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*A review:*

**Phytochemicals in regulating fatty acid  $\beta$ -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  $\beta$ -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  $\beta$ -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- $\gamma$

Peroxisome Proliferator-Activated Receptor  $\delta$ , PPAR $\delta$

Raspberry Ketone, RK

Respiratory Quotient, RQ

Small Non-Coding RNAs, miRNAs

Triacylglycerol, TAG

Tricarboxylic Acid, TCA

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1 **1. Introduction**

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

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

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

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

28

## 29 **2. Fatty acid $\beta$ -oxidation and its regulation**

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

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

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

52

### 53 **3. Metabolic understanding of obesity**

54 Cellular energy is produced from energy sources in the mitochondria. The major two  
55 sources of energy in a human body are carbohydrates and fatty acids. The body produces energy  
56 in the form of ATP by oxidation of carbohydrates, fats and proteins through tricarboxylic acid  
57 (TCA) cycle; and by fatty acid oxidation through  $\beta$ -oxidation. The body derives energy for its  
58 cellular processes by breaking down ATP to ADP and AMP. Under normal conditions, more ATP  
59 is produced through  $\beta$ -oxidation of fatty acids in the mitochondria as compared to carbohydrates.  
60 The first requirement in fatty acid  $\beta$ -oxidation is the presence of fatty acyl-CoA and its transport  
61 into the mitochondria facilitated by CPT-1 (a rate-limiting step for  $\beta$ -oxidation) (McGarry et al.,  
62 1983; Eaton et al., 2001). Malonyl-CoA (a precursor of fatty acid synthesis) is a competitive  
63 inhibitor of CPT-1 meaning that when an energy level is high, it prevents fatty acid oxidation  
64 whereas when energy level is low, malonyl and acetyl CoA levels fall and consequently  $\beta$ -  
65 oxidation is induced by the activation of CPT-1 (Zammit et al., 1999). Therefore, the enzymes  
66 CPT-1 and fatty acid synthase (FAS) directly regulate catabolism and anabolism of fatty acids  
67 (Ronnett et al., 2005). In addition, glucose oxidation directly inhibits fatty acid oxidation in a  
68 manner characterized by an insulin dependent response where a high glucose level (after a meal)  
69 is regulated by insulin thus facilitating glucose uptake in the cells and consequently inhibiting

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

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

85

#### 86 **4. Possible mechanisms of weight loss**

- 87 i. One of the popular approach of weight loss is through appetite control. The food urge and  
88 satiety is controlled by serotonin, histamine, dopamine and their receptors. Sibutramine is  
89 an anti-obesity drug which functions as appetite suppressant; however, coupled with  
90 various side effects such as dry mouth, constipation and insomnia (Tziomalos et al., 2009).
- 91 ii. Stimulated energy expenditure can be used to reduce body weight by induction of non-  
92 shivering thermogenesis. Thermogenesis is mainly regulated by leakage of protons

93 generated in oxidative phosphorylation, bypassing ATP generation and activating UCP-1  
94 which thereby, dissipates energy as heat (Kumar et al., 1999). UCP-1 is expressed in  
95 mitochondria-rich brown adipose tissue. Likewise, UCP-3 also mediates thermogenesis  
96 regulated by the thyroid hormone,  $\beta$ -adrenergic receptor agonist and leptin (Gong et al.,  
97 2000). The function of UCP family was demonstrated in a mice study, where the mice  
98 over-expressing UCP-1, UCP-2 and UCP-3 were resistant to diet-induced obesity;  
99 however, they were susceptible to cold due to the lack of thermogenesis (Arsenijevic et al.,  
100 2000, Gong et al., 2000).

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

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

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

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

116 2005). Activation of AMPK by exercise and fuel deprivation (AMP:ATP ratio) have led to  
117 studies of the effects of AMPK on lipid metabolism, obesity and metabolic syndrome–  
118 related diseases (O’Neill, 2013).

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

124 viii. SIRT1 and SIRT3 belong to the sirtuin family of the silent information regulator 2  
125 enzymes which have been found to regulate insulin secretion as well as lipid metabolism.  
126 SIRT1 plays an important role in regulation of obesity during fasting and feeding  
127 (Chalkiadaki and Guarente, 2012; Guarente, 2006). Its major role is played in hepatic fatty  
128 acid metabolism, at various steps such as activation of the AMPK/LKB1 pathway thus  
129 facilitating fatty acid oxidation (Hou et al., 2008). The specific action of SIRT1 in  
130 regulating PPAR- $\alpha$  was demonstrated in mice studies when hepatocyte specific deletion of  
131 the SIRT1 gene led to decreased rate of fatty acid oxidation (Purushotham et al., 2009). On  
132 the other hand, SIRT3 directly regulates hydroxyacyl-CoA dehydrogenase, acyl-CoA  
133 dehydrogenases and deacetylates as well as activates acyl-CoA synthetase short-chain  
134 hereby, modulating  $\beta$ -oxidation (Hallows et al., 2011, Hirschev et al., 2010, Hallows et al.,  
135 2006).

## 136 **5. Phytochemicals stimulating fatty acid $\beta$ -oxidation**

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

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

148

### 149 **5.1 Epigenetic properties of phytochemicals**

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

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

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

184

## 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- $\gamma$ , C/EBP- $\alpha$ , 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

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

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

217

## 218 5.2.2 Resveratrol

219 Resveratrol (3,4,5-trihydroxystilbene) is a naturally occurring stilbene sub-group of  
220 polyphenol in grapes, red wine and some berries (Freemont, 2000). It has been studied for its  
221 involvement in regulating fatty acid  $\beta$ -oxidation in relation to preventing degradation of  
222 intracellular cyclic adenosine monophosphate (cAMP) through inhibition of cAMP  
223 phosphodiesterase enzymes which in turn activate the AMPK enzyme (Park et al., 2012a, Chung,  
224 2012a,b), which consequently activates mitochondrial biogenesis and function by activating PGC-  
225  $1\alpha$  (Wu et al., 1999). A recent review has also revealed that anti-obesity activity of resveratrol  
226 could also be through down-regulation of PPAR- $\gamma$ , CCAAT-enhancer-binding protein (C/EBP $\alpha$ ),  
227 and sterol regulatory element binding protein 1c (SREBP-1c) (Aguirre et al., 2014). In an another  
228 resveratrol supplementation (0.02% of diet) study conducted using ApoE-deficient mice,  
229 resveratrol exerts not only anti-obesity and hypolipidemic effects, but also protective effects for  
230 the liver and aorta through the modulation of lipid metabolism in liver and white adipose tissue

231 (Jeon et al., 2014). In addition, resveratrol has been proposed as a natural SIRT-1 activator which  
232 can also further activate PGC-1 $\alpha$  (Lagouge et al., 2006). Moreover, in several animal studies, the  
233 supplementation of resveratrol resulted in a remarkable increase of AMPK activity (Baur et al.,  
234 2006; Shang et al., 2008b; Rivera et al., 2009). Exposure to resveratrol has reported to increase  
235 fatty acid  $\beta$ -oxidation in CPT-II and very long chain acyl CoA dehydrogenase deficient cultured  
236 patient fibroblast model (Aires et al., 2014). In another study, resveratrol increased fatty acid  $\beta$ -  
237 oxidation by inhibiting the production of malonyl-CoA (Szkudelska and Szkudelski, 2010).

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

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

254

### 255 **5.2.3 Capsaicinoids**

256 Red hot chillies or peppers are a commonly used spice in food worldwide. Capsaicinoid is  
257 the class of pungent polyphenol derivative compound in red chillies. The genus capsicum includes  
258 more than 200 varieties and concentration of capsaicin also varies (0 - 13,000 mg/kg) (Kozukue et  
259 al., 2005). Capsaicin (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonamide) is the  
260 pungent compound which has been reported to increase thermogenesis and secretion of  
261 catecholamines from adrenal medulla (Watanbe et al., 1987) which stimulate adrenergic receptors  
262 in liver and adipose tissue resulting in lipolysis and energy expenditure (Diepvens and Westerterp,  
263 2007). A meal containing red pepper instantaneously increases energy expenditure in humans  
264 (Yoshioka et al., 1995). Although supplementation with capsaicinoids has been reported to  
265 increase BMR in human subjects by increasing fat oxidation (Lejeune et al., 2003) they cannot be  
266 generally consumed in high dosages due to their strong pungency and nociceptive stimulus.  
267 However, capsiate (a non-pungent capsaicinoid analogue derived from *Capsicum annuum* L.; CH-  
268 19 Sweet) has been reported to increase body temperature and increase mRNA and protein levels  
269 of uncoupling proteins (UCPs) of brown adipose tissues in a two-week mice study (Masuda et al.,  
270 2003). The thermogenic effects of capsaicin are attributed to its structure and not its pungency  
271 (Ohnuki et al., 2001a). Similarly, there was an increase in catecholamine and free fatty acid levels  
272 together with a decrease in triacylglycerol levels resulting in elevated levels of fat oxidation in  
273 mice after supplementation with a single oral dosage of capsiate (Ohnuki et al., 2001b; Haramizu  
274 et al., 2006).

275 CPT-1 $\alpha$  is the rate-limiting enzyme in mitochondrial  $\beta$ -oxidation and a target for reducing  
276 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-1 $\alpha$  and UCP-  
279 2 in adipocytes (Lee et al., 2011). Capsaicin-induced thermogenesis is proposed to function  
280 through stimulation of  $\beta$ -adrenergic receptors as various studies have demonstrated decreased  
281 thermogenesis after administration of  $\beta$ -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-1 $\alpha$  production (Mulvihill et al., 2009;  
299 Mulvihill et al., 2011; Jung et al., 2006). **Interestingly, dietary supplementation of citrus peel**

300 flavonoid extract (rich in nobiletin, tangeretin, rutin and hesperidin) to high-fat diet-induced obese  
301 C57BL/6 mice reversed the suppressed activities of AMPK and ACC (Kang et al., 2012). In mature  
302 3T3-L1 adipocytes, the citrus peel flavonoid extract increased AMPK and ACC phosphorylation  
303 and also enhanced lipolysis by phosphorylation of cAMP-dependent protein kinase (PKA) and  
304 hormones-sensitive lipase (HSL) (Kang et al., 2012).

305         Apart from the citrus flavonoids, the alkaloid synephrine is also a bioactive component of  
306 bitter orange (*Citrus aurantium*). The fruit is also often used for herbal medicine as appetite  
307 suppressant. Bitter orange alkaloids act as adrenergic agonists with octapamine and synephrine  
308 being similar to epinephrine and norepinephrine, respectively. Para-synephrine has properties of  
309 both  $\alpha$ -adrenergic and  $\beta$ -adrenergic agonists and is also known as oxedrine. Its anti-obesity effects  
310 are proposed to be due to its action on  $\beta$ 3-receptors and increased thermogenesis leading to  $\beta$ -  
311 oxidation (Arbo et al., 2008). On the other hand, in a rat study, bitter orange extracts with 4-6%  
312 synephrine decreased body weight after 7 days (Calapai et al., 1999). However, there is a little  
313 evidence reported the ability of synephrine for weight loss in human.

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

323

### 324 **5.2.5 Piperine**

325           This is a pungent lipophilic alkaloid found in black pepper which is prepared from ground  
326 unripe berries from the plant *Piper nigrum* Linn. Piperine has been found to increase  
327 catecholamine secretion (particularly epinephrine) from the adrenal medulla in rats. These effects  
328 are similar to capsaicin but not as much potent. This effect can be described as a sympathetic  
329 nervous system (SNS)-mediated thermogenesis given that it is diminished after administration of  
330 cholinergic blockers (Kawada et al., 1984). Finally, piperine was shown to inhibit the  
331 differentiation of 3T3-L1 cells to adipocytes as it induced the down-regulation of PPAR $\gamma$ , SREPB-  
332 1c and C/EBP $\beta$  and thus implying its potentially beneficial use in the treatment of metabolic  
333 disorders (Park et al., 2012b).

334

### 335 **5.2.6 Anthocyanins**

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

346 blueberries (*Vaccinium angustifolium*), blackberries (*Rubus* species) and mulberry (*Morus*  
347 *australis* P.) have been reported to exhibit anti-obesity effects in various *in vivo* studies (Tsuda et  
348 al., 2003; Titta et al., 2010; Prior et al., 2008; Prior et al., 2012; Kaume et al., 2012; Wu et al.,  
349 2013a).

350 In addition, other studies have suggested that treatment with anthocyanin induced ACC  
351 phosphorylation and increased mitochondrial fatty acid oxidation via the allosteric regulation of  
352 CPT-1, which catalyses the entry of long-chain fatty acyl-CoA into mitochondria in HepG2 cells.  
353 Therefore, a decrease in malonyl CoA levels is directly responsible for increase in CPT-1  
354 expression, leading to fatty acid oxidation (Hurley et al., 2005). On the other hand, AMPK  
355 regulates the enzymes of lipid metabolism and also directs fatty acid both in oxidative and  
356 biosynthetic pathways in the liver (Kahn et al., 2005). AMPK knockdown failed to stimulate  
357 AMPK and reduce hepatocellular lipid accumulation. Thus, the possible mechanism of  
358 anthocyanin-induced fatty acid oxidation is via AMPK directed inhibition of ACC and FAS which  
359 are two key downstream regulators of AMPK in the control of lipid metabolism. A recent study,  
360 in mice, has demonstrated down-regulation of CPT-1 gene expression after supplementation with  
361 anthocyanin-rich blueberry and mulberry juices, indicating an anthocyanin-induced stimulation of  
362 fatty acid oxidation while inhibiting fatty acid synthesis (Wu et al., 2013b). In addition, evidence  
363 from a current report further supports the ability of anthocyanins to differentially regulate various  
364 genes participating in fatty acid oxidation (e.g. PPAR- $\alpha$ , PPAR- $\delta$ , UCP-2, UCP-3, mitochondrial  
365 transcription factor A) as their mRNA levels were considerably increased when C57BL/6J mice  
366 were fed a high in fat and cholesterol diet with a polyphenol-rich blackcurrant extract (Benn et al.,  
367 2014).

368

### 369 **5.2.7 Curcumin**

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

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

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

393

### 394 **5.2.8 Raspberry ketons**

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

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

413

## 414 **5.2.9 Cocoa polyphenols**

415 Cocoa is a major ingredient of chocolate and it is derived from the beans of the *Theobroma*  
416 *cacao* (Baba et al., 2000). The cocoa beans consist of approximately 6-8% polyphenols (by weight)  
417 with their presence contributing to dark chocolate being a rich source of antioxidants. These are  
418 predominantly flavonoids and mainly epicatechin, catechin and proanthocyanidins with a small  
419 amount of quercetin also present (Manach et al., 2004; Andres-Lacueva et al., 2008). Polyphenol-  
420 rich cocoa extracts possess many bioactivities including anti-hyperlipidemic (Hamed et al., 2008),  
421 anti-diabetic (Grassi et al., 2005), antioxidant (Galleano et al., 2009), in addition to improving  
422 cognitive and visual performance (Field et al., 2011) and boosting the immune system (Katz et al.,  
423 2011).

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

434 Even though various studies have mentioned different types of cocoa flavonoids, it is not  
435 evident yet which phytochemicals are efficacious for exerting their anti-obesity (Farhat et al.,  
436 2014). Nogueira et al., (2011) reported that the supplementation of 2 mg/kg/day of cocoa-derived

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

448

#### 449 **5.2.10 Soybean phytochemicals**

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

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

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

478

### 479 **5.2.11 Hydroxycitric acid**

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

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

491 Although, currently there are no reports supporting the contribution of HCA in regulating  
492 the expression of genes involved in FAO, a recent study showed that cambogin (a compound from  
493 the *Garcinia genus*) was responsible for inducing epigenetic changes (via an increase in the  
494 trimethylation of histone H3K9) in a different experimental setting and in order to exhibit its anti-  
495 proliferative effects in various human breast cancer cell lines (Shen et al., 2015). Nevertheless, to  
496 this end, other compounds of *G. cambogia*, like HCA, might also exhibit an ability to induce  
497 epigenetic alterations in the context of anti-obesity and consequently management of weight control.  
498

## 499 **6. Conclusions**

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

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

515

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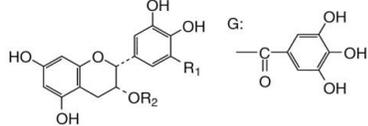
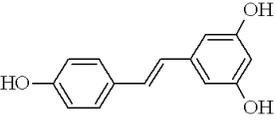
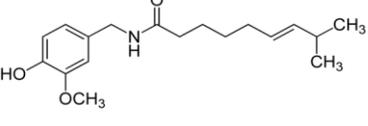
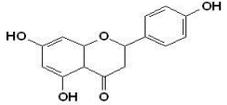
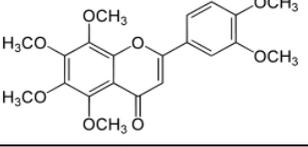
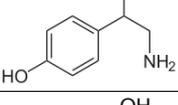
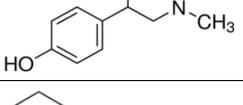
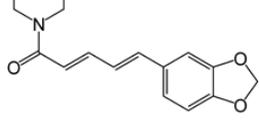
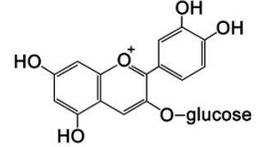
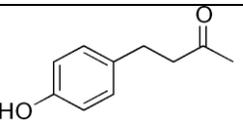
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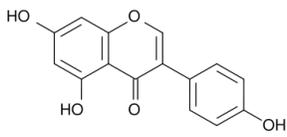
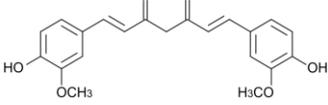
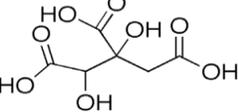
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**Table 1:** Classification of major phytochemicals

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 $\beta$ -oxidation
Catechin Epicatechin Epigallocatechin		Green tea, Cocoa	catechol- <i>O</i> -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	$\beta$ -adrenergic receptors CPT-1, UCP-2 ↑
Naringin		Citrus	CPT-1 $\alpha$ ↑
Nobiletin		Citrus	CPT-1 $\alpha$ ↑
Octapamine		Bitter orange	$\beta$ -adrenergic agonist
Synephrine		Bitter orange	$\beta$ -adrenergic agonist
Piperine		Black pepper	SNS-mediated thermogenesis ↑
Anthocyanins		Purple corn, Blueberry, Strawberry, Bitter orange Pomegranat	CPT-1, AMPK ↑
Raspberry ketones (4-(4-hydroxyphenyl)butan-2-one)		Raspberry	PPAR- $\alpha$ , AMPK ↑ HSL

Genistein isoflavones		Soyabeans, Cocoa	AMPK, adiponectin, PPAR- $\alpha$ , CPT $\uparrow$
Curcumin		Turmeric	CPT-1 $\uparrow$ FAS $\downarrow$
(-)Hydroxycitric Acid		<i>Garcinia cambogia</i>	Acetyl-CoA $\downarrow$

## Figure Legends

**Figure 1:** Key elements involved in the regulation of fatty acid  $\beta$ -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- $\delta$ , peroxisome proliferator-activated receptor  $\delta$ ; TAG, triacylglycerol; TCA, tricarboxylic acid; UCP-2, mitochondrial uncoupling protein-2.

Figure 1

