Ginsenosides Derived from Asian (Panax ginseng), American Ginseng (Panax quinquefolius) and Potential Cytoactivity

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ABSTRACT
Ginseng is a slow-growing, deciduous perennial plant that belongs to the Araliaceae family and the Panax genus. There are a variety of species but the two main types are Panax ginseng C.A Meyer (Asian ginseng) and Panax quinquefolius (American ginseng). Asian ginseng is further subdivided by drying method of the root into either red or white ginseng. Traditionally, both Asian and American ginsengs have been used for a wide array of preventive and therapeutic purposes. Ginsenosides or dammarane triterpenoids are plant secondary metabolites and are thought to be the major active constituents of the Panax species. Ginsenosides are primarily classified into two groups, which are the 20(S)-protopanaxadiol (PD) and the 20(S)-protopanaxatriol (PT), which is based on their chemical structural differences. Differences in ginsenosides chemical structure are due to the type, position, and the number of sugar moieties attached by glycosidic bonds. Both Asian and American ginsengs generally contain a similar ginsenosides profile but vary in terms of amount of individual compounds. Rare ginsenosides which may not naturally be present in ginseng extracts can be obtained via processing methods such as steaming, microbial or enzymatic transformation. The detection and generation of rare ginsenosides can produce ginsenosides such as Rg3, Rb2, IH-901 (K), 25-OH-PD, 25-0CH3-PD among others and this has increased the interest into the biological activity of ginseng. This review focuses on the recent developments in ginseng research.

Keywords: Panax ginseng, Panax quinquefolius, ginsenosides, dammarane triterpenoids, apoptosis, adipocytes

Abbreviations: AMP kinase, S’ adenosine monophosphate-activated protein kinase; ELISA, Enzyme-linked immunosorbsent assay; ESI, Electrospray ionization; GLUT4, Glucose transporter type 4; HPLC, High-performance liquid chromatography; HPTLC, High performance thin-layer chromatography; NIRS, Near infrared spectroscopy; PD, Protopanaxadiol; PPARy, Peroxisome proliferator activated receptors gamma; PT, Protopanaxatriol

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INTRODUCTION
Ginseng has a long history of usage and recent literature suggests that it has broad effects and multiple plausible mechanisms of action. Ginseng research, in general, is hampered by the structural complexity of the bioactive dammarane triterpenoids also known as ginsenosides, which can make specific determinants of bioactivity difficult. Furthermore, the combination of ginsenosides in extracts renders chemical and biological classification extremely difficult and variable. Ginseng is likely the most researched natural health product and a number of reviews have been written (Shibata et al. 1985; Kitts and Popovich 2003; Popovich and Kitts 2003; Popovich and Kitts 2006); however, recently there has been an increased interest into specific rare ginsenosides present or metabolites produced from lactic acid bacterial fermentation and utilization of enzymes to produce specific ginsenosides. This review will mainly focus on the recent literature which includes the characterization of rare types of ginsenosides, detection of ginsenosides, and the effect of ginsenosides on cultured adipocyte regulation.

GINSENG AND GINSENOSIDE CLASSIFICATIONS
Asian ginseng (Panax ginseng C.A. Meyer) has traditionally been the main source of ginseng root utilized in traditional medicines and it is subdivided into two main categories based on the drying conditions used to preserve the root. Ginseng root which is typically air or oven dried is known as white ginseng. If ginseng root is steamed prior to oven drying a second type of ginseng is produced, known as red ginseng and is also referred to as Korean ginseng. The red color of this type of ginseng is a result of caramelization of sugars present in the root. American ginseng (Panax quinquefolius L.), a plant native to North America and has
Ginsenosides are secondary plant metabolites, and as such, have been traditionally used as an alternative to Asian ginseng for its purported cooling effects (yin) as opposed to Asian ginseng which has heating effects (yang). These heating and cooling effects are representative of the main principles of traditional Chinese medicine which aims to achieve the correct balance between yin and yang forces (Shi and Chu 1987). Most of the scientific literature generally focuses on white or red Asian ginseng and American ginseng. Differences in biological activity between these main types of ginseng have been reported and it is thought to be a result of differences in biochemical compounds (ginsenosides) attributed to each type.

Classification of the dammarane triterpenoids or ginsenosides generally falls into two main categories based on the attachment position of various water soluble sugar moieties to the non-polar aglycone. The amphiphilic nature of ginsenosides is influenced by the polarity of the different sugar moieties attached to the ring structure. The first classification is known as the protopanaxadiol (PD) type and the second one is referred to as the protopanaxatriol (PT) type (Fig. 1). The various combinations of sugar moieties are attached at position C-3 of the PD dammarane ring structure while PT has two attachment sites positions C-3 and C-6, respectively. These two types of ginsenoside make up the bulk of the reported ginsenosides. The PD type includes commonly reported ginsenosides Rb1, Rb2, Rc, Rd and rarer types known as Rg3 and Rh2 while the PT type includes Re, Rf, Rg1, Rg2 and Rh1. Ginsenosides were originally named for the migratory pattern when separated on a one dimensional thin layer chromatograph plate but this method of identification has been replaced by more robust methods of detection such as high performance liquid chromatography with an electrospray ionizing mass spectrometer (Popovich and Kitts 2004) (refer below).

Ginsenosides are secondary plant metabolites, and as such, have been detected in all parts of the plant including the root, stems, leaves (Popovich and Kitts 2004) and flowers (Wang et al. 2009a). Ginsenosides have been detected in the dried leaves of American ginseng (Popovich and Kitts 2002). For example, Rg3 and Rh2 have been reported in American ginseng extracts that were subjected to elevated temperatures during extraction and were formed from deglycosylation of sugars present on Rb1 which resulted in increased amounts of structurally related molecules Rd, Rg3 and Rh2. Both Rg3 and Rh2 have been detected in the dried leaves of American ginseng (Popovich and Kitts 2004) and Asian ginseng (Huang et al. 2008) and Panax notoginseng (Dan et al. 2008).

Panax notoginseng (also known as Sanchi Ginseng) is another well-known Panax species that has ginsenosides Rg1 and Rb1 as the most abundant ginsenosides (Dan et al. 2008; Wang et al. 2009a; Chen et al. 2010). Interestingly, ginsenoside Rg3 seems to be readily present in the rhizome, root and flower bud of P. notoginseng, with up to 6.90 ± 0.36 mg/g in the flower bud (Dan et al. 2008). The unique notoginsenosides fingerprints that includes notoginsenoside R1, -R2, -R4, -Fa, -Q, -S, -Fc, -H, -A, -B, -C, -D, -E, -F, -G, -H, -I, -J have allowed P. notoginseng to be easily distinguished (Yoshikawa et al. 1997; Ng 2006; Dan et al. 2008) from American and Asian ginseng. Panax vietnamensis (also known as Vietnamese Ginseng) ginsenoside composition includes Rb1, Rb2, Rd, Rf, Rh5, Rg1, Rh1, Rh4 and also contains ginsenosides R1, R2, R10, R25, pseudo-ginsenoside RT4, and majonoside R2 (Tran et al. 2001).

**DETECTION AND ANALYSIS**

Generally, ginsenosides can be extracted with a variety of solvents but hot water, methanol and ethanol are typically used. Methanol extraction tends to extract higher abundance of ginsenosides than hot water extraction. However, there has been limited usage for food grade application, resulting in ethanol and water extraction being favored. Various methods such as high performance thin-layer chromatography (HPTLC)-densitometry (Chen and Staba 1980; Vanhaelen-Fastre et al. 2000), gas chromatography (GC) (Cui et al. 1993; Cui et al. 1997), high-performance liquid chromatography (HPLC) (Cui et al. 1993; Goran et al. 2005; Christensen et al. 2005; Tran et al. 2001) and also contains ginsenosides R1, R2, R10, R25, pseudo-ginsenosides RT4, and majonoside R2 (Tran et al. 2001).
Christensen et al. 2006; Zhou et al. 2008a; Christensen and Jensen 2009; Hu et al. 2009; Lee et al. 2009b; Han et al. 2010). Most reported HPLC methods use a reverse phase C18 column with water or phosphate buffers and acetonitrile mixture as solvent system, run in either isocratic or gradient elution mode. Ginsenosides are however poor chromophores that require low-wavelength UV (198-205 nm) detection, resulting in high baseline noise and consequently, poor sensitivity. To counter this, HPLC is often coupled with various other detections techniques such as electro-spray ionization (ESI) (Song et al. 2005; Zhang and Cheng 2006; Li et al. 2007; Zhang et al. 2007; Xia et al. 2008; Joo et al. 2010), evaporative light scattering detection (ELSD) (Kim et al. 2007; Wan et al. 2007; Zhao et al. 2009a), MS/MS (Ji et al. 2001; Zhang et al. 2003; Qin et al. 2005; Song et al. 2005; Qin et al. 2006). HPLC-ESI-MS is known to be a sensitive and fast technique that has been widely used for the qualitative studies on saponins, including ginsenosides (Popovich and Kitts 2004; Zhang et al. 2009b).

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>Empirical formula</th>
<th>Molecular weight (Da)</th>
<th>[M-H]-</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rg1</td>
<td>C_{24}H_{37}O_{14}</td>
<td>801</td>
<td>800.0</td>
<td>859.5, 1199.9</td>
</tr>
<tr>
<td>Re</td>
<td>C_{24}H_{39}O_{13}</td>
<td>947</td>
<td>946.0</td>
<td>975.7, 1021.0</td>
</tr>
<tr>
<td>Rf</td>
<td>C_{24}H_{37}O_{14}</td>
<td>801</td>
<td>800.1</td>
<td>845.4, 859.3, 860.4</td>
</tr>
<tr>
<td>Rb1</td>
<td>C_{24}H_{39}O_{13}</td>
<td>1109</td>
<td>1108.0</td>
<td>1137.3, 1249.8</td>
</tr>
<tr>
<td>Rg2</td>
<td>C_{24}H_{39}O_{13}</td>
<td>1079</td>
<td>1077.9</td>
<td>1107.4, 1137.1</td>
</tr>
<tr>
<td>Rh2</td>
<td>C_{24}H_{39}O_{14}</td>
<td>1079</td>
<td>1077.8</td>
<td>1107.2, 1123.2, 1437.2</td>
</tr>
<tr>
<td>Rd</td>
<td>C_{24}H_{39}O_{14}</td>
<td>947</td>
<td>946.6</td>
<td>1021, 968.7, 1087.6</td>
</tr>
<tr>
<td>Rg3</td>
<td>C_{24}H_{39}O_{14}</td>
<td>785</td>
<td>784.8</td>
<td>843.5, 873.4, 1039.3</td>
</tr>
<tr>
<td>Rh2</td>
<td>C_{24}H_{39}O_{14}</td>
<td>623</td>
<td>622.1</td>
<td>681.6, 933.5,1243.6</td>
</tr>
</tbody>
</table>

**Table 1** Selective ginsenosides molecular weight and main ion fragments detected by MS-ESI analysis.

ESI conditions: The molecular weights of ginsenosides standards were confirmed by ThermoFinnigan (Thermo Fisher Scientific, Waltham, MA, USA) LCQ-ESI quadrupole ion trap MS system with MS* capabilities in negative mode. The standards were delivered to ESI-MS at an ion spray voltage of 4.5 kV, a capillary temperature of 250°C and a capillary voltage of 40 eV. A full scan mass spectrum over the range of 100-1500 m/z was recorded using Xcalibur 2.0 data processing software.

**MEASUREMENT IN BIOLOGICAL FLUIDS**

Ginsenosides Rb1 and Rg1 have been detected in rat serum using an enzyme-linked immunosorbsent assay (ELISA) with highly specific monoclonal antibodies (Bae et al. 2000; Hasegawa 2004; Chao et al. 2006). This methodology was shown to have good correlations for Rb1 (γ = 0.997) and Rgl (γ = 0.998) between assay values from both ELISA and HPLC (Chao et al. 2006). Detection of ginsenosides transformed by intestinal microbiota (see below) was successfully detected by HPLC equipped with high-resolution Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS) (Kong et al. 2009). There are increasing number of reports on ginsenoside detection in rat plasma (Qian et al. 2005; Xie et al. 2005; Qian et al. 2006; Li et al. 2007; Xia et al. 2008; Joo et al. 2010), rat urine (Li et al. 2004), dog plasma (Wang et al. 2007b) and in clinical pharmacokinetic studies (Zhang et al. 2009a). LC/MS-MS was validated to be a rapid and sensitive technique for the determination of PD in human plasma and was successfully applied to a clinical pharmacokinetic study of PD in healthy volunteers with a detection limit of 0.05 ng/mL (Zhang et al. 2009a).

**COMPOUND K**

Oral administration of ginseng or ginsenosides can result in biotransformation in the large intestine by the microflora; these microflora include *Bacteroides*, *Fusobacterium*, *Eubacterium* and *Provetella* species of bacteria (Lee et al. 2009a). Intestinal bacterial have been reported to hydrolyze fingerprint ginsenosides such as Rb1, Rc, Rd into more active deglycosylated products that tend to show more bioactivity in a variety of animal and cultured cell experiments. Different species of bacteria may be able to selectively cleave sugar moieties attached to either PD or PT aglycone. As a result there is slight variability in the literature with regard to the specific products that are produced by bacterial biotransformation. It is generally thought that the intestinal bacteria can transform ginsenoside Rb1 into Rg3, Rh2, PD and compound K (Fig. 2). Compound K is one of the major metabolites produced (Bae et al. 2000, 2002; Hasegawa 2004; Zhang et al. 2009a) and has been proposed as the most bioavailable metabolite produced from colonic fermentation (Hasegawa 2004). Many different schemes have been reported to produce compound K. Compound K has been produced utilizing fungal biotransformation with *Paecilomyces bainier* sp. 229 (Zhou et al. 2008b). Thermolabile β-glucosides from *Sulfolobus solfataricus* has been reported to be able to hydrolyze ginsenosides and biotransform them into compound K at an optimal pH of 5.5 from a ginseng extract (Noh et al. 2009). Conversion of both Rb1 and Rb2 to Ginsenoside Rd is one route to the production of compound K (Noh et al. 2009). Breakdown products of PD-type ginsenosides utilizing crude enzyme preparation of lactase, and β-galactosidase from *Aspergillus oryzae* and cellulase from *Trichoderma viride* were found to produce ginsenoside Rd, and intermediate ginsenoside product F2 (Fig. 2) and compound K (Ko et al. 2007). Lactase from *Penicillium* sp produced Rhl from PT-type of ginsenosides while it produced Rd, Rg3 and compound K from the PD-type of ginsenosides (Ko et al. 2007). Ginsenoside Rg3 has also been reported to be produced from a crude ginseng extract with the commercial enzyme cellulase-12T (*Bioland*) (Chang et al. 2009). Selective transformation of ginsenoside Rg3 to Rh2 has been reported using β-glucosidase from *Fusarium proliferatum* (Su et al. 2009). A variety of other metabolites have been reported to be produced based on whether the source ginsenosides was either a PD or PT type of ginsenoside and have been effectively reviewed with an absorption scheme proposed (Hasegawa 2004). These metabolites are thought to be preferentially absorbed and esterified with either stearic, oleic or palmitic fatty acids in the liver (Hasegawa 2004).

An 80 KDa enzyme termed ginsenosides type I was isolated and described from *Aspergillus* sp. g48p strain and is reported to selectively hydrolyze sugar moieties glucose, arabinose, xylose on region R1 (Fig. 1) of dammarane ring structure of PD-type ginsenosides such as Rb1, Rb2, Rb3, Rc, Rd but not PT-type to produce F2, compound K and Rh2 (Yu et al. 2007). A second ginsenoside type II further isolated from the same *Aspergillus* strain removes glyco-
sides containing glucose from Rb1, arabinose-pyranose (Rb2), xylose (Rb3) arabinose-furanose (Rc) at region R3 (Fig. 1) of PD-type to yield ginsenosides Rd and Rg3 (Yu et al. 2009). A β-glucosidase termed G-II extracted from a fungus Cladosporium fulvum has been reported to selectively cleave the glycoside bond at R3 of ginsenoside Rb1 to produce Rd at an optimal pH and temperature of 5.5 and 45°C, respectively (Zhao et al. 2009b).

**COMPOUND K AND CYTOACTIVITY**

Compound K produced by microbial transformation of commercial obtained ginsenoside extract with Aspergillus niger were found to inhibit the growth of a variety of cultured cells including melanoma (B16-B6, LC50 12.7 μM), hepatocarcinoma (Hep-G2, LC50 11.4 μM), myeloid leukemia (K562, LC50 8.5 μM) and lung carcinoma (95-D, LC50 9.7 μM) cells (Zhou et al. 2006). Treatment induced apoptotic cell death with a cell cycle arrest at the G0/G1 phase at 9.7 μM cells (Zhou et al. 2006). The molecular regulation of adipocyte is now thought to contribute to a number of factors that have been identified as involved in the development of the metabolic syndrome (Ming et al. 2007). In human malignant astrocytoma cells, 13 ginsenosides and metabolites were screened and compound K and Rh2 were identified to induce apoptotic cell death by activating the caspases, p38, and MAPK while not affecting the growth of primary astrocytes (Choi and Choi 2009). The effects were magnified when combined with a Fas ligand which is part of the TNF/NGF receptor family (Choi and Choi 2009).

**NEWLY CHARACTERIZED GINSENOSIDES**

A variety of newly isolated and characterized ginsenosides have been reported recently (Table 2). A panaxadiol type (dammar-(E)-20(22)-ene-3β,12β,25-triol) has been isolated from Asian ginseng utilizing acid hydrolysis for 6 h at 80°C with 10% HCl in 50% ethanol (Tao et al. 2009). Three newly characterized ginsenoside-like saponins were extracted from the flower buds of Asian ginseng and are referred to as floralginsenosides Ta, Tb, and Tc (Tung et al. 2010) (Fig. 2). The cytotoxicity of these compounds were tested on human leukemia cells (HL-60) and floraginsenosides Ta was found to have an LC50 of 36.3 μM assessed by the MTT viability assay and induced apoptosis whereas as Tb and Tc did not show cytotoxicity (Tung et al. 2010). Extraction and characterization of the leaves of American ginseng yield a new compound named quinquifolioside-Lc (Fig. 2) (Qiu et al. 2009). This new compound showed some cytotoxicity with an LC50 value determined to be 93.8 μmol/L in estrogen dependent cultured breast cancer cells (MCF-7) but it was not as cytotoxic as ginsenoside Rh2 (LC50, 20 μmol/L) (Qiu et al. 2009). A further new type of dammarane triterpenoid from the American ginseng root was identified by infra red (IR), MS, 13C-NMR and was named as ginsenoside Rg8 and was detected along with two previously identified ginsenosides (20E)-F4 and F1 which have been detected in American ginseng root for the first time (Dou et al. 2006).

Two new ginsenosides 25-OH-PPD and 25-OCH3-PPD were identified from Asian ginseng and cytotoxicity established in cultured pancreatic cells (Panc-1, HPAC) by the MTT assay (Tung et al. 2009b). The LC50 of 25-OH-PPD was determined to be 21.2 μM in Panc-1 cells and 22.5 μM in HPAC whereas the 25-OCH3-PPD was more potent with LC50 values of 7.8 and 5.8 μM in the respective cells lines (Wang et al. 2009b). Both compounds showed an ability to arrest the cell cycle at the G1 phase (Wang et al. 2009b). It is likely that as more attention is paid to complete identification of compounds present in ginseng and ginseng plant parts that further new compounds will be characterized and bioactivity assessed.

**ADIPOCYTE REGULATION**

As obesity levels in the developed world and especially in North America have increased substantially in the past few decades (Flynn et al. 2006), adipocyte regulation by natural products such as ginseng has become a burgeoning research topic area. The molecular regulation of adipocyte is now thought to contribute to a number of factors that have been either linked to the development of the metabolic syndrome.
murine fibroblast cell line is typically utilized to study inhibition of adipogenesis is currently unclear. The 3T3-L1 sides on the adipocyte regulation and the promotion or the maintenance of health. The effect of specific ginsenosides on insulin resistance and diabetes (Gil-Campos et al. 2004) or the maintenance of health. The effect of specific ginsenosides on the adipocyte regulation and the promotion or inhibition of adipogenesis is currently unclear. The 3T3-L1 murine fibroblast cell line is typically utilized to study in vitro adipocyte metabolism as it differentiates from a fibroblast into an adipocyte-like cell. Ginsenoside Rh1 treatment (10 μM) of differentiating 3T3-L1 fibroblast (3T3-L1 cells) increased adipogenesis or lipid acquisition measured by Oil-Red-O staining of cells in a dose-dependent manner (Shang et al. 2007). Rh1 treatment further increased both peroxisome proliferator activated receptors gamma (PPARγ), C/EBPα quantified by RT-PCR and up-regulated GLUT4 (glucose transporter type 4) (Shang et al. 2007). Expression of both PPARγ and C/EBPα are important for cellular differentiation. Ginsenoside Rb2 has also been reported to have an influence on cultured 3T3-L1 cells (Kim et al. 2009). Under high cholesterol condition and elevated serum conditions of the culture media, Rb2 prevented lipid acquisition and decreased triglyceride levels while stimulating the expression of leptin mRNA (Kim et al. 2009). Ginsenoside Rh2 has been reported to possess anti-obesity like properties in 3T3-L1 cells (Hwang et al. 2007). Ginsenoside Rh2 effectively inhibited the differentiation of preadipocyte-like fibroblasts into adipocytes by PPARγ inhibition and reduced the lipid acquisition at concentrations of 20 and 40 μM (Hwang et al. 2007). AMP kinase (5’t adenosine monophosphate-activated protein kinase) which is involved in cellular energy homeostasis was also up-regulated after Rh2 treatments. As with ginsenoside Rh2, Rg3 has similarly been reported by the same research group to inhibit both PPARγ and activating AMP kinase. Both PPARγ inhibition and AMP kinase activation are desirable traits and are thought to decrease potential risk factors of metabolic diseases such as diabetes. Protopanaxatriol (PT) was reported to activate PPARγ dose-dependently in 3T3-L1 cells and this activity was similar to the thiazolidinedione troglitazone a PPARγ agonist (Han et al. 2006); at concentration of between 1 – 25 μM treatment increased the GLUT4 expression (Han et al. 2006).

Ginsenoside Rg3 and Re at concentrations between 1 – 10 μM were reported to increase glucose uptake in 3T3-L1 cells by approximately 10 and 12% and this increase was likely through increase in GLUT4 expression (Lee et al. 2011). Similarly compound K and Rg1 both increase glucose transport in 3T3-L1 cells by increasing the expression of GLUT4 but not GLUT1 and compound K was reported to suppress lipid accumulation while Rg1 increase it (Huang et al. 2010).

In our laboratory we have attempted to establish a baseline response of ginsenosides contained in extracts derived from American ginseng on 3T3-L1 differentiation and adiponectin expression (Yeo et al. 2011). An extract that contained Rg1 (347.3 ± 99.7 μg/g, dry weight), Re (8280.4 ± 792.3 μg/g), Rb1 (1585.8 ± 86.8 μg/g), Re (32.9 ± 8 μg/g), Rb2 (62.6 ± 10.6 μg/g) and Rd (90.4 ± 3.2 μg/g) dose-dependently reduce the growth of 3T3-L1 fibroblasts with an LC50 value determined to be 40.3 ± 5 μg/mL (Yeo et al. 2011). When the ginseng extract was included along with the differentiation hormone cocktail required for 3T3-L1 cells differentiation, it significantly reduced lipid acquisition by 13% and 22% when treated at concentrations of 20.2 μg/mL and 40.3 μg/mL compared to untreated differentiating control cells. Furthermore, this extract increased adiponectin release measured by western blot. In vivo, decreased adiponectin has been observed in the obese and is related to insulin resistance (Abbasi et al. 2004; Antuna-Puente et al. 2008). Fig. 3 shows a representation of the potential interaction of ginsenosides with the preadipocyte, differentiating adipocyte and the mature adipocyte.

CONCLUSION

The complexity of the triterpenoids contained in ginseng both from American and Asian ginseng sources allow for an interesting field of research. Novel metabolites produced by colonic fermentation with intestinal microbiota or biotransformation of ginseng with other microorganism or enzymes have expanded the number of ginsenosides. As new a more sensitive analytical detection techniques are focused on ginseng more novel compounds will be uncovered. It is likely that these new metabolites or compounds would convey the potential interaction of ginsenosides with the preadipocyte in an in vivo environment. As ginseng research progresses, the determination of biological activity such as the influence on adipocyte function becomes increasingly important to the overall understanding of impact of these roots with a long history of use.

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