nitric oxide synthase and induction of calcium fluxes (McCarty *et al*., 2015). As a consequence, cardiovascular effects as an increase in heart rate and blood pressure because of capsaicin-induced release of the catacholamines is counteracted, and capsaicin therefore acts as a non-stimulant thermogenic.

Adverse effects associated with capsaicin are primarily related to its direct irritation of the eyes, mucus membranes, and respiratory tract (Copeland and Nugent, 2013; Srinivasan, 2015). If ingested in large amounts, capsaicin can cause nausea, vomiting, abdominal pain, and burning diarrhea (Srinivasan, 2015). Although case studies have suggested a link with adverse cardiovascular events when consuming red pepper (Sayin *et al*., 2012), no adverse effects have ever been shown to be directly associated with capsaicin, and various studies have indicated cardioprotective and chemoprotective effects (Srinivasan, 2015).

Green tea

Various studies have indicated that consumption of green tea and green tea extracts can increase thermogenesis and fat oxidation (Dulloo *et al*., 2000; Diepvens *et al*., 2007; Westerterp-Platenga, 2010; Turkozu and Acer Tek, 2015). The constituents responsible are believed to be caffeine and catechins including epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG), with EGCG being the most abundant (50–80%) and most potent. The amount of caffeine in a cup (250 mL) of green tea may be in the range of 15–100 mg, depending on the manner in which the tea is prepared. The effects of caffeine on energy expenditure and thermogenesis have been described earlier. In general, the amount of caffeine to which an individual is exposed via green tea or green tea extracts is much less than through coffee consumption or where caffeine is directly used in a product.

The catechins in green tea are believed to influence energy expenditure through inhibition of the enzyme catechol-0-methyl transferase (Diepvens *et al*., 2007; Westerterp-Platenga, 2010; Turkozu and Acer Tek, 2015). This enzyme is responsible for the degradation of catecholamines including norepinephrine. Because the degradation of norepinephrine and epinephrine are slowed, continuous stimulation of adrenergic receptors occurs with a resultant increase in energy expenditure and fat oxidation. As a consequence, the data indicate that the thermogenic effects of green tea and green tea extracts are due to a combination of mechanisms associated with caffeine and catechins. In general, green tea extracts produce mild stimulatory effects that result in clinically insignificant cardiovascular effects (Diepvens *et al*., 2007).

Green tea is widely consumed, and in general, its consumption is considered to be very safe and associated with health benefits because in part of its antioxidant activity. However, on rare occasions, cases of hepatotoxicity have been reported, particularly when green tea is consumed in large amounts (Mazzanti *et al*., 2009).

Forskolin

Forskolin is a diterpene derived from the roots of the plant *Coleus forskohlii.* It has long been known to be an effective activator of the enzyme adenylate cyclase (Insel *et al.*, 1982), which is responsible for the formation to cAMP. Initial studies were conducted in human platelet membranes. As described earlier, cAMP serves as a second messenger with numerous functions. Forskolin (Forslean®) via cAMP may affect body metabolism and body fat by increasing lean body mass and metabolic activity (Badmaev *et al*., 2002). cAMP elevating agents as forskolin induce thermogenesis only through the beta-receptors and the resulting increase in cAMP levels (Zhao *et al*., 1997). Forskolin *per se* does not stimulate beta-receptors. Typical human doses of forskolin are in the range of 10–25 mg twice daily with *C. forskohlii* extracts being most commonly standardized to 10% forskolin. No studies have examined the long-term effects of forskolin at these doses.

Various studies have shown that forskolin (Forslean) can decrease fat mass in humans and do so without significant effects on the cardiovascular system (Badmaev *et al*., 2002; Godard *et al*., 2005). Furthermore, forskolin (*C. forskohlii* extract) has been shown to work synergistically with extracts of *Salacia reticulata* and *Sesamum indicum* in formula FB^3® to inhibit pancreatic lipase and prevent dietary fat absorption (Badmaev

et al., 2015). Thus, the ability of this combination of ingredients to decrease body fat may primarily involve a combination of mechanisms including inhibition of pancreatic lipase.

Chlorogenic acid

Chlorogenic acid is the major hydroxycinnamic acid derivative present in green coffee beans. Human and animal studies have shown that chlorogenic acid and green coffee bean extracts (45–55% chlorogenic acid) enhance energy metabolism and expenditure, decrease blood lipid levels, improve glucose tolerance, and support weight management without cardiovascular effects. Typical human doses are in the range of 300–400 mg of the extract two to three times daily (Onakpoya *et al*., 2011; Cho *et al*., 2010; Ho *et al*., 2012; Ma *et al*., 2015). No studies have examined the long-term effects of green coffee bean extracts or chlorogenic acid at these doses.

Several mechanisms of action appear to be involved. Chlorogenic acid and the related hydroxycinnamic acid analogs cinnamic acid and ferulic acid have been shown to inhibit cAMP phosphodiesterase, which results in upregulation of adenosine monophosphate activated protein kinase (AMPK), a key sensor of energy metabolism, with a resultant increase in fatty acid oxidation (Bruckbauer and Zemel, 2014). A supporting mechanism that contributes to the weight management effects is the inhibition of the enzyme pancreatic lipase, which results in a decrease in lipid absorption (Narita *et al*., 2012).

Carotenoids

Carotenoids are pigments with anti-oxidant activity and with potential to convert to vitamin A. Chemically carotenoids are tetrapenoid compounds divided into groups of carotenes, which are hydrocarbons with no oxygen in the molecule, and xanthophylls, which are hydrocarbons with oxygen in the molecule. Carotenes include beta-carotene, alpha-carotene, beta-cryptoxanthin, and gamma-carotene, which besides being anti-oxidants can be converted in the body to vitamin A. Xanthophylls include lutein, astaxanthin, zeaxanthin, and fucoxanthin and play important roles as antioxidants. The effect of carotenoids on brown adipocyte proliferation in mice and differentiation in tissue culture has shown that beta-carotene, alpha-carotene, and lutein can enhance the expression of mitochondrial UCP1 expression in a dose-dependent manner. The carotenoids with provitamin A activity had the most potential to affect the expression of UCP1 and enhance thermogenesis. (Serra *et al*., 1999).

The xanthophyll fucoxanthin, a major carotenoid found in edible brown seaweeds, has the ability to increase resting energy expenditure by induction of UCP1 (Maeda, 2015). Furthermore, fucoxanthin has been shown to upregulate UCP1 gene expression in white adipose tissue, which then contributes to the reduction in white adipose tissue and overall body weight in mice. Maeda and associates (2015) also demonstrated that fucoxanthin inhibited glycerol-3-phosphate dehydrogenase activity, which suppressed adipocyte differentiation and lipid accumulation, and was associated with lower body mass index, fat mass, and fasting blood glucose. That study also revealed a downregulation of the peroxisome proliferator-activated receptor (PPAR) γ that is responsible for adipogenic gene expression (Maeda, 2015).

Isoflavones

Isoflavones, abundant in legumes as soy, red clover, and kudzu, are polyphenolic compounds that exert biological effects similar to estrogens. They are classified as phytoestrogens or plant-derived compounds with estrogenic activity. Isoflavones are present in nature as glycosides (bound to a sugar molecule) or a digested form released of the sugar molecule leaving an isoflavone aglycone. Genistin, daidzin, and glycitin are examples of isoflavone glycosides, while the aglycones are called genistein, daidzein, and glycitein, respectively. The biological effects of isoflavones depend on their metabolism, which in turn depends on the activity of gastrointestinal bacteria. For example, isoflavone daidzein may be metabolized in the intestine to equol, a metabolite that has greater estrogenic activity than daidzein. Studies that measure urinary equol excretion after soy consumption indicate that only about 33% of individuals from Western populations metabolize daidzein to equol (Zheng *et al*., 2013; Franke *et al*., 2014). Thus, individual differences in the metabolism of isoflavones could be decisive in use of those compounds as thermogenic food supplements.

Other examples of isoflavones enhancing energy metabolism exist. Extracts of kudzu flowers in a crude form or with isoflavone-rich fraction fed with a high-fat diet to C57BL/6 J mice for 42 days prevented statistically significantly adiposity and development of fatty liver. Kudzu fed groups also exhibited significant increases in oxygen consumption and UCP1-positive brown adipose tissue (Kamiya *et al*., 2012).

Fourteen-day treatment with daidzein (50 mg/kg) of obese rats on a high-fat diet reduced weight gain and fat content in the liver, accompanied by high leptin and low adiponectin levels in plasma. Both adipose tissue and the liver showed marked changes after treatment with daidzein, affecting transcription factors and lipogenic enzymes, particularly stearoyl coenzyme A desaturase 1 – considered a pivotal enzyme in obesity. Expression of UCP1, an important enzyme for thermogenesis, was increased in brown adipose tissue after daidzein treatment (Crespillo *et al*., 2011).

An isoflavone-rich ethanolic extract of sea buckthorn fed to C57BL/6 J mice on high-fat diet for 13 weeks significantly reduced the food intake, body weight gain, epididymal fat pad weight, hepatic triglyceride content, hepatic, and serum total cholesterol levels and serum leptin levels. The hepatic mRNA expression of PPARα and carnitine palmitoyl transferase 1 along with PPARγ were significantly increased, whereas the level of acetyl-CoA carboxylase was significantly reduced with the sea buckthorn regimen (Pichiah *et al*., 2012).

Flavonoids

Flavonoids are polyphenolic plant pigments with a versatile biological role as chemical messengers, physiological regulators, and cell cycle inhibitors. They can be classified into flavonoids or bioflavonoids, isoflavonoids, and neoflavonoids.

Citrus flavonoids, including naringenin, hesperetin, nobiletin, and tangeretin, have emerged as promising therapeutic agents for the treatment of metabolic dysregulation. In animal models, citrus flavonoid supplements prevent hepatic steatosis, dyslipidemia, and insulin sensitivity primarily through inhibition of hepatic fatty acid synthesis and increased fatty acid oxidation (Mulvihill *et al*., 2009). Citrus flavonoids blunt the inflammatory response in metabolically important tissues including liver and adipose tissue, which may prevent obesity (Alam *et al*., 2014; Parhiz *et al*., 2015).

The citrus flavonoid naringenin is one of the most abundant citrus flavonoids. Particularly in its aglycone form, naringenin, which also exists in a glycosidic form naringin, has been shown *in vitro* to regulate steps in carbohydrate and lipid metabolism. Naringenin may target transcriptional regulation of metabolism through nuclear receptors, a family of ligand-activated transcription factors. The flavonoid inhibits adipocytes differentiation and may induce *in vitro* the fatty acid oxidation genes including the UCP1 as well as PPAR-regulated genes for CYP4A11, acyl-CoA oxidase, and apolipoproteins (Mulvihill *et al*., 2009; Goldwasser *et al*., 2010). Naringin is widely distributed in citrus species and other plants. Rat studies have shown that exceedingly high doses are without toxic effects. The no-observed-adverse-effect level of naringin in rats was shown to be greater than 1250 mg/kg/day when administered orally for 13 weeks (Li *et al*., 2013).

Cocoa beans and by extension chocolate-contained flavan-3-ols have been credited with enhancing metabolic activity and preventing obesity. In an *in vivo* study, a mixture of flavan-3-ols administered to mice significantly enhanced systemic energy expenditure, as evidenced by an accompanying increase in the type of gene expression responsible for thermogenesis and lipolysis. By comparison, a tea that contained polyphenols exhibited less metabolic activity. The uncoupling protein1 (UCP-1) and PPARγ coactivator-1 alpha (PGC-1α) in brown adipose tissue were significantly increased 2 h after administration of cocoa flavonoids to mice (Matsumura *et al*., 2014). Flavan-3-ols derived from cocoa fed to rats maintained on high-fat diet for 4 weeks showed epididymal adipose tissue weight significantly lower with the UCP1 in brown adipose tissue, and UCP3 in gastrocnemius significantly increased. The nutritional flavan-3-ols may reduce white adipose tissue and weight gain by enhancing thermogenesis and lipolysis (Osakabe *et al*., 2014).

Combination products

Examples of the use of combinations of herbal ingredients to enhance thermogenesis are presented in the succeeding discussion. The addition of the flavonoids naringin and hesperidin enhance the non-stimulant thermogenic effect of *p*-synephrine (as Advantra Z) (Stohs *et al*., 2011c). Caffeine when combined with *p*-synephrine (as Advantra Z) with respect to sports performance has been shown to significantly increase mean power and velocity of squat performance, suggesting an enhanced thermogenic effect (Ratamess *et al*., 2015).

The combination of carotenoids and isoflavones with other thermogenic agents offers great potential to enhance and facilitate energy metabolism. It has been known for years that carotenoids exhibit thermogenic activities that involve altered carbohydrate and lipid metabolism without cardiovascular effects (Serra *et al*., 1999; Muriach *et al*., 2008; Maeda, 2015). Examples of carotenoids that may modulate energy metabolism include lutein, β-carotene, zeaxanthin, lycopene, and astaxanthin (McNulty *et al*., 2008).

Various other plant extracts may enhance thermogenesis when combined with well-known thermogenic agents. Studies have shown that aqueous extracts of *S. reticulata* modulate glucose and lipid metabolism through multiple mechanisms (Stohs and Ray, 2015). Extracts of the seeds of *S. indicum* have also been shown to modulate lipid metabolism (Biswas *et al*., 2010; Asgary *et al*., 2013). As noted earlier, the combination of forskolin with extracts of *S. reticulata* and *S. indicum* (FB^3) have been shown to work synergistically with respect to prevention of dietary fat absorption decreasing body fat content (Badmaev *et al*., 2015).

Extracts of *Lagerstroemia speciosa* (banaba) have been shown to enhance glucose and lipid metabolism in both humans and animals (Stohs *et al*., 2012a). Corosolic acid is believed to be the primary active agent in banaba with effects being mediated through a variety of signal transduction mechanisms. Similarly, extracts of the leaves of *Moringa oleifera* enhance metabolism of glucose and lipids, presumably through a wide variety of polyphenolic constituents (Stohs and Hartman, 2015). Extracts of *Cissus quadrangularis* represent another example of a plant extract that offers potential for enhancing thermogenesis when combined with other well-known thermogenic agents (Stohs and Ray, 2013).

Administration of punicic acid, the primary fatty acid present in pomegranate seed oil, has been shown to significantly reduce white adipose tissue in rats and suppress the production and secretion of triglycerides and apolipoprotein B100 (Arao *et al*., 2004a, 2004b). Lai *et al.* (2012) investigated the effects of fucoxanthin combined with pomegranate seed oil standardized for punicic acid in a compound formula (Xanthigen®). The combination of these two supplements suppressed accumulation of lipid droplets in adipocytes, downregulated PPARγ, cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein, and fatty acid synthase.

Abidov *et al.* (2010) conducted a human trial examining the effects of Xanthigen in soft gelatin capsules containing 100 mg pomegranate seed oil (70% punicic acid) and 100 mg of brown sea weed extract (0.8% fucoxanthin). Subjects had either normal liver fat content or had non-alcoholic fatty liver disease (NAFLD). Sixteen weeks of 200 mg of Xanthigen supplementation three times daily resulted in significant loss of body mass, body fat, and liver fat and decreased systolic and diastolic blood pressure, serum triglyceride levels, and C-reactive protein levels in both the normal liver fat and NAFLD groups as compared with placebo.

An additional interesting observation from the clinical study of Xanthigen is the change in the respiratory quotient (RQ) in the Xanthigen versus placebo group. A decrease in RQ (towards 0.7) indicates a shift in substrate metabolism to a greater dependence upon fat. The RQ also known as respiratory exchange ratio (RER) is an index of the body's metabolic activity. Typically, when an individual is utilizing 100% carbohydrate as a fuel for energy, the RER is 1.0. For fats, the RER is approximately 0.7. For a starving individual,

the RER may be as low as 0.7, reflecting utilization of body fat, which in starvation often co-exists with lean body mass wasting. This shift is commonly observed in stimulatory thermogenic weight-loss supplements such as caffeine and ephedra (Vukovich *et al*., 2005; Jitomir *et al*., 2008) and has been associated with cardiovascular side effects such as an increased blood pressure. Therefore, potential for non-stimulant thermogenic compounds or combinations thereof which shift metabolism towards fat utilization and without 'starvation' or cardiovascular effects is highly valuable in the nutritional field and offers much promise.

DISCUSSION AND SUMMARY

Weight-related health issues are a major concern worldwide. Overweight and obesity are associated with increased risks for heart diseases, strokes, hypertension, diabetes, many forms of cancer, and other disease states. The most straight-forward approach to weight management and weight control is calorie intake control and greater calorie expenditure through exercise and physical activities. However, the majority of people fail in their attempts to do so. As a consequence, much interest exists in nutrients and supplements that may facilitate calorie utilization, satiety, and weight loss. A wide variety of plant-derived substances offer great potential for assisting with weight loss and weight management. However, it should be kept in mind that while these plant-derived substances may assist with weight loss and weight management, they do not guarantee long lasting effects, which must be based on lifestyle changes.

Both natural stimulant and non-stimulant ingredients exist, with the non-stimulant agents providing enhanced thermogenesis without CNS stimulation and the associated adverse cardiovascular effects as an increase in heart rate and blood pressure. Typical stimulant thermogenic substances include ephedrine and caffeine, with ephedrine being generally banned because of the reported high incidence of adverse effects when used at doses higher than recommended, while caffeine is the worlds most consumed stimulant.

Examples of non-stimulant thermogenic substances include *p*-synephrine (bitter orange extracts), forskolin (*C. forskohlii* extracts), chlorogenic acid (green coffee bean extracts), and capsaicin. Although *p*-synephrine is structurally related to ephedrine, because of structural differences, it exhibits little binding to α-, β-1, and β-2 adrenergic receptors that are responsible for cardiovascular effects. Capsaicin is limited in its value as a non-stimulant thermogenic because of its pungency. The non-pungent analog capsiate may prove to be more useful. Green tea extracts exhibit stimulant thermogenic activity while producing clinically insignificant increases in heart rate and blood pressure because of a combination of mechanisms.

In recent years, a wide variety of plant extracts as well as isolated carotenoids and flavonoids have been shown to exhibit beneficial effects with respect to lipid and carbohydrate metabolism and do so without adverse effects. Examples include extracts of *S. reticulata, S. indicum, L. speciosa* (banaba), *C. quadrangularis*, and *M. oleifera.* These plant extracts when used in combination with well-known thermogenic agents offer great potential for enhancing energy metabolism and production without adverse effects. Potential benefits of various combination products include weight loss and weight management, increased alertness and energy, and enhanced sports performance.

Finally, comparing effects of thermogenic botanicals to the effects of exercise induced thermogenesis are appropriate because ultimately those two different approaches trigger the similar biochemical events leading to increases in thermogenesis and energy expenditure. The energy expenditure due to food consumption, cold exposure, or exercise ultimately has a common denominator, that is, thermogenesis. However, it should be noted that although increases in thermogenesis are mechanistically similar, they are smaller when contributed exclusively by botanicals versus that which can be achieved through exercise. Furthermore, exercise can stimulate cellular protein synthesis leading to heightened energy expenditure and increased muscle mass, effects not reported following the use of the thermogenic botanicals summarized in this report. The US National Institutes of Health guidelines for evaluation of weight loss compounds versus placebo typically include balanced diet and daily physical activity in both study groups. To date, proper clinical research proving or disproving the usefulness of most thermogenic botanicals in weight management is lacking (Bahmani *et al*., 2015). However, their thermogenic mechanisms of natural non-stimulant botanical products constitute a basis for further investigation of their potential in weight loss and weight management.

Conflict of Interest

The authors have served as consultants for Novel Ingredients, a company that markets various thermogenic ingredients as well as other herbal products. No funds were received by the authors in support of this review.

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