A review:

Phytochemicals in regulating fatty acid β-oxidation: Potential underlying mechanisms and their involvement in obesity and weight loss

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Abstract

Excessive accumulation of fat as the result of more energy intake and less energy expenditure is known as obesity. Lipids are essential components in the human body and are vital for maintaining homeostasis, physiological as well as cellular metabolism. Fatty acid synthesis and catabolism (by fatty acid oxidation) are normal part of basic fuel metabolism in animals. Fatty acids are degraded in the mitochondria by a biochemical process called β-oxidation in which two-carbon fragments are produced in each cycle. The increase in fatty acid oxidation is positively correlated with body mass index. Although healthy life style, avoiding Western diet, dieting and strenuous exercise are commonly used methods to lose weight, they are not considered a permanent solution in addition to risk attenuation of in basal metabolic rate (BMR). Pharmacotherapy offers benefits of weight loss by altering the satiety and lowering absorption of fat from the food; however, its side effects may outweigh the benefits of weight loss. Alternatively, dietary phytochemicals and natural health products offer great potential as an efficient weight loss strategy by modulating lipid metabolism and/or increasing BMR and thermogenesis. Specifically, polyphenols such as citrus flavonoids, green tea epigallocatechin gallate, resveratrol, capsaicin and curcumin, have been reported to increase lipolysis and induce fatty acid β-oxidation through modulation of hormone sensitive lipase, acetyl-coA carboxylase, carnitine acyl transferase and peroxisome proliferator-activated receptor gamma coactivator-1. In this review article, we discuss selected phytochemicals in relation to their integrated functionalities and specific mechanisms for weight loss.

Key words: Lipid metabolism, obesity, weight loss, beta-oxidation, phytochemicals, epigenetics

Abbreviations

Acetyl-CoA Carboxylase, ACC

Acyl CoA Synthetase, ACS

5' Adenosine Monophosphate-Activated Protein Kinase, AMPK

Activated or phosphorylated AMPK, AMPK-P

Body Mass Index, BMI

Carnitine Palmitoyl Transferase, CPT

Carnitine Palmitoyl Transferase-1, CPT-1

Carnitine Palmitoyl Transferase-1B, CPT-1B

Citrate Lyase, CL

Cyclic Adenosine Monophosphate, cAMP

DNA Methyltransferases, DNMTs

Fatty Acid, FA

Fatty Acid Oxidation, FAO

Fatty Acid Synthase, FAS

Glycerol-3-Phosphate Acyl Transferase-1, GPAT-1

Histone Acetyltransferases, HATs

Histone Deacetylases, HDACs

Hormone Sensitive Lipase, HSL

Hydroxycitric Acid, HCA

Lipoprotein Lipase, LPL

Mitochondrial Electron Transport Chain, ETC

Mitochondrial Uncoupling Protein-2, UCP-2

Peroxisome Proliferator-Activated Receptor-Gamma, PPAR-γ

Peroxisome Proliferator-Activated Receptor δ, PPARδ

Raspberry Ketone, RK

Respiratory Quotient, RQ

Small Non-Coding RNAs, miRNAs

Triacylglycerol, TAG

Tricarboxylic Acid, TCA

Table of Contents

1. Introduction

The prevalence of obesity has progressively increased over the past 30 years worldwide especially in the Western countries. Obesity is a condition characterized by accumulation of excessive body fat. It is classified by body mass index (BMI) [a ratio of body weight (in kg) to height (in meter squared)] in a way where individuals with a value over 30 are considered obese (Witkamp, 2011; Bessesen, 2008). Obesity is an alarming indicator of onset of metabolic disorder which is a cluster of health complications including hypertension, type 2 diabetes and cardiovascular disease (Faulds et al., 2012; Salas-Salvado et al., 2011). Therefore, apart from personal interest, the treatment of obesity is of clinical significance.

Weight management is a commonly recommended approach which is based on lifestyle modifications including dieting, increased physical activity, exercise, etc. However, physical exercise and dieting is often a difficult routine to maintain for lifetime and the results can be disappointing in long term. At present, the combination therapy of reducing calorie intake, increased energy expenditure and pharmacotherapy is becoming more popular. To this end, several drugs such as Fenfluramine, R-Fenfluramine, Temin, Sibutramine, Orlistat, Qsymia, and Belviq have been approved, by FDA, towards weight management aid. However, four of these were removed later on due to their adverse health effects (WHO, 2000). In addition, all current weight management drugs in the market have high cost as well as potential side effects thus causing dissatisfaction to the consumers. Finally, gastric surgery has had the most effective approach in severely obese to show long term effects.

Despite the progress in weight management strategy in recent years, obesity still poses a serious challenge for the scientific community (WHO, 2000; González-Castejón and Rodriguez-Casado, 2011). Therefore, there is considerable demand to explore natural therapies in developing

an alternative, safer and effective strategy. For this reason, a variety of natural phytochemicals have been explored for their ability to increase fatty acid oxidation, fat absorption and suppress appetite control. This review article will focus on most recent evidence on those phytochemicals that potentially increase fatty acid β-oxidation in relation to weight loss.

2. Fatty acid β-oxidation and its regulation

Fats are stored in our body as triacylglycerols (TAG) which are hydrolyzed into free fatty acids and glycerol by lipases as the first step of lipid catabolism. The fatty acid β-oxidation pathway consists of multistep reactions which oxidizes fatty acids by degrading two carbons at a time (Fig. 1). It takes place in mitochondria and peroxisomes, in eukaryotes, and it is a major source of energy supply by providing more energy as compared to equivalent amount of glucose. In the peroxisomes, long-chain fatty acids are converted to acyl CoA which cannot diffuse across the inner mitochondrial membrane to be utilized for the fatty acid β-oxidation pathway. Therefore, a transport system is required, called the carnitine shuttle system, catalyzed by carnitine acyltransferase-1 or carnitine palmitoyltransferase-1 (CPT-1). While in cytosol, fatty acyl CoA is converted into acylcarnitine (by carnitine acyltransferase I) which enters the mitochondrial matrix and fatty acyl CoA is regenerated by a reaction catalyzed by carnitine acyltransferase II (Horton et al., 2006). Beta-oxidation is catalyzed by the sequential action of four enzyme families: acyl CoA dehydrogenase (E1), enoyl CoA hydratase (E2), 3-hydroxy acyl CoA dehydrogenase (E3), and 3-ketoacyl CoA thiolase (E4) (Fig. 1).

Acetyl-CoA carboxylase (ACC) plays as central element both in fatty acid β-oxidation and fatty acid biosynthesis. ACC catalyzes the carboxylation of acetyl-CoA producing malonyl-CoA, which can be used by fatty acid synthase for fatty acid biosynthesis. As malonyl-CoA is the

substrate for fatty acid biosynthesis, malonyl-CoA is also a direct inhibitor of mitochondrial fatty acid uptake as well as inhibition of CPT-1. 5' Adenosine monophosphate-activated protein kinase (AMPK) regulates fatty acid metabolism by phosphorylation-induced inhibition of ACC activity and eventually stimulate fatty acid β-oxidation and down-regulate fatty acid biosynthesis (Fig. 1) (Lopaschuk et al., 2010).

3. Metabolic understanding of obesity

Cellular energy is produced from energy sources in the mitochondria. The major two sources of energy in a human body are carbohydrates and fatty acids. The body produces energy in the form of ATP by oxidation of carbohydrates, fats and proteins through tricarboxylic acid (TCA) cycle; and by fatty acid oxidation through β-oxidation. The body derives energy for its cellular processes by breaking down ATP to ADP and AMP. Under normal conditions, more ATP is produced through β-oxidation of fatty acids in the mitochondria as compared to carbohydrates. The first requirement in fatty acid β-oxidation is the presence of fatty acyl-CoA and its transport into the mitochondria facilitated by CPT-1 (a rate-limiting step for β-oxidation) (McGarry et al., 1983; Eaton et al., 2001). Malonyl-CoA (a precursor of fatty acid synthesis) is a competitive inhibitor of CPT-1 meaning that when an energy level is high, it prevents fatty acid oxidation whereas when energy level is low, malonyl and acetyl CoA levels fall and consequently β-oxidation is induced by the activation of CPT-1 (Zammit et al., 1999). Therefore, the enzymes CPT-1 and fatty acid synthase (FAS) directly regulate catabolism and anabolism of fatty acids (Ronnett et al., 2005). In addition, glucose oxidation directly inhibits fatty acid oxidation in a manner characterized by an insulin dependent response where a high glucose level (after a meal) is regulated by insulin thus facilitating glucose uptake in the cells and consequently inhibiting

lipolysis and β-oxidation. Furthermore, low circulating levels of glucose and increased energy demand can both stimulate cellular fatty acid β-oxidation pathway (Smith, 1994).

Obesity can lead to impaired cellular metabolism including dependence on glucose oxidation (for ATP production) and decrease in fatty acid oxidation, thus leading to more fat deposition in skeletal muscles, hepatocytes and other cells (Rogge, 2009). The reduced fatty acid oxidation can be marked relative to the respiratory quotient (RQ). This way, when energy is produced from fats (by β-oxidation) more oxygen is consumed and the RQ is low (e.g. 0.7) and alternatively, when carbohydrates are the main source of ATP generation in the body, less oxygen is consumed and the RQ is high (e.g. 1.0). Obese individuals have been reported to have high RQ values, indicating low fat oxidation and thus more dependence on glucose than lean individuals (Filozof et al., 2000; Simoneau et al., 1999). Therefore, reduced fatty acid oxidation is considered as a risk factor for the development of obesity. Other studies indicate that obese individuals have reduced CPT-1 activity, which impairs the flow of fatty acid transfer to mitochondria and hereby reduce β-oxidation, suggesting that fatty acids cannot be oxidized even after lipolysis if CPT-1 is not activated (Simoneau et al., 1999; Rogge 2009).

4. Possible mechanisms of weight loss

i. One of the popular approach of weight loss is through appetite control. The food urge and satiety is controlled by serotonin, histamine, dopamine and their receptors. Sibutramine is an anti-obesity drug which functions as appetite suppressant; however, coupled with various side effects such as dry mouth, constipation and insomnia (Tziomalos et al., 2009).

ii. Stimulated energy expenditure can be used to reduce body weight by induction of non-shivering thermogenesis. Thermogenesis is mainly regulated by leakage of protons

generated in oxidative phosphorylation, bypassing ATP generation and activating UCP-1 which thereby, dissipates energy as heat (Kumar et al., 1999). UCP-1 is expressed in mitochondria-rich brown adipose tissue. Likewise, UCP-3 also mediates thermogenesis regulated by the thyroid hormone, β-adrenergic receptor agonist and leptin (Gong et al., 2000). The function of UCP family was demonstrated in a mice study, where the mice over-expressing UCP-1, UCP-2 and UCP-3 were resistant to diet-induced obesity; however, they were susceptible to cold due to the lack of thermogenesis (Arsenijevic et al., 2000, Gong et al., 2000).

iii. Adipocytes increase in size and differentiate when fat storage increases under obesity. Thus, the compounds that inhibit adipocyte differentiation and induce apoptosis in mature adipocytes can be considered as potentially promising anti-obesity agents (Kim et al., 2006; Yun, 2010).

iv. Many pharmaceutical drugs stimulate triacylglycerol hydrolysis and release fatty acids. Lipolysis diminishes storage fat (leading to dyslipidemia) thus, intervening the β-adrenergic receptor agonist is required to oxidize the released fatty acids (Langin, 2006).

v. In lipid metabolism, peroxisome proliferator-activated receptor gamma (PPAR-γ) and 5' adenosine monophosphate-activated protein kinase (AMPK) play crucial roles. PPAR-γ is a transcriptional factor (mediating gene expression) predominately expressed in adipose tissue that stimulates adipose differentiation. Therefore, PPAR-γ agonists can ameliorate dyslipidemia, as well as improve adiposity and insulin resistance (Cornalius et al., 1994).

vi. AMPK is an enzyme which regulates the target proteins controlling metabolism. AMPK activation regulates glucose transport and fatty acid oxidation. Increase in AMPK in muscle stimulates CPT-1 production and eventually increases fatty acid oxidation (Lee et al.,

2005). Activation of AMPK by exercise and fuel deprivation (AMP:ATP ratio) have led to studies of the effects of AMPK on lipid metabolism, obesity and metabolic syndrome–related diseases (O'Neill, 2013).

vii. One of the most promising approaches to weight management is the decrease in fat absorption. In gastrointestinal tract, before fat gets absorbed, it is subjected to the action of pancreatic lipase with its inhibition being a clinically approved strategy for controlling obesity. One such drug compound is Orlistat; however, also associated with certain side effects like oily spotting, liquid stools, abdominal cramps, etc. (Chaput et al., 2007).

viii. SIRT1 and SIRT3 belong to the sitrulin family of the silent information regulator 2 enzymes which have been found to regulate insulin secretion as well as lipid metabolism. SIRT1 plays an important role in regulation of obesity during fasting and feeding (Chalkiadaki and Guarente, 2012; Guarente, 2006). Its major role is played in hepatic fatty acid metabolism, at various steps such as activation of the AMPK/LKB1 pathway thus facilitating fatty acid oxidation (Hou et al., 2008). The specific action of SIRT1 in regulating PPAR-α was demonstrated in mice studies when hepatocyte specific deletion of the SIRT1 gene led to decreased rate of fatty acid oxidation (Purushotham et al., 2009). On the other hand, SIRT3 directly regulates hydroxyacyl-CoA dehydrogenase, acyl-CoA dehydrogenases and deacetylates as well as activates acyl-CoA synthetase short-chain hereby, modulating β-oxidation (Hallows et al., 2011, Hirschey et al., 2010, Hallows et al., 2006).

5. Phytochemicals stimulating fatty acid β-oxidation

Nutritional supplements have been claimed to increase energy metabolism, reduce fat absorption, increase fat oxidation all of which thereby increase weight loss and consequently

described popularly as fat burners (Jeukendrup and Randall, 2011). The majority of the ingredients used in these nutritional supplements are from plant origin and commonly referred as phytochemicals. These phytonutrients are secondary metabolites produced by plants and play a central role in defensive mechanism against stress, pathogens, herbivores and disease conditions. Phytochemicals are divided into polyphenols, alkaloids and isoprenoids on the basis of their basic structure and biosynthesis (Table 1). The list of phytochemicals capable of facilitating weight loss by reducing appetite suppressants and/or fat absorption is still on-growing; however, not all of them regulate fatty acid β-oxidation. Thus, it is within the scope of this review article to focus on those phytochemicals capable of influencing the β-oxidation pathway (Table 2).

5.1 Epigenetic properties of phytochemicals

Over the past few decades, there is a growing interest in investigating and understanding the beneficial properties of phytochemicals. A number of studies have revealed that the presence of phytochemicals is responsible for exerting a plethora of different biological effects such as antioxidant, anti-inflammatory, anti-aging, anti-proliferative, etc. To this end, after their isolation and characterisation, there is a continuously increasing trend towards promoting their utilization in various fields of biology and medicine such as drug design, disease therapy, cosmeceuticals, nutrition/dietetics, etc. (Su et al., 2013, Szarc del Szic et al., 2015). In recent years, emerging reports have provided evidence that phytochemicals can exert their advantageous effects by targeting epigenetic mechanisms via regulation of specific epigenetic components such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs), histone acetyltransferases (HATs) and small non-coding RNAs (miRNAs) (Guo et al., 2015, Shankar et al., 2013). Epigenetic modifications are defined as reversible and heritable alterations in gene expression without

changes in the DNA sequence. The most common types are DNA methylation as well as histone acetylation, deacetylation and methylation all of which are capable for modulating gene expression. In addition, miRNAs have been implicated in several cellular processes while at the same time they have been shown to regulate gene expression (Sharma et al., 2010).

Current research reports have outlined that there is a relation between epigenetic modifications and metabolic disorders like obesity. More specifically, evidence from a recent report showed that there are different methylation patterns of genes implicated in fatty acid β-oxidation (FAO) in samples obtained from lean and severely obese women in response to lipid exposure. According to the results, there was an immediate induction of genes participating in FAO in response to lipid exposure among lean women whereas this was not observed in the case of the severely obese ones. The mRNA levels of peroxisome proliferator-activated receptor δ (PPAR-δ; a molecule participating in FAO) were found to be differentially regulated in the case of severe obesity, a fact that was attributed to different methylation patterns of the gene (Maples et al., 2015a). Moreover, data from a similar study demonstrated that the expression of carnitine palmitoyltransferase 1B (CPT-1B; a protein responsible for transferring the long-chain fatty acids across the outer mitochondrial membrane) was reduced in skeletal muscle cells isolated from severely obese women in contrast to lean women following lipid exposure. The observed differential expression of CPT-1B, in obese women, was due to alterations in DNA methylation, histone acetylation and transcription factor binding (Maples et al., 2015b). As a consequence, it is logical that the link between epigenetic modifications and obesity could be influenced by phytochemicals (given their ability to modulate key epigenetic processes); however, such link is purely speculative and yet to be established.

185 **5.2 Classes of phytochemicals**

186 **5.2.1 Green tea catechins**

187 Health benefits of regular consumption of green tea are mostly attributed to the large
188 amount of catechins, polyphenols of flava-3-ol sub-family of flavonoids. Unlike black tea, green
189 tea manufacturing preserves high amount of epicatechin, epigallocatechine, epicatechin-3-gallate
190 and epigallocatechine-3-gallate (EGCG) as it is prepared from non-oxidized and non-fermented
191 leaves. Catechins are considered to inhibit catechol-O-methyltransferase which is responsible for
192 breaking down norepinephrine and thereby stimulate fat oxidation (Borchardt, 1975). The hepatic
193 fatty acid oxidation and ATP production directly influence appetite by influencing appetite
194 regulating centers of the brain. Green tea catechins can control appetite as a result of up-regulation
195 of hepatic fat oxidation and ATP generation (Friedman 2007; Kamphuis et al., 2003).

196 Green tea catechins have been supported as fat burning phytochemicals in various animal
197 studies; however, the clinical evidence is still lacking behind in confirming these findings. For
198 instance, results from a study using obese C57BL/6J mice showed that green tea-EGCG had the
199 ability to induce body mass reduction while it also caused changes in the mRNA expression levels
200 of PPAR-γ, C/EBP-α, SREBP-1c, aP2, LPL and FAS all of which decreased in white adipose
201 tissue. On the other hand, the mRNA levels of CPT-1, UCP2, HSL and ATGL increased (Lee et
202 al., 2009). Additionally, another study associated the supplementation of green tea catechins in the
203 diet of lactating maternal rats with the increase of mRNA expression levels of DNMT1, DNMT3a,
204 SIRT1 and SIRT2 in the kidneys of their three week old offspring. This, in turn, supports the
205 correlation between maternal levels of catechins and increased levels of enzymes (in newborn
206 female offspring) capable of influencing epigenetic marks capable of potentially regulating energy
207 metabolism (Sun et al., 2013). In a recent study, addition of 1% green tea to high-fat diet of mice

has reduced mass of adipose tissue and TAG, glucose, insulin, and leptin levels of blood (Lee et al., 2015). It was postulated that green tea has the ability of modulation of abnormal fatty acid β–oxidation caused by high-fat diet.

Beneficial effects of combined flavonoids on diet-induced obesity have been demonstrated. Recently, supplementation of flavonoids from green tea combined with cocoa, coffee and Garcinia has shown to stimulate lipid metabolism in high-energy diet-induced obese rats, which is attributable to fat mobilization from adipose tissue (Huang et al., 2016). A recent review on dietary polyphenols and obesity also confirmed that green tea catechins (especially EGCG), resveratrol and curcumin all exert anti-obesity properties (Wang et al., 2014).

5.2.2 Resveratrol

Resveratrol (3,4,5-trihydroxystilbene) is a naturally occurring stilbene sub-group of polyphenol in grapes, red wine and some berries (Freemont, 2000). It has been studied for its involvement in regulating fatty acid β-oxidation in relation to preventing degradation of intracellular cyclic adenosine monophosphate (cAMP) through inhibition of cAMP phosphodiesterase enzymes which in turn activate the AMPK enzyme (Park et al., 2012a, Chung, 2012a,b), which consequently activates mitochondrial biogenesis and function by activating PGC-1α (Wu et al., 1999). A recent review has also revealed that anti-obesity activity of resveratrol could also be through down-regulation of PPAR-γ, CCAAT-enhancer-binding protein (C/EBPα), and sterol regulatory element binding protein 1c (SREBP-1c) (Aguirre eta l., 2014). In an another resveratrol supplementation (0.02% of diet) study conducted using ApoE-deficient mice, resveratrol exerts not only anti-obesity and hypolipidemic effects, but also protective effects for the liver and aorta through the modulation of lipid metabolism in liver and white adipose tissue

(Jeon et al., 2014). In addition, resveratrol has been proposed as a natural SIRT-1 activator which can also further activate PGC-1α (Lagouge et al., 2006). Moreover, in several animal studies, the supplementation of resveratrol resulted in a remarkable increase of AMPK activity (Baur et al., 2006; Shang et al., 2008b; Rivera et al., 2009). Exposure to resveratrol has reported to increase fatty acid β-oxidation in CPT-II and very long chain acyl CoA dehydrogenase deficient cultured patient fibroblast model (Aires et al., 2014). In another study, resveratrol increased fatty acid β-oxidation by inhibiting the production of malonyl-CoA (Szkudelska and Szkudelski, 2010).

Animal studies have demonstrated the role of resveratrol in energy expenditure in a way where animals were capable of surviving cold longer with supplementation of high doses of resveratrol than untreated ones (Lagouge et al., 2006). Similar observations were recorded after one year of treatment with resveratrol (200 mg/kg/day) where such treatment was found to increase basal metabolic rate and total daily energy expenditure in the non-human primate Microcebus murinus (Dal-Pan et al., 2010; Dal-Pan et al., 2011). These studies further strengthen the capacity of resveratrol to enhance energy expenditure and potentially promote weight loss. Only recently, resveratrol has become the subject of intense research as being a phytochemical associated with a great range of health promoting properties. For this reason, it has attracted the attention of the nutraceutical industry as it is consumed by two-thirds of consumers taken dietary nutritional supplements (Block et al., 2007).

Finally, according to the findings from a recent report, the combined administration of resveratrol and pterostilbene (in rats) resulted in preventing the up-regulation of the FAS gene (induced in response to a high fat and sucrose contained diet) while pterostilbene was also demonstrated to be responsible for the differential methylation pattern of the gene as well (Gracia et al., 2014).

5.2.3 Capsaicinoids

Red hot chillies or peppers are a commonly used spice in food worldwide. Capsaicinoid is the class of pungent polyphenol derivative compound in red chillies. The genus capsicum includes more than 200 varieties and concentration of capsaicin also varies (0 - 13,000 mg/kg) (Kozukue et al., 2005). Capsaicin (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonamide) is the pungent compound which has been reported to increase thermogenesis and secretion of catecholamines from adrenal medulla (Watanbe et al., 1987) which stimulate adrenergic receptors in liver and adipose tissue resulting in lipolysis and energy expenditure (Diepvens and Westerterp, 2007). A meal containing red pepper instantaneously increases energy expenditure in humans (Yoshioka et al., 1995). Although supplementation with capsaicinoids has been reported to increase BMR in human subjects by increasing fat oxidation (Lejeune et al., 2003) they cannot be generally consumed in high dosages due to their strong pungency and nociceptive stimulus. However, capsiate (a non-pungent capsaicinoid analogue derived from Capsicum annuum L.; CH-19 Sweet) has been reported to increase body temperature and increase mRNA and protein levels of uncoupling proteins (UCPs) of brown adipose tissues in a two-week mice study (Masuda et al., 2003). The thermogenic effects of capsaicin are attributed to its structure and not its pungency (Ohnuki et al., 2001a). Similarly, there was an increase in catecholamine and free fatty acid levels together with a decrease in triacylglycerol levels resulting in elevated levels of fat oxidation in mice after supplementation with a single oral dosage of capsiate (Ohnuki et al., 2001b; Haramizu et al., 2006).

CPT-1α is the rate-limiting enzyme in mitochondrial β-oxidation and a target for reducing body fat (McGarry and Brown, 1997). On the other hand, UCP-2 is a mitochondrial proton

277 transporter and has been suggested to influence body temperature, energy expenditure and fat mass
278 (Rousset et al., 2004). Capsaicin is reported to stimulate lipolysis by mediating CPT-1α and UCP-
279 2 in adipocytes (Lee et al., 2011). Capsaicin-induced thermogenesis is proposed to function
280 through stimulation of β-adrenergic receptors as various studies have demonstrated decreased
281 thermogenesis after administration of β-adrenergic blockers (Kawada, 1986). In a combination
282 study of capsaicin with green tea, a decrease in fat mass was observed (Tsi et al., 2003); however,
283 long term supplementation of capsaicin is found to be more effective in weight loss (Lejeune et
284 al., 2003). CH-13 Sweet has similar capsaicin structure and is more suitable for long term use by
285 maintaining effectiveness and without pungency (Reinbach et al., 2009). Furthermore, only
286 recently, another study has demonstrated a different approach to minimize the pungency of
287 capsaicin (and thus increase the possibility of its long term use) by preparing chitosan
288 microspheres (Tan et al., 2014). Chitosan is a polysaccharide extracted from crab shells and it aids
289 to overcome strong pungent taste and smell of capsaicin. Finally, the findings of a study using rats
290 demonstrated that the administration of capsiate resulted in a reduced abdominal fat volume and
291 body weight gain, which were associated with the differential gene expression levels of UCP3 and
292 more specifically a reduction in its mRNA levels (Faraut et al., 2009).
293
294 **5.2.4 Citrus flavonoids**
295 These are a class of polyphenols found in citrus. Naringin and hesperidin belong to
296 flavanone sub-group and nobiletin and tangeretin to O-polymethoxylated flavones. In animal
297 studies, supplementation of naringin (3%) and nobiletin (0.3%) with high fat diet has demonstrated
298 increase in fatty acid oxidation by up-regulating CPT-1α production (Mulvihill et al., 2009;
299 Mulvihill et al., 2011; Jung et al., 2006). Interestingly, dietary supplementation of citrus peel

flavonoid extract (rich in nobiletin, tangeretin, rutin and hesperidin) to high-fat diet-induced obese C57BL/6 mice revered the suppressed activities of AMPK and ACC (Kang et al., 2012). In mature 3T3-L1 adipocytes, the citrus peel flavonoid extract increased AMPK and ACC phosphorylation and also enhanced lipolysis by phosphorylation of cAMP-dependent protein kinase (PKA) and hormones-sensitive lipase (HSL) (Kang et al., 2012).

Apart from the citrus flavonoids, the alkaloid synephrine is also a bioactive component of bitter orange (Citrus aurantium). The fruit is also often used for herbal medicine as appetite suppressant. Bitter orange alkaloids act as adrenergic agonists with octapamine and synephrine being similar to epinephrine and norepinephrine, respectively. Para-synephrine has properties of both α-adrenergic and β-adrenergic agonists and is also known as oxedrine. Its anti-obesity effects are proposed to be due to its action on β3-receptors and increased thermogenesis leading to β-oxidation (Arbo et al., 2008). On the other hand, in a rat study, bitter orange extracts with 4-6% synephrine decreased body weight after 7 days (Calapai et al., 1999). However, there is a little evidence reported the ability of synephrine for weight loss in human.

Finally, according to a research report, naringenin (a grapefruit flavonoid) is capable of regulating the activation of PPARα and PPARγ, while it is also responsible for the induction of several genes in fatty acid oxidation including CYP4A11, ACOX, UCP1 and ApoAI in hepatocytes (Goldwasser et al., 2010). Data from a similar study showed that the administration of naringenin, in rats, led to a differential regulation of the expression levels of PPARα, CPT1 and UCP2, with the up-regulation of PPARα consequently resulting in the increase of CPT1 and UCP2 expression levels (Cho et al., 2011). As well, Huong et al. (2006) has also demonstrated that naringenin (1% of the diet) increases hepatic fatty acid oxidation through up-regulation of gene expression of enzymes involved in peroxisomal β-oxidation in mice.

5.2.5 Piperine

This is a pungent lipophilic alkaloid found in black pepper which is prepared from ground unripe berries from the plant Piper nigrum Linn. Piperine has been found to increase catecholamine secretion (particularly epinephrine) from the adrenal medulla in rats. These effects are similar to capsaicin but not as much potent. This effect can be described as a sympathetic nervous system (SNS)-mediated thermogenesis given that it is diminished after administration of cholinergic blockers (Kawada et al., 1984). Finally, piperine was shown to inhibit the differentiation of 3T3-L1 cells to adipocytes as it induced the down-regulation of PPARγ, SREPB-1c and C/EBPβ and thus implying its potentially beneficial use in the treatment of metabolic disorders (Park et al., 2012b).

5.2.6 Anthocyanins

These are well-known phytochemicals for their antioxidant effects. Apart from dietary antioxidants, they also have several biological activities including anti-convulsant, anti-carcinogenic, anti-atherosclerotic, anti-diabetic and anti-inflammatory thus reducing the risk of disease and in particular coronary heart disease (Drenska et al., 1989; Satue-Gracia et al., 1997; Wang et al., 1999; Koide et al., 1997; Sancho et al., 2012). Recently, studies have documented the role of anthocyanins as anti-obesity agents (Tsuda et al., 2003; Jayaprakasam et al., 2006; Matsui et al., 2001; Kwon et al., 2007). Anthocyanins are water-soluble compounds widely found in fruits and vegetables and responsible for most of the red, purple, and blue colors exhibited by flowers, fruits, and other plant tissues (Castañeda et al., 2009). In the last decade, anthocyanins from purple corn (Zea mays L.), blood orange (Citrus sinensis L.Osbeck), strawberries (Fragaria ananassa),

blueberries (Vaccinium angustifolium), blackberries (Rubus species) and mulberry (Morus australis P.) have been reported to exhibit anti-obesity effects in various in vivo studies (Tsuda et al., 2003; Titta et al., 2010; Prior et al., 2008; Prior et al., 2012; Kaume et al., 2012; Wu et al., 2013a).

In addition, other studies have suggested that treatment with anthocyanin induced ACC phosphorylation and increased mitochondrial fatty acid oxidation via the allosteric regulation of CPT-1, which catalyses the entry of long-chain fatty acyl-CoA into mitochondria in HepG2 cells. Therefore, a decrease in malonyl CoA levels is directly responsible for increase in CPT-1 expression, leading to fatty acid oxidation (Hurley et al., 2005). On the other hand, AMPK regulates the enzymes of lipid metabolism and also directs fatty acid both in oxidative and biosynthetic pathways in the liver (Kahn et al., 2005). AMPK knockdown failed to stimulate AMPK and reduce hepatocellular lipid accumulation. Thus, the possible mechanism of anthocyanin-induced fatty acid oxidation is via AMPK directed inhibition of ACC and FAS which are two key downstream regulators of AMPK in the control of lipid metabolism. A recent study, in mice, has demonstrated down-regulation of CPT-1 gene expression after supplementation with anthocyanin-rich blueberry and mulberry juices, indicating an anthocyanin-induced stimulation of fatty acid oxidation while inhibiting fatty acid synthesis (Wu et al., 2013b). In addition, evidence from a current report further supports the ability of anthocyanins to differentially regulate various genes participating in fatty acid oxidation (e.g. PPAR-α, PPAR-δ, UCP-2, UCP-3, mitochondrial transcription factor A) as their mRNA levels were considerably increased when C57BL/6J mice were fed a high in fat and cholesterol diet with a polyphenol-rich blackcurrant extract (Benn et al., 2014).

5.2.7 Curcumin

This is the main bioactive polyphenol (hydroxycinnamic acid derivative) present in the rhizome of turmeric (Curcuma longa) which is commonly used as dietary spice and food color in Asian countries. In addition, it has been found to regulate signal transduction and gene expression apart of its anti-inflammatory and antioxidant properties and thus of potential benefit in disease prevention and therapy (Ohara et al., 2009; Zingg et al., 2013). Furthermore, an animal study has demonstrated that curcumin reduced the body weight gain in high fat fed mice without altering food intake in addition of influencing energy metabolism and fatty acid β-oxidation in adipocytes, through AMPK (Ejaz et al., 2009). Likewise, curcumin facilitated β-oxidation in in vitro experiments (by up-regulation of CPT-1) and reduced lipid biosynthesis (by down-regulation of glycerol-3-phosphate acyl transferase-1; GPAT-1 and acyl-CoA carboxylase) (Ejaz et al., 2009). Finally, another suggested mechanism of fatty acid oxidation, by curcumin, can be explained in terms of an increase in mitochondrial biogenesis by activation of PGC-1 (Chung et al., 2012a,b; Zingg et al., 2013).

On another note, curcumin i) inhibits lipogenic enzymes in liver, ii) stimulates lipid mobilization from adipose tissue by activating HSL, iii) inhibits fatty acid synthase (FAS) activity and iv) activates fatty acid β-oxidation (Prakash and Srinivasan, 2012; Zhao et al., 2011; Jang et al., 2008). In particular, curcumin has been shown to specifically down-regulate FAS leading to an effective decrease in fat storage. Thus, there is substantial evidence to suggest that curcumin is effective in inhibiting lipid synthesis and storage as well as stimulating fatty acid degradation (Smith, 1994). To this end, data from a recent in vitro study demonstrated that curcumin was able to reduce the mRNA levels of DNMT3B suggesting its ability to affect epigenetic mechanisms

thus leading to altered gene expression (Jiang et al., 2015), a fact that might account for curcumin's observed beneficial effects in weight loss and activation of fatty acid degradation.

5.2.8 Raspberry ketons

Raspberry ketones [4-(4-hydroxyphenyl) butan-2-one; RK] are major phenolic acid derivative compounds present in red raspberry (Rubus idaeus) and are responsible for the sweet aroma of raspberries. Like other berries, raspberry has also been reported to have significant biological effects (Ravai, 1996). RKs have similar structures with capsaicin and synephrine, which are known for their active role in obesity and lipid metabolism (Harada et al., 2008).

RKs' supplementation inhibits body weight gain in high fat-fed rats as they are unable to bind beta-adrenergic receptors and do not trigger lipolysis in the absence of norepinephrines. Therefore, RKs can stimulate norepinephrine-induced lipolysis by facilitating the translocation of HSL from the cytosol to the lipid droplets in the fat cells in addition to increasing fat oxidation and energy expenditure by stimulating thermogenesis (Morimoto et al., 2005). In another study, treatment with 10 μM of RK induced lipolysis, fat oxidation and increased the adiponectin levels in cultured 3T3-L1 pre-adipocytes all of which led to decreased fat mass in adipocytes and potentially have a key role in body weight regulation (Park, 2010). According to the literature, administration of adiponectin increases fat oxidation in obese mice circulating free fatty acid levels by enhancing skeletal muscle fat oxidation (Wolf, 2003; Mullen et al., 2007). The other suggested mechanism of RK regulated fat loss can be through reversing leptin resistance and elevating PPAR-α (Meng et al., 2008; Wang et al., 2012). Leptin is a hormone secreted by adipocytes which stimulate fatty acid oxidation by induction of AMPK (Monokoshi et al., 2002).

5.2.9 Cocoa polyphenols

Cocoa is a major ingredient of chocolate and it is derived from the beans of the Theobroma cacao (Baba et al., 2000). The cocoa beans consist of approximately 6-8% polyphenols (by weight) with their presence contributing to dark chocolate being a rich source of antioxidants. These are predominantly flavonoids and mainly epicatechin, catechin and proanthocyanidins with a small amount of quercetin also present (Manach et al., 2004; Andres-Lacueva et al., 2008). Polyphenol-rich cocoa extracts possess many bioactivities including anti-hyperlipidemic (Hamed et al., 2008), anti-diabetic (Grassi et al., 2005), antioxidant (Galleanoet al., 2009), in addition to improving cognitive and visual performance (Field et al., 2011) and boosting the immune system (Katz et al., 2011).

Genistein, which is the main isoflavone in cocoa extract, directly interacts with PPAR-α and PPAR-γ and functions as an activator for stimulating fatty acid catabolism (Kim et al., 2004a; Kim et al., 2004b). Furthermore, activation of PPAR-α is reported to stimulate the expression of β-oxidation genes, including CPT-1, ACO and UCP3. Adiponectin expression also increases with the activation of PPAR-γ (Maeda et al., 2001) in addition to activating the AMPK pathway which regulates glucose and lipid metabolism (Arts and Hollman, 2005; Kurlandsky and Stote, 2006). Finally, cocoa polyphenols have been reported to increase plasma adiponectin levels and also increase thermogenesis through activation of the AMPK pathway and specifically via up-regulation of UCPs which are involved in facilitating thermogenesis and energy expenditure (Yamashita et al., 2012; Corti et al., 2009).

Even though various studies have mentioned different types of cocoa flavonoids, it is not evident yet which phytochemicals are efficacious for exerting their anti-obesity (Farhat et al., 2014). Nogueira et al., (2011) reported that the supplementation of 2 mg/kg/day of cocoa-derived

epicatechin stimulated fat oxidation whereas in another study, supplementation with a dose of cocoa (containing 18.4 mg epicatchin and 380 mg of polyphenols and equivalent to 40 g/day in humans) exhibited anti-obesity effects in mice (Gu et al., 2014). Moreover, the weight reducing effects of dark chocolate can be partially attributed to caffeine which is present in significant amount (Stark et al., 2006; Zheng et al., 2004). Findings from a very recent study demonstrates that cocoa polyphenol administration in the diet of Sprague-Dawley rats resulted in the differentially regulated expression of genes implicated in lipid metabolism in mesenteric white adipose tissue, as the mRNA levels of several lipolysis enzymes were found to be increased (Ali et al., 2015). Finally, further studies support the ability of cocoa polyphenols to affect DNA methylation patterns of peripheral leukocytes in subjects with cardiovascular risk factors including obesity (Crescenti et al., 2013).

5.2.10 Soybean phytochemicals

Soybeans (Glycine max) are consumed mainly as a source of protein, besides being also rich in micronutrients such as isoflavones, phytate, soyasaponins, phytosterol, vitamins and minerals (Rupasinghe et al., 2003). They are known to be the richest source of isoflavones in food (Cederroth and Nef, 2009) whereas soya-derived phytoestrogens (non-steroidal plant-derived compounds which can bind estrogen receptors and thus mimic estrogen) have been shown to exert beneficial effects in cardiovascular disease, diabetes, osteoporosis and prostate cancer (Setchell, 1998; Tham et al., 1998; Sacks et al., 2006; Kuiper et al., 1997). Soybean isoflavones have been the subject of intense research and thus shown to exert estrogenic effects hence influencing glucose and lipid metabolism (Velasquez and Bhathena, 2007). Various animal studies have demonstrated that a soya-rich diet significantly reduces fat accumulation (Bu et al., 2005; Lephart et al., 2004) and increases

energy expenditure and locomotor activity by utilizing lipid resources (Cederroth et al., 2007; Cederroth et al., 2008). In a study of high-fat diet-induced obesity in C57BL/6 mice, supplementation of fermented black soybean has significantly lowered the body and liver weight and the levels of blood glucose, total cholesterol and leptin (Oh et al., 2014). Similarly, when high fat-diet is supplemented with 0.15% of kaempferol glycosides isolated from soybean leaves, body and adipose tissue weight and blood TAG of C57BL/6J mice were reduced significantly. Furthermore, expression of genes of PPAR-γ and SREBP-1c was also reduced by the diet supplementation of soybean flavonoids (Zang et al., 2015).

Although the anti-obesity effect of soya isoflavones is well-evident, the exact mechanism remains unclear. To this end, suggested mechanisms include correlation of decrease of adiposity with increase in AMPK and ACC activation (Hwang et al., 2005) along with increased lipolysis through inhibition of cAMP phosphodiesterases (Szkudelska et al., 2000). The up-regulation of AMPK, PPAR-γ co-activator-1α (PGC-1α) and PPAR-α resulted in increased β-oxidation and energy expenditure (Cederroth et al., 2007; Cederroth et al., 2008). Although speculative, it may be that such gene up-regulation is the result of the induction of epigenetic mechanisms as recently, a study utilizing monkeys showed the presence of epigenetic alterations (by means of altered DNA methylation patterns) induced when a high in fat content of a soy-based diet was changed to one without soy (Howard et al., 2011).

5.2.11 Hydroxycitric acid

Hydroxycitric acid (HCA), an organic acid, is one of widely known supplements for anti-obesity and weight management. G. cambogia extract is a commercially available and richest source of HCA that contributes to anti-obesity mainly by suppressing appetite (Leonhardt et al., 2002),

inhibiting de novo lipogenesis (Kovacs et al., 2006) and increasing fat oxidation (Preuss et al. 2004). In addition, another suggested mechanism is reduction of the acetyl-CoA by HCA and thus, eventually inhibiting lipogenesis by regulating the availability of precursors for fatty acid and cholesterol biosynthesis (Chuah et al., 2013). In addition, a study by Ishihara et al., (2000) conducted in mice suggested that chronic HCA administration increased fatty acid oxidation during a 3-week experimental period. Moreover, another study determined increase in HCA-induced fatty acid oxidation by means of measuring urinary concentration of fatty acid oxidation by-products (Preuss et al., 2004).

Although, currently there are no reports supporting the contribution of HCA in regulating the expression of genes involved in FAO, a recent study showed that cambogin (a compound from the Garcinia genus) was responsible for inducing epigenetic changes (via an increase in the trimethylation of histone H3K9) in a different experimental setting and in order to exhibit its anti-proliferative effects in various human breast cancer cell lines (Shen et al., 2015). Nevertheless, to this end, other compounds of G. cambogia, like HCA, might also exhibit an ability to induce epigenetic alterations in the context of anti-obesity and consequently management of weight control.

6. Conclusions

There is a vast majority of numerous phytochemicals being the subject of intense research as potentially efficient dietary agents for the management of weight control. However, only some of them are directly involved in weight reduction by stimulation of fatty acid β-oxidation. To this end, the phytochemicals enlisted in this review have demonstrated the capacity for weight loss in both cell-based assays and pre-clinical studies. Even though the clinical evidence is very limited, these plant-based compounds have been traditionally used for their anti-obesity benefits without any

toxicity or health hazard concerns. Most of these phytochemicals, apart from their weight loss properties, also have other additional health benefits including anti-inflammatory, antioxidant and other biological functions. Overall, the benefit of weight loss leads to reduction in fat mass, decrease in inflammation and further reduction of the risk of developing metabolic disease. In addition, it should be noted that there is also evidence to support a role of phytochemicals in regulating the differential expression of various genes, implicated in various cellular pathways through epigenetic mechanisms. Although the current evidence is substantially speculative, the fatty acid β-oxidation pathway can be one such target pathway the significance of which is of extreme importance given its relevance to weight loss and the overall management of weight control.

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8. References

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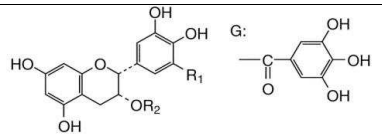
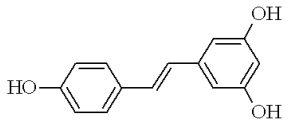
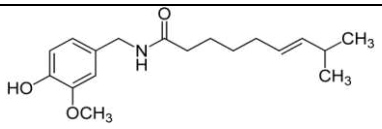
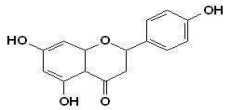
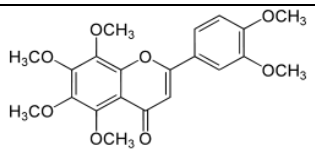
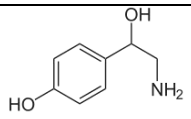
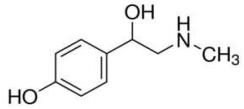
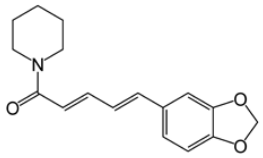
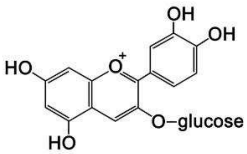
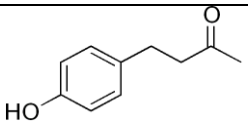
Table 1: Classification of major phytochemicals

Phytochemicals	Examples
Polyphenols	Anthocyanins, flavonols, catechins, isoflavonoids, flavones, flavanones, stilbenes, phenolic acids, capsaicinoids, curcuminoids
Alkaloids	Caffeine, nicotine, piperine
Isoprenoids	Beta-carotene, lycopene, essential oils

Table 2: Structure of phytochemicals and their sources

Phytochemicals	Structure	Source	Effect on β-oxidation
Catechin Epicatechin Epigallocatechin		Green tea, Cocoa	catechol-O-methyltransferase ↓
Resveratrol (3,4,5-trihydroxystilbene)		Grapes, Red wine	SIRT1, AMPK ↑ Malonyl CoA ↓
Capsaicin (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonamide)		Red chillies	β-adrenergic receptors CPT-1, UCP-2 ↑
Naringin		Citrus	CPT-1α ↑
Nobiletin		Citrus	CPT-1α ↑
Octapamine		Bitter orange	β-adrenergic agonist
Synephrine		Bitter orange	β-adrenergic agonist
Piperine		Black pepper	SNS-mediated thermogenesis ↑
Anthocyanins		Purple corn, Blueberry, Strawberry, Bitter orange Pomegrant	CPT-1, AMPK ↑
Raspberry ketones (4-(4-hydroxyphenyl) butan-2-one)		Raspberry	PPAR-α, AMPK HSL ↑

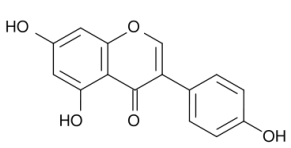
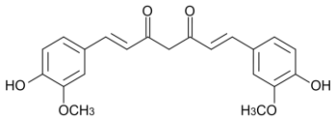
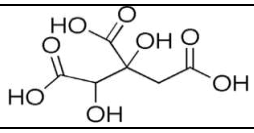
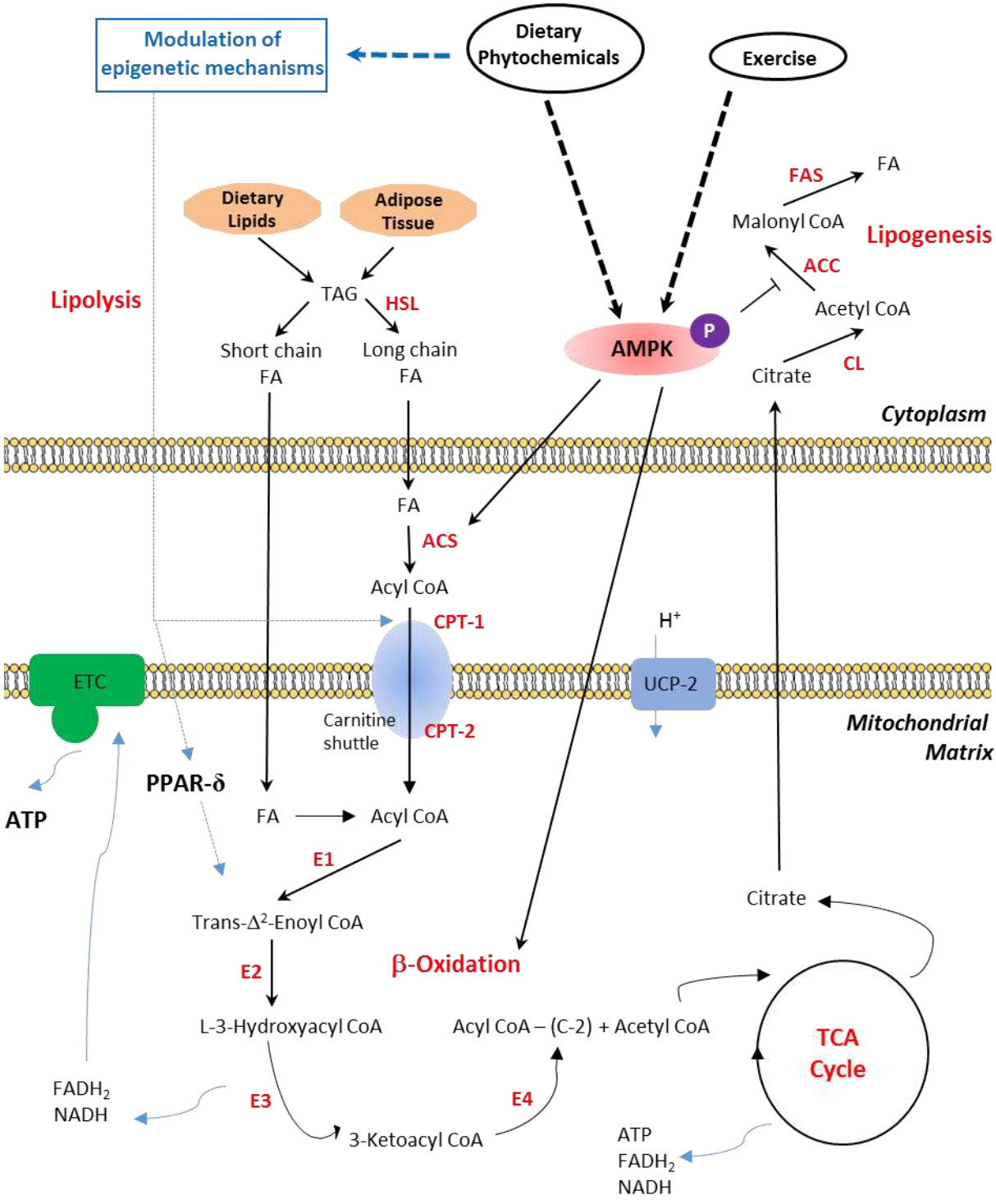
Genistein isoflavones		Soyabeans, Cocoa	AMPK, adiponectin, PPAR-α, CPT ↑
Curcumin		Turmeric	CPT-1 ↑ FAS ↓
(-)Hydroxycitric Acid		Garcinia cambogia	Acetyl-CoA ↓

Figure Legends

Figure 1: Key elements involved in the regulation of fatty acid β-oxidation at various steps. ACC, acetyl CoA carboxylase; ACS, acyl CoA synthetase; AMPK-P, phosphorylated AMP-activated protein kinase; CL, citrate lyase; CPT, carnitine palmitoyl transferase; ETC, mitochondrial electron transport chain; E1, acyl CoA dehydrogenase; E2, enoyl CoA hydratase; E3, 3-hydroxy acyl CoA dehydrogenase; E4, 3-ketoacyl CoA thiolase; FA, fatty acid; FAS, fatty acid synthase; HSL, hormone-sensitive lipase; PPAR-δ, peroxisome proliferator-activated receptor δ; TAG, triacylglycerol; TCA, tricarboxylic acid; UCP-2, mitochondrial uncoupling protein-2.

Figure 1


Modulation of epigenetic mechanisms
Dietary Phytochemicals
Exercise
Dietary Lipids
Adipose Tissue
Lipolysis
TAG
HSL
Short chain FA
Long chain FA
AMPK
P
FAS
FA
Malonyl CoA
Lipogenesis
ACC
Acetyl CoA
Citrate
CL
Cytoplasm
FA
ACS
Acyl CoA
CPT-1
H+
ETC
UCP-2
Carnitine shuttle
CPT-2
Mitochondrial Matrix
ATP
PPAR-δ
FA
Acyl CoA
E1
Trans-Δ2-Enoyl CoA
β-Oxidation
Citrate
E2
L-3-Hydroxyacyl CoA
Acyl CoA – (C-2) + Acetyl CoA
TCA Cycle
FADH2
NADH
E3
E4
3-Ketoacyl CoA
ATP
FADH2
NADH

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