Herbal Remedies against Adipogenesis

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Received Date: March 25, 2015, Accepted Date: June 24, 2015, Published Date: June 30, 2015.

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Abstract
The epidemic of obesity is a public health crisis. Obesity contributes to varied comorbid conditions including cardiovascular diseases, type II diabetes, hypertension, stroke and certain cancers. Obesity is mainly characterized by an excess accumulation of white adipose tissues; therefore, inhibiting adipogenesis is an anti-obesity strategy. This review aims to discuss the different stages of adipocyte development, and the potentials of targeting adipogenesis with natural products or phytochemicals. Strategies to increase the efficacy of using the natural products to target adipogenesis will also be discussed.

Keywords: Obesity; Adipogenesis; Herbal extract; Phytochemical

Adipogenesis refers to the process of formation of adipose tissue. It is a multistep process starting with clonal expansion of mesenchymal cells and the differentiation of these mesenchymal cells into pre-adipocytes and finally into mature adipocytes. In human, the development of white adipose tissue occurs to a large extent post-natally and continues throughout life. Indeed, fat depots of very old mice contain cells that express early differentiation markers [5]. Adipocyte differentiation involves changes in the levels of more than 100 proteins [5,6]. These proteins are involved in the specialized metabolic roles of mature adipocytes, including lipid transport and metabolism and hormone responsiveness. Therefore, differentiation of pre-adipocytes to mature adipocytes involves striking biochemical and morphological changes (Figure 1 and Table 1). Understanding

Introduction
Obesity has become a public health crisis. Incidence of obesity has been steadily increasing over the past few decades. In 2013, as reported by the US Centers for Disease Control and Prevention, no state had a prevalence of obesity less than 20%. Instead, 23 states had a prevalence of obesity between 25% and 30%; and 18 states had a prevalence of obesity between 30% and 35%. The obesity epidemic is not restricted to industrialized societies. Indeed, over 115 million people in developing countries are suffering from obesity-related problems.

Obesity is mainly caused by an excess accumulation of white adipose tissues [1]; these excess adipose tissues will lead to increased release of free fatty acids, tumor necrosis factor α and resistin, and reduced release of adiponectin, which eventually lead to the development of insulin resistance or chronic hyperinsulinemia [2]. Clinical and epidemiological studies revealed that the obesity-related problems included cardiovascular diseases, type II diabetes, hypertension, stroke and many types of cancers [3]. World Health Organization reported that around 3.4 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of the ischaemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity.

Adipose tissue
Physiologically, white adipose tissue serves as a good triglyceride (TG) store in periods of energy excess. During energy deprivation, the TG stores will be used to provide energy. TG, or fat, has advantage over glycogen or protein as energy store because fat has high energy density and is very little hydrated. Indeed, a fat reserve of 15kg contains 590MJ, which is enough to provide energy for over 50 days if the average daily energy expenditure is 10 MJ. The normal range of relative body fat mass is only 12–20% in men and 20–30% in women. However, adipose tissue can increase its mass by hypertrophy as well as hyperplastic growth. In white adipose tissue, adipocytes accounts for 1/3 to 2/3 of the cells. The increase in the adipose tissue mass is mainly due to enlargement of the adipocytes (hypertrophy) or increased adipogenesis (hyperplasia) [4].

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action of Hh appears to be mediated by transcription factors of the Hedgehog pathway blocks formation of fat body in drosophila [10]. The anti-adipogenic role in the commitment of MSC to adipocyte lineage. Activation of the Hedgehog (Hh) signaling and GATA transcription factors also play a significant role PPARγ 1 and 2 in adipogenesis remain an open question [6]. Studies also suggest that PPARγ is not only crucial for adipogenesis but is also required for maintenance of the differentiated state [6]. Recent studies have suggested that PPARγ is not only crucial for adipogenesis but is also required for maintenance of the differentiated state [6].

Bone morphogenetic proteins are a family with 14 members, and bone morphogenetic proteins-4 has been shown to stimulate the differentiation of MSC to adipocytes [7]. Besides, fibroblast growth factors (FGFs) such as FGFs 1, 10, 16 and 19 have been implicated in adipose development [8]. Interestingly, FGF1 not only enhances adipogenesis of human preadipocytes but also supports development of vascular tissue within the fat pad [9]. Hedgehog (Hh) signaling and GATA transcription factors also play a role in the commitment of MSC to adipocyte lineage. Activation of the Hedgehog pathway blocks formation of fat body in drosophila [10].

Table 1: Markers in different stages of the adipocyte development (Reference: 1-7,12,23,26,27,32-35).

<table>
<thead>
<tr>
<th>stage</th>
<th>Emerging markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipoblasts</td>
<td>Lipoprotein lipase, Adipose differentiation-related protein</td>
</tr>
<tr>
<td>Pre-adipocytes</td>
<td>CCAAT-enhancer-binding proteins (C/EBPβ), Clone 5, Insulin-like growth factor-1, KLFL</td>
</tr>
<tr>
<td>Immature adipocytes</td>
<td>Adipocyte genes (ADD/SREBP1), ATP citrate lyase, Malic enzyme, Acetyl-CoA carboxylase, Steroyl-CoA desaturase, Glycerol-phosphate acyltransferase, Glycerol-3-phosphate dehydrogenase, Fatty acid synthase, Glyceraldehyde-3-phosphate dehydrogenase, C/EBPa, Peroxisome proliferator-activated receptors (PPARγ), Stat5A, Adipocyte-specific fatty acid binding protein 2, Monobutyrin, Serine protease complement factor D, Adipsin, Lipoysis, Perilipin, Hormone sensitive lipase, Lymphatic network, Pref-1, Adipsin, Angiotensin, Plasminogen activator inhibitor-1</td>
</tr>
</tbody>
</table>
| Mature adipocytes | Secretion, Leptin, Adipin, Angiotensinogen, Plasminogen activator inhibitor-1, GABAergic fibers, Pref-1, DLK1, an epidermal growth factor-repeat-containing protein [8], which acts by maintaining the preadipocyte state and preventing adipocyte differentiation [13]. Recently, a study showed that Pref-1 was required for adipose tissue development and expansion [14]. In a transgenic mouse model, the Pref-1-marked florescent-labeled cells appeared in the dorsal mesenteric regions as early as embryonic day 10.5 (E10.5) and these cells became lipid-laden adipocytes at E17.5 in the subcutaneous region, whereas visceral white adipose tissue developed after birth [14]. Interestingly, ablation of Pref-1 prevented white adipose tissue development and also the adult adipose expansion upon high-fat feeding [14]. Clone 5 is another early marker of adipocyte differentiation [5]. High cell density and treatment with adipogenic agents increases clone 5 mRNA levels, and agents that inhibit clone 5 expression inhibit differentiation [15]. Some other pro-adipogenic factors induce PPARγ and C/EBPβ expressions in the adipogenic program. For example, Krox20 is activated early in the adipogenic program of 3T3-L1 cells and contributes to induction of C/EBPβ expression [16]. The increase in C/EBPβ and C/EBPα will turn the induction of the expression of C/EBPβ and PPARγ. Sterol regulatory element-binding transcription factor (SRBP1c/ ADD) and signal transducer and activator of transcription 5 (STAT5) also induce PPARγ expression [17]. Over-expression of SREBP1 [18] or STAT5 [17] significantly enhances the adipogenic activity of PPARγ. It is also suggested that SREBP1c contributes to the production of PPARγ ligands, thereby facilitating the action of PPARγ [18]. Subsequently, C/EBPa and PPARγ will trigger the expression of genes that are important for lipid storage during the adipocyte differentiation program. Indeed, C/EBPβ and PPARγ are the two well-established transcription factors that play a critical role in adipocyte differentiation [19-21]. PPARγ had two isoform, 1 and 2, which are generated by alternative splicing and promoter usage. Both PPARγ1 and 2 are induced during adipogenesis [6]. However, the relative role PPARγ 1 and 2 in adipogenesis remain an open question [6]. Studies also suggest that PPARγ is not only crucial for adipogenesis but is also required for maintenance of the differentiated state [6]. Interestingly, PPARγ can induce adipogenesis in C/EBPβ-deficient mouse embryonic fibroblast, whereas C/EBPβ is incapable of driving the adipogenic program in the absence of PPARγ [22], suggesting
that PPARγ is the dominant factor in the adipose development [23]. PPARγ and C/EBPα expressions can also be induced by ectopic expression of C/EBPβ in NIH-3T3 fibroblast, alone or in combination with C/EBPδ [24-26]. Besides, KLF5 is also in the early stage of adipocyte differentiation by C/EBPβ and C/EBPδ, both of which directly bind to the KLF5 promoter [27]. KLF15 promotes adipocyte differentiation [28] and induces expression of the insulin-sensitive glucose transporter 4 (GLUT4) [29]. There are many other transcription factors which promote adipocyte differentiation such as Krox20 [16] and cAMP regulatory element binding protein (CREB) [30]. In the contrary, other transcription factors may inhibit adipocyte differentiation such as CHOP10 which functions as a negative modulator through hetero-dimerization with C/EBPα mRNA [5]. Besides, GATA2/3, ETO/MTG8, GILZ, and delta-interacting protein A are expressed in preadipocytes and their expression is down-regulated during differentiation [23]. Ectopic expression of each of these proteins in preadipocytes inhibits adipogenesis through antagonism of C/EBPβ activity thereby prevents the induction of PPARγ and C/EBPα [31-35].

In terminal differentiation, the pre-adipocyte takes on the characteristics of the mature adipocyte; it acquires the machinery that is necessary for lipid transport and synthesis, insulin sensitivity and secretion of adipocyte-specific proteins. C/EBPα provides a critical function during terminal adipogenesis since failure to express C/EBP results in insulin resistance in cell culture models and an inability to develop white adipose tissue in vivo [36-37]. Study showed that use of antisense C/EBPα to reduce C/EBPα expression blocked TG accumulation but not the expression of these proteins in preadipocytes and their expression is down-regulated during differentiation [23]. Ectopic expression of each of these proteins in preadipocytes inhibits adipogenesis through antagonism of C/EBPβ activity thereby prevents the induction of PPARγ and C/EBPα [31-35].

Effects of Phytochemicals on Adipogenesis

Plants have always been a source of drugs, and these natural products have been used worldwide as traditional medicines for thousands of years to treat various diseases. Interestingly, some of them have been reported to affect adipogenesis, which can be further developed as anti-obesity agent (Table 2A).

Resveratrol (3,5,4’-trihydroxystilbene) is a natural phytoalexin that can be found in red wines and grape juice [40]. Study showed that resveratrol potently inhibited adipocyte differentiation by down-regulating the expression of PPARγ, C/EBPα, SREBP1c, fatty acid synthase (FAS), hormone sensitive lipase (HSL) and LPL [41]. Besides, some other phytochemicals also show anti-adipogenesis effects. For examples, genistein, a major soy isoflavone, inhibits lipid accumulation and down-regulates expressions of PPARγ, C/EBPα, glycerol-3-phosphate dehydrogenase, adipocyte protein 2 (aP2), FAS, SREBP1, perilipin, leptin, LPL and HSL in primary human adipocytes [42]. Icaritin is a bioactive compound in herb Epimedium, it inhibits adipogenesis of mesenchymal stem cell by decreasing PPARγ, LPL and aP2 [43]. 18β-Glycyrrhetinic acid in the herb liquorice inhibits adipogenic differentiation by down-regulating the expressions of PPARγ, C/EBPα, and adiponectin [44]. Oroxylin A is a flavonoid found in Oroxyllum indicum, a medicinal plant with multiple biological activities. It is found that oroxylin A enhanced lipolysis and decreased Akt-phosphorylation in mature adipocytes, suggesting that it affects adipocyte life cycle at critical point of differentiation and maturity [45]. Curcumin is a well-known component of the cook seasoning and traditional herb turmeric (curcuma longa). Curcumin inhibits FAS activity and differentiation of 3T3-L1 cells [46]. A sulfur-containing compound from garlic, ajene, also inhibits adipogenesis [47]. Antoﬁne is a phenanthroindolizidine alkaloid isolated from the root of Cynanchum paniculatum Kitagawa (asclepiadaceae), which is used as herbal remedy for pain and inflammation. Study showed that chronic administration of antoﬁne suppressed adipocyte

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**Table 2A: Phytochemicals affect adipogenesis.**

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Class</th>
<th>Adipogenesis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>18β-Glycyrrhetinic acid</td>
<td>Aglycone of the triterpenoid Glycyrrhizic acid</td>
<td>Inhibit</td>
<td>40</td>
</tr>
<tr>
<td>Ajene</td>
<td>Sulfur-containing compound</td>
<td>Inhibit</td>
<td>43</td>
</tr>
<tr>
<td>Antoﬁne</td>
<td>Alkaloid</td>
<td>Inhibit</td>
<td>44</td>
</tr>
<tr>
<td>Butein</td>
<td>Chalconoid</td>
<td>Inhibit</td>
<td>45</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Diarylheptanoid</td>
<td>Inhibit</td>
<td>42</td>
</tr>
<tr>
<td>Genistein</td>
<td>Isoflavone</td>
<td>Inhibit</td>
<td>38, 69</td>
</tr>
<tr>
<td>Icaritin</td>
<td>Hydrolytic product of icarin from Epimedium genus</td>
<td>Inhibit</td>
<td>39</td>
</tr>
<tr>
<td>Oroxylin A</td>
<td>Flavonoid</td>
<td>Inhibit</td>
<td>41</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Phytoalexin</td>
<td>Inhibit</td>
<td>37</td>
</tr>
<tr>
<td>Rhein</td>
<td>Glycoside</td>
<td>Inhibit</td>
<td>58</td>
</tr>
<tr>
<td>Wedelolactone</td>
<td>Fumonosoumarin</td>
<td>Inhibit</td>
<td>57</td>
</tr>
</tbody>
</table>

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Effects of Herbal Extracts on Adipogenesis

Herbal extracts contain many bioactive components and therefore exert a diverse array of biological activates. Recent studies showed that herbal extracts also affected adipogenesis (Table 2B). Ulmus pumila L. is a deciduous trees found in many parts of Asia. The stem and root of this species have been used as traditional remedy for the management of edema, mastitis, gastric cancer and inflammation. Interestingly, the extract of Ulmus pumila inhibits adipogenesis through regulation of cell cycle progression in 3T3-L1 cell model [51]. Another traditional Chinese medicinal herb, Rehmannia glutinosa, has been used to increase physical strength. A study showed that the extract of Rehmannia glutinosa inhibited adipogenesis by inhibiting expressions of C/EBPβ, PPARγ, and the terminal marker protein 422/ap2 [52]. Polygonum cuspidatum has been used clinically for the treatment of constipation, gallstones, hepatitis and inflammation in East Asian countries; its extract also inhibits adipogenesis by reducing expressions of PPARγ and C/EBPβ [53]. Sibiraea angustata is a traditional Chinese herb used for improving digestive function. A study demonstrated that the extract of Sibiraea angustata inhibited expression of C/EBPβ, PPARγ, aP2, LPL and glucose transporter 4, it also blocked the cell cycle at G1-S transition phase and caused the cells to remain in the preadipocytes state [54]. Aristolochia manshuriensis Kom is a medicinal herb used for treatment of arthritis, rheumatism, hepatitis. Its extract also inhibited adipocyte differentiation by regulating ERK1/2 and Akt pathway. Besides, expressions of FAS, LPL and aP2 were significantly reduced by the extract treatment during adipogenesis [55]. Root of Panax ginseng C.A. Meyer (Radix Ginseng) is one of the most popular Korean herbal medicine that is known to improve “well-being” by being restorative and enhancing qi and fluid at the same time. Veratrum nigrum, commonly known as Black False Hellebore, is a coarse highly poisonous perennial herb native to Asia and Europe. Interestingly, a combined application of the extracts of both Panax ginseng and Veratrum nigrum significantly inhibited expressions of PPARγ and C/EBPβ, and reduced the lipid accumulation in 3T3-L1 cells [56]. Zizyphus jujube is a fruit used in traditional Chinese medicine for treating diseases related to gastrointestinal health and digestion, as well as being a combination sedative or anxiolytic or pain-killer. It is found that the extract of Zizyphus jujube fruit exerted anti-adipogenesis effect in 3T3-L1 cells [57]. Stem leave and flowers of Cyclopia have been consumed as herbal tea honeybush tea to treat various medical ailments since the 19th century. Interestingly, the total polyphenol contents of Cyclopia maculaga and Cyclopia subternata inhibit adipogenesis in 3T3-L1 pre-adipocytes [58]. Hibiscus sabdariffa L. is a tropical beverage material and medicinal plant, used as in folk medicines against hypertension, pyrexia, inflammation, liver disorders. Its water extract inhibits adipocyte differentiation through PI3K and MAPK pathways, and also reduces expressions of C/EBPβ and PPARγ [59]. Rhizoma Polygonati faltcum is used as traditional herbal medicine in Asia for its anti-hyperglycemia, anti-triglyceric and anti-tumor activities. Its extract and its component kaempferol inhibit adipocyte differentiation. Microarray analysis revealed that Rhizoma Polygonati treatment significantly decreased expression levels of adipogenic transcription factors including Pparγ, Cebpβ, Sreb1, Rxrβ, Lxrβ and Rora [60]. Kaempferol significantly repressed rosiglitazone-induced PPARγ transcriptional activity [60]. Wedelolactone, a major coumarin ingredient in Wedelia chinensis, is used to treat septic shock, hepatitis and venom poisoning. Wedelolactone also inhibits adipogenic differentiation of human adipose tissue derived mesenchymal stem cells through ERK pathway [61]. Radix et Rhizoma rhei has been used to alleviate liver and kidney damage, its compound Rhein inhibits preadipocyte differentiation by down-regulating PPARγ, C/EBPγ, C/EBPδ, and the PPARγ target genes aP2, acyl-CoA oxidase, uncoupled protein 2, acyl-CoA carboxylase and FAS in a cell model. More importantly, Rhizoma Rhei treatment also significantly reduced adiposity in high fat diet-fed mouse model [62], which further suggests its clinical

Table 2B: Herbal extracts affect adipogenesis.

<table>
<thead>
<tr>
<th>Herbal Extract</th>
<th>Extraction</th>
<th>Adipogenesis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aristolochia manshuriensis Kom</td>
<td>Water</td>
<td>Inhibit</td>
<td>51</td>
</tr>
<tr>
<td>Cyclopia maculate</td>
<td>Water</td>
<td>Inhibit</td>
<td>54</td>
</tr>
<tr>
<td>Cyclopia subternata</td>
<td>Water</td>
<td>Inhibit</td>
<td>54</td>
</tr>
<tr>
<td>Hibiscus sabdariffa L</td>
<td>Water</td>
<td>Inhibit</td>
<td>55</td>
</tr>
<tr>
<td>Hwangryunhaedok-tang</td>
<td>Water</td>
<td>Inhibit</td>
<td>61</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>Water</td>
<td>Promote</td>
<td>59</td>
</tr>
<tr>
<td>Mai Tong Fang (Radix astragali, Radix sahiae, Fructus mori)</td>
<td>Water</td>
<td>Inhibit</td>
<td>60</td>
</tr>
<tr>
<td>Morus alba, Melissa officinalis, Artemisia capillaris</td>
<td>Water</td>
<td>Inhibit</td>
<td>62</td>
</tr>
<tr>
<td>Panax ginseng &amp; Veratrum nigrum</td>
<td>Water</td>
<td>Inhibit</td>
<td>52</td>
</tr>
<tr>
<td>Polygonum cuspidatum</td>
<td>Fractions of n-hexane, ethyl acetate, n-butanol, water of the ethanol extract</td>
<td>Inhibit</td>
<td>49</td>
</tr>
<tr>
<td>Rehmannia glutinosa</td>
<td>Ethanol</td>
<td>Inhibit</td>
<td>48</td>
</tr>
<tr>
<td>Rhizoma Polygonati faltcum &amp; Kaempferol</td>
<td>Methanol</td>
<td>Inhibit</td>
<td>56</td>
</tr>
<tr>
<td>Sibiraea angustata</td>
<td>Water</td>
<td>Inhibit</td>
<td>50</td>
</tr>
<tr>
<td>Ulmus pumila</td>
<td>Methanol</td>
<td>Inhibit</td>
<td>47</td>
</tr>
<tr>
<td>Zizyphus jujube</td>
<td>Fractions of chloroform, ethyl acetate, butanol, water of the water extract</td>
<td>Inhibit</td>
<td>53</td>
</tr>
<tr>
<td>Trigonella foenum-graecum (seeds)</td>
<td>70% Ethanol</td>
<td>Inhibit</td>
<td>64</td>
</tr>
<tr>
<td>Securigera securidaca (seeds)</td>
<td>70% Ethanol</td>
<td>Inhibit</td>
<td>65</td>
</tr>
</tbody>
</table>

application in anti-obesity therapy. Indeed, some of the herbal extract promotes adipogenesis. For example, St. John’s wort, or Hypericum perforatum, is a perennial herb used to treat depression in several countries; it promotes adipogenesis by increasing expressions of PPARY and adiponectin [63]. Besides, extracts of fenugreek [64] and Securigera securidaca [65] also inhibit adipogenesis, respectively.

Effects of traditional Chinese formulas on adipogenesis

In clinical setting, traditional Chinese medicine formulas are commonly prescribed to treat various diseases. Interestingly, many of these traditional Chinese formulas also possess anti-adipogenesis properties. Mai Tong Fang is a Chinese herbal combination that is used to treat diabetic nephropathy. Its key ingredients include Radix astragali, Radix salviae, and Fructus mori. Study showed that Mai Tong Fang treatment inhibited differentiation of 3T3-L1 adipocytes, controlled body weight in ob/ob mice, and also blocked the increase of adipocyte size in the adipose tissue [66]. Another formula Hwangryunhaedok-tang, also known as Orenegokuto, is a well-known Chinese, Korean and Japanese traditional herbal medicine that consists of four crude drugs including Coptis japonica, Phellodendron amurense, Gardenia jasminoides and Scutellaria baicalensis. This herbal medicine has been used to remove “heat” and “posion” to treat inflammation, cerebrovascular disease, hypertension, gastritis and liver disease. A study showed that Hwangryunhaedok-tang inhibited adipogenesis by downregulating PPARY, C/EBPα and C/EBPβ via inhibition of Raf/MEK1/ERK1/2 phosphorylation and PDK1/Akt phosphorylation [67]. It is suggested that the active antiobesity constituents in Hwangryunhaedok-tang includes palmitate, berberine, geniposide, baicalin, baicalein and wogonin [67]. The herbal extracts from Morus alba, Melissa officinalis, and Artemisia capillaris also suppress adipogenesis, reduce expressions of genes involved in lipogenesis, angiogenesis, and change the matrix metalloproteinases system [68].

Perspectives

Many phytochemicals and herbal extracts show inhibitory effects on adipogenesis in cell models and mouse models. However, lack of clinical evidence and epidemiological data to support their roles in inhibiting adipogenesis hindered their development to become an anti-obesity therapeutic agent. Furthermore, many of these phytochemicals have low bioavailability. Chemical structural modification or targeted delivery system may help to increase their anti-adipogenesis or anti-obesity efficacies. Nevertheless, many of these phytochemicals are abundantly found in our daily food, or they are the herbs for cooking or seasoning. For example, resveratrol is rich in red wine and grapes; genistein is rich in soy; quercetin in apples and onions, and curcumin is a well-known component of the cook seasoning. Therefore, a healthy diet can definitely help us to increase the uptake of these phytochemicals in our daily life. Moreover, combination of phytochemicals or herbal extracts may act synergistically to inhibit adipogenesis.

Indeed, obesity is not simply an excess accumulation of white adipose tissue but is usually associated with insulin resistance and an increased production of metabolic hormones coupled with chronic low-grade state of inflammation. To effectively reduce obesity, a holistic strategy with the consumption of phytochemicals or herbal extracts can be designed not only to reduce adipose tissue mass, but also increase thermogenic energy expenditure, improve insulin sensitivity, reduce plasma lipids which can help to reduce the obesity-associated dyslipidemia and other comorbid conditions.

Conclusion

Obesity has become a worldwide public health crisis. Consumption of herbal extracts or phytochemicals that can inhibit adipogenesis should be an attractive anti-obesity strategy. Development of these herbal extracts or phytochemicals to an effective anti-obesity therapeutic agent should be beneficial to the obese population.

Acknowledgements

This work was partially supported by GRF grants HKBU262512 and HKBU260613 from Research Grant Council of Hong Kong, FRG1/14-15/061, FRG2/14-15/056, and FRG2/13-14/030 from Hong Kong Baptist University.

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