Anti-obesogenic and antidiabetic effects of plants and mushrooms

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Abstract | Obesity is reaching global epidemic proportions as a result of factors such as high-calorie diets and lack of physical exercise. Obesity is now considered to be a medical condition, which not only contributes to the risk of developing type 2 diabetes mellitus, cardiovascular disease and cancer, but also negatively affects longevity and quality of life. To combat this epidemic, anti-obesogenic approaches are required that are safe, widely available and inexpensive. Several plants and mushrooms that are consumed in traditional Chinese medicine or as nutraceuticals contain antioxidants, fibre and other phytochemicals, and have anti-obesogenic and antidiabetic effects through the modulation of diverse cellular and physiological pathways. These effects include appetite reduction, modulation of lipid absorption and metabolism, enhancement of insulin sensitivity, thermogenesis and changes in the gut microbiota. In this Review, we describe the molecular mechanisms that underlie the anti-obesogenic and antidiabetic effects of these plants and mushrooms, and propose that combining these food items with existing anti-obesogenic approaches might help to reduce obesity and its complications.

Insulin resistance
Pathological condition in which the body produces insulin but fails to adequately respond to it.

The incidence of obesity has more than doubled since 1980, and has now reached worldwide epidemic status[1,2]. In 2014, the WHO estimated that overweight affected 39% of the human adult population (1.9 billion people), and that obesity affected 13% (600 million people)[2]. Most people with obesity show signs of chronic inflammation, hypertension and insulin resistance[3,4], and obesity increases the risk of developing various health problems, including heart disease and stroke, osteoarthritis, type 2 diabetes mellitus (T2DM) and various cancers[5–7]. As such, obesity is associated with poor quality of life and premature death[3,8,9]. Although genetic predispositions have a role in the development of obesity in some individuals[10–12], the obesity epidemic has largely been attributed to high-calorie diets and sedentary lifestyles[2,13]. Excess body weight, therefore, represents a preventable condition that could be largely avoided by lifestyle changes.

Obesity essentially represents an imbalance between intake and expenditure of energy. Reducing body weight by ≥5% has beneficial effects on health and reduces the risk of developing cardiovascular disease and T2DM[14–16]. Although the combination of a low-calorie diet and regular physical exercise leads to weight loss, and represents the best approach to prevent and treat obesity, this strategy is hard to implement and its efficacy is variable[17], mainly because of adaptive mechanisms that act to maintain energy stores in the body[18]. Pharmaceutical drugs have also been approved for anti-obesogenic treatment. Orlistat, the main drug for long-term anti-obesogenic treatment, leads to an average reduction in body weight of 3% over a 1-year period[16], but can also produce gastrointestinal adverse effects, subacute liver failure and acute kidney injury[19]. Other anti-obesogenic drugs, such as fenfluramine, sibutramine and rimonabant, have been withdrawn from the market because of severe adverse effects, including cardiovascular problems, high blood pressure, mood disorders and even suicidal tendencies[20]. Molecules that mimic endogenous peptide hormones such as glucagon-like peptide 1 (GLP-1) represent another potential class of anti-obesogenic drugs, but these need to be delivered intravenously, intranasally or subcutaneously. Additionally, these drugs are rapidly cleared from the blood, and their long-term safety remains to be established[21,22]. Compared with anti-obesogenic drugs, weight-loss surgery by gastric bypass or gastric banding is more effective[23], but is relatively expensive, physically invasive and inapplicable to the majority of overweight people. Alternative anti-obesogenic treatments that are effective, safe and widely available would be beneficial.

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Key points

- The prevalence of obesity is increasing worldwide as a result of high-calorie diets and sedentary lifestyles
- Current anti-obesogenic therapies have limited effectiveness and/or severe adverse effects
- Substances in plants and mushrooms have anti-obesogenic and antidiabetic effects by regulating appetite, nutrient digestion and absorption, adipogenesis, energy expenditure, insulin sensitivity and composition and function of the gut microbiota
- Clinical data relating to the effectiveness of plants and mushrooms are limited, but preliminary evidence suggests they can have beneficial effects on body weight and fat accumulation in humans
- Herbal and fungal phytonutrients could be combined with existing weight-loss treatments to optimize anti-obesogenic effects

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In this Review, we describe the anti-obesogenic effects of plants and mushrooms that are used in traditional Chinese medicine (TCM) or as functional foods (nutraceuticals). Although the anti-obesogenic effects of several plants have been described before[24–26], we focus here on the cellular and physiological mechanisms that underlie their effects on obesity, and highlight results relating to the modulation of hormones that control satiety, adipocyte function and insulin sensitivity. We also describe the role of the gut microbiota in these anti-obesogenic effects. As T2DM is intimately associated with the development of obesity, we examine the possible antidiabetic effects of these phytochemicals. Finally, we assess the epidemiological and clinical evidence that plant-based preparations can beneficially affect body weight in humans, and highlight the remaining challenges in this area.

Traditional Chinese medicine
A system of medical treatments that has been practiced in China for at least 2,000 years, including herbal medicine, acupuncture, *qigong* and meditation.

Nutraceuticals
Dietary supplements or purified compounds that produce beneficial physiological effects on the human body, in addition to their nutritive values.

Historical perspective

Plants have historically been widely used for medicinal purposes[27,28]. For instance, wounded limbs have been wrapped in plant leaves to improve healing, and plant concoctions have been used as laxatives, emetics, anti-pyretics and anti-parasitics. Active compounds have now been isolated from plants, and ~50% of pharmaceutical drugs are estimated, directly or indirectly, to be plant derivatives[29,30]. Notable examples of plant-derived drugs include salicylic acid (isolated from the bark of the willow tree, leading to the development of aspirin), morphine (isolated from the opium poppy), quinine (an antimalarial isolated from cinchona bark) and atropine (a muscle relaxant isolated from nightshade plants)[31].

Epidemiological results indicate that consumption of plant-based foods can be associated with health benefits relating to the incidence of T2DM, obesity, cardiovascular disease and some cancers. These effects have been attributed to the high content of fibre, phytonutrients, vitamins and minerals found in vegetables, in addition to the low content of saturated fat[32]. Herbal remedies, in the form of plant extracts or isolated phytochemicals, are routinely consumed as health supplements. In 2001, US consumers spent US$1.3 billion on weight-loss supplements[33]. However, questions remain about the effectiveness, mode of action and safety of these supplements and functional foods[33,34].

Plant remedies have been widely used in TCM, a 2,000-year-old medical system that includes herbal medicine, acupuncture, *qigong* and meditation. Although the efficacy, safety and mechanisms of action of TCM remain to be established, several plant compounds derived from TCM remedies are now routinely used in conventional medicine. For example, artemisinin is one of the main anti-malarial drugs currently available, and its discovery and isolation from sweet wormwood resulted in the award of half of the 2015 Nobel Prize in Physiology or Medicine[35]. The amphetamine-like compound ephedrine was isolated from the plant *Ephedra sinica*, and is a treatment for asthma[27]. Similarly, the immunosuppressive drug fingolimod was derived from a compound produced by the mushroom *Isaria sinclairii*, and has been approved in the USA as a treatment for multiple sclerosis[36]. In addition, several exotic mushrooms used in TCM remedies, including *Ganoderma lucidum* (commonly known as lingzhi), *Ophiocordyceps sinensis* (previously called *Cordyceps sinensis*) and *Agaricus blazei* Murrill, have shown antidiabetic, anti-inflammatory and anticancer effects in experiments involving cell lines, laboratory animals and humans[37–39]. Notably, herbal and fungal TCM remedies have anti-obesogenic effects in laboratory animals[40,41], which suggests that they might also have effects on body weight and lipid metabolism in humans. The potential application of a single herb or mushroom to the treatment of a human condition differs from the practice of TCM, which has a holistic approach that generally involves the combination of several herbal remedies and other treatments that are selected on the basis of specific traits or symptoms of the patient.

Suppression of appetite

Feelings of hunger and satiety are regulated by complex neural and endocrine interactions between the gut, brain and adipose tissues[42–44]. For instance, the hormone ghrelin, which is released by the gastrointestinal tract when the stomach is empty, induces hunger by acting on hypothalamic brain cells in the central nervous system (CNS). The presence of food in the gastrointestinal tract activates the vagus nerve afferent pathway, leading to inhibition of the hunger centre in the brain. Similarly, food intake induces the release of cholecystokinin by epithelial cells of the small intestine, which inhibits the activity of hunger-stimulating neuropeptide Y in the hypothalamus. Leptin is a satiety-inducing hormone that is released by adipocytes upon stimulation with insulin. Leptin inhibits the activity of neuropeptide Y and the hunger-stimulating fatty acid neurotransmitter anandamide, and activates the hunger-suppressing peptide α-melanocyte-stimulating hormone. Serotonin, noradrenaline, dopamine and endocannabinoids also regulate appetite and satiety. Sibutramine, an anti-obesogenic drug that has been removed from the market because of associated risks of cardiovascular events, reduces appetite by inhibiting the reuptake of serotonin, noradrenaline and dopamine in the CNS[20]. Rimonabant, an anti-obesogenic drug that was marketed in Europe before its withdrawal because of adverse effects, reduces appetite by blocking cannabinoid receptor 1 (REF. 20).

Potential appetite suppressants have been isolated from plants that have uses in TCM. Celastrol is a pentacyclic triterpenoid compound that is found in the roots of the thunder god vine (FIG. 1), a plant with therapeutic uses in TCM for rheumatoid arthritis and fever. Celastrol reduces appetite and food intake in mice that are fed a high-fat diet (HFD)[40], and led to a 45% reduction in body weight when given orally (10 mg/kg daily) to HFD-fed mice for 3 weeks, an effect that was mainly attributed to increased leptin sensitivity relative to vehicle-treated controls. The leptin-sensitizing effect of celastrol was identified by a screening assay[40] for molecules that reduce endoplasmic reticulum stress, which occurs in cells when misfolded proteins accumulate. Hypothalamic endoplasmic reticulum stress and activation of the unfolded-protein response occur in individuals with obesity and are thought to contribute to low levels of leptin-receptor signalling and to leptin resistance, both of which are associated with obesity[45]. Leptin resistance is the lack of appetite reduction in response to leptin, and it occurs despite high blood levels of leptin in obesity[46]. Celastrol causes reduction of endoplasmic reticulum stress and activation of leptin-receptor signalling in the hypothalamus, thereby reducing leptin resistance (FIG. 2). Compared with vehicle-only controls, celastrol also increases glucose tolerance in HFD-fed mice[40]. Endoplasmic reticulum stress occurs in the pancreatic β cells of patients with T2DM, and has been associated with β-cell death induced by hyperglycaemia and hyperlipidaemia[47]. The antidiabetic properties of celastrol could result from its effect on endoplasmic reticulum stress, as well as from antioxidant and anti-inflammatory effects[48].

Fenugreek has culinary uses as a spice or a vegetable in various countries, and has been studied for its satiety-inducing effects. In a small, randomized crossover study involving 18 otherwise-healthy individuals with obesity, fenugreek fibre (8 g) given with breakfast increased feelings of satiety compared with placebo[49]. Natural plant compounds such as ephedrine from *Ephedra sinica* (FIG. 1) also suppress appetite, by activating adrenergic receptors in the hypothalamus (FIG. 2)[50,51]. However, the use of amphetamine-related compounds such as ephedrine is associated with severe adverse effects, including addiction, psychiatric symptoms, tachycardia, hypertension and heart disease[20,52]. The possibility of developing safe appetite suppressants from plants is still an area of intense investigation.

Effects on digestion and absorption

Dietary fats consisting of triglycerides are hydrolysed to release fatty acids, which are absorbed by the mucosa of the small intestine. The hydrolysis step is mainly performed by pancreatic lipase, an enzyme that is secreted by the pancreas into the small intestine in response to food intake. The anti-obesogenic drug orlistat inhibits the activity of human pancreatic lipase by forming a covalent bond with the enzyme at its catalytic site[53]. Various plant compounds, including caffeine, flavonoids, polyphenols and saponins, also inhibit pancreatic lipase *in vitro* (FIG. 2)[54], as do extracts of yerba mate leaves, which are infused to make a traditional South American drink known as mate (chimarrão in Portuguese)[55]. Notably, the inhibitory effect of some herbal extracts is comparable to that of orlistat. In a screen of 37 plants from TCM, an extract of *Prunella vulgaris* (self-heal) inhibited pancreatic lipase activity by 75%, compared with 94% for orlistat[56]. The plant flavonoid quercetin, which is found in many fruits, vegetables and grains (FIG. 1), inhibited lipase activity by 27%, whereas luteolin, which is found in broccoli, celery and green pepper, produced 17% inhibition. Plant derivatives might also inhibit other enzymes that are involved in food digestion. For example, the plant flavonol glycoside montbretin A inhibits human pancreatic α-amylase[57], which catalyses the hydrolysis of starch into sugars.

Food fibre found in the diet or consumed as nutraceuticals, such as chitosan (which can be prepared from crustaceans, and also from mushrooms), guar gum (from guar beans) and pectin (from plants), is not digested by human gastric enzymes, and can reduce blood lipid and cholesterol levels by binding to dietary fats and inhibiting their absorption (FIG. 2)[58,59]. Dietary fibre has a bulking effect that can induce satiety and delay gastric emptying, leading to a reduction in the glycaemic index of a meal. Fibre provides less energy than digested carbohydrates, although some types of fibre undergo breakdown by fermentation in the large intestine, and contribute to dietary energy intake. However, plant fibres can also inhibit absorption of prescription drugs[60], although this effect can be avoided by following prescription guidelines.

Gut microbiota
Community of microorganisms living in the gastrointestinal tract in animals and humans, which has been shown to participate in various physiological and pathological processes in the gut and systemically.

Phytochemicals
Bioactive plant components that can have physiological effects in the human body.

Endoplasmic reticulum
An organelle of eukaryotic cells that is involved in protein synthesis and sorting, and lipid synthesis and metabolism, as well as detoxification.

Endoplasmic-reticulum stress
Condition in which misfolded proteins accumulate in the endoplasmic reticulum, leading to organelle dysfunction.

Leptin resistance
Pathological condition associated with obesity in which the body produces the hormone leptin, but fails to adequately respond to it.

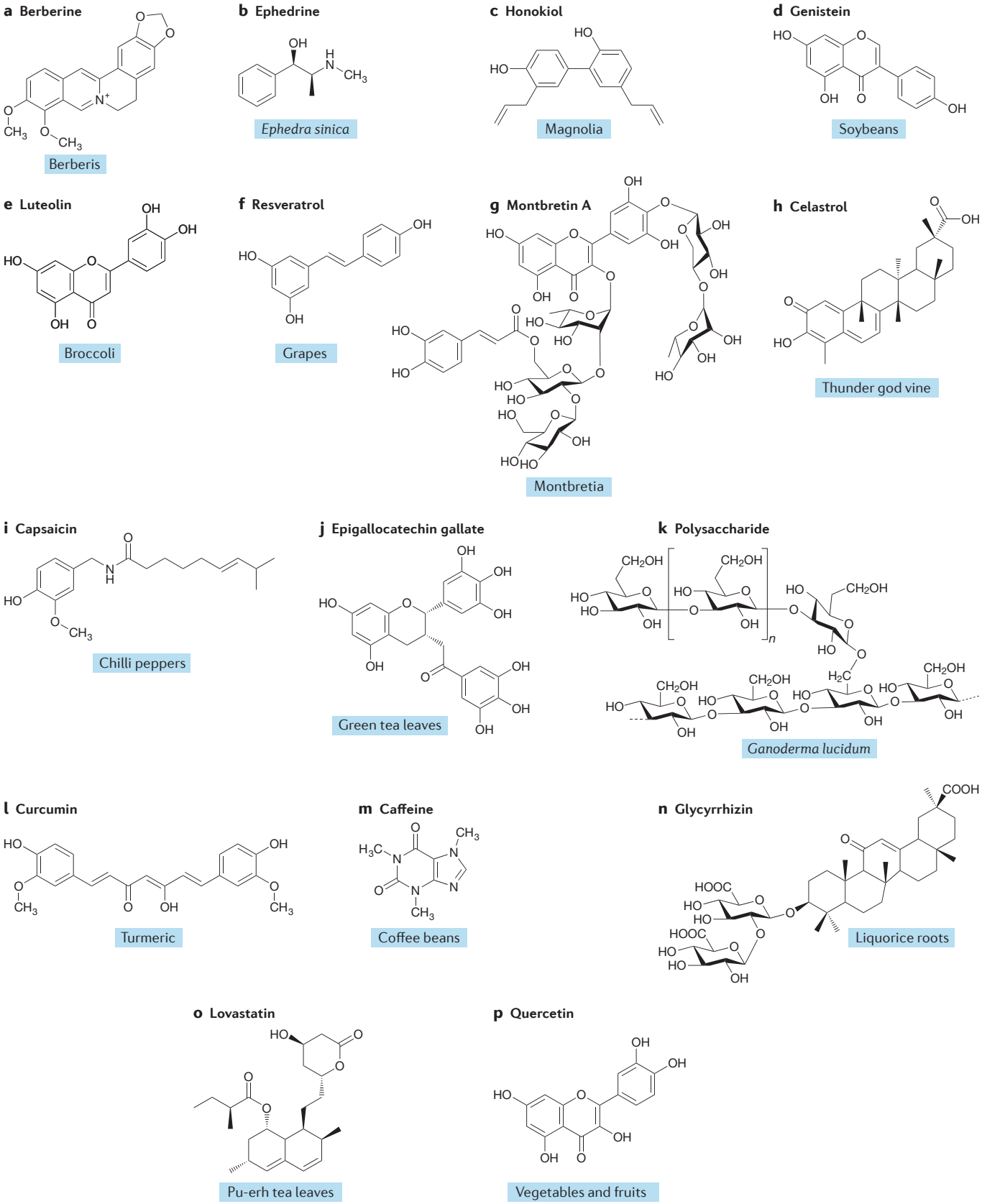

Figure 1 | **Active substances in plants and mushrooms with anti-obesogenic and antidiabetic effects.** Examples are shown of active compounds that have been identified in plants and mushrooms with anti-obesogenic and antidiabetic effects. An expanded version of this figure can be found in Supplementary information S1.

Phytochemicals such as polyphenols and dietary fibre can bind to bile acids (FIG. 2), which are produced by the liver from cholesterol and secreted into the small intestine to facilitate the digestion and absorption of dietary lipids. Bile acids are reabsorbed by enterocytes and transported back to the liver, in a process known as enterohepatic circulation. When phytochemicals bind to bile acids, they inhibit enterohepatic circulation and increase bile-acid excretion in faeces[59,61], which can cause reductions in blood cholesterol levels and potentially beneficial effects on the blood lipid profile.

Alteration of adipocyte function

Although HFDs are associated with weight gain, obesity and T2DM[62], a normal amount of adipose tissue is essential as a source of energy and to regulate body temperature. Body fat consists of white adipose tissue (WAT), which is the major site of energy storage, and brown adipose tissue (BAT), which contributes to thermogenesis[63]. A white adipocyte contains a large vacuole of lipids in the form of triglycerides and cholesteryl esters. In a state of energy shortage, triglycerides can be hydrolysed by lipolysis to release fatty acids, which can enter the blood and undergo β-oxidation in most tissues to produce energy. Compared with normal levels, in the presence of an excess of lipids, white adipocytes increase in both size and number.

Adipocytes have important endocrine functions, as they release hormones and cytokines (adipokines) that regulate homeostatic processes including satiety, energy levels and immune function[64]. Hypertrophied adipocytes secrete more pro-inflammatory adipokines, such as tumour necrosis factor (TNF) and IL-6, than adipocytes of normal size[64]. These pro-inflammatory adipokines interfere with insulin signalling and induce chronic inflammation. Systemic insulin resistance augments the demand for insulin and can eventually lead to the development of T2DM if the demand exceeds the secretory capacity of pancreatic β cells[65].

Phytochemicals can inhibit the proliferation and differentiation of pre-adipocytes and/or induce apoptosis in mature adipocytes. Epigallocatechin gallate (EGCG) from green tea (FIG. 1) reduces the viability of pre-adipocytes in a dose-dependent and time-dependent manner in culture[66]. EGCG at 50–200 μmol/l for 12–24 h and the stilbenoid resveratrol (which is found in grapes and red wine) at 100 μmol/l for 48 h also induce apoptosis in mature adipocytes[67–69] (FIG. 2). Other phytochemicals (FIG. 1), including genistein[70,71] (an isoflavone found mainly in soy), glycyrrhizin[72] (a constituent of liquorice), capsaicin[73] (found in chilli peppers), and quercetin[68] have similar antiproliferative and pro-apoptotic effects on adipocytes. Resveratrol and quercetin inhibit expression of peroxisome proliferator-activated receptor-γ (PPARγ)[68], which is the transcription factor that is primarily responsible for activating the differentiation of mesenchymal stem cells into adipocytes[74], and this effect might be responsible for the inhibition of adipogenesis by these compounds. In experiments involving HFD-fed mice[75], an ethanolic extract of ginseng roots (500 mg/kg daily for 8 weeks) reduced the size of white adipocytes by 62% relative to controls without ginseng treatment.

Because adipocytes help to control sensitivity to insulin, compounds that affect adipocytes might also regulate insulin sensitivity. Activation of PPARγ downregulates expression of several adipokines (including TNF, leptin and IL-6), and induces expression of adiponectin, an adipokine that sensitizes the liver and muscle to insulin[76,77]. Thiazolidinediones are a class of antidiabetic drugs that activate PPARγ. Similarly, many plant-derived molecules (such as curcumin and honokiol) are partial agonists of PPARγ (FIG. 2)[78]. The results of *in vivo* studies indicate that some natural PPARγ agonists improve glucose tolerance and insulin sensitivity in animal models, producing fewer adverse effects than thiazolidinediones[78]. Although PPARγ agonists have antidiabetic effects, they might also induce weight gain by promoting adipocyte development and function[79].

Energy expenditure and lipid storage

Various plant products, including ephedrine and caffeine, have sympathomimetic and other physiological activities that induce lipolysis[51]. Lipid accumulation and energy storage might also be reduced by the induction of thermogenesis in BAT and muscles. Results suggest that substantial amounts of metabolically active BAT are present in humans[63,80]. BAT is innervated by sympathetic nerves, and contains the thermogenic mitochondrial brown fat uncoupling protein 1 (UCP1), which produces heat by β-oxidation of lipids and glucose metabolism, instead of producing ATP. Thermogenesis is normally activated by cold, which stimulates transient receptor potential (TRP) channels on sensory neurons, transmitting signals to the brain and activating sympathetic activity. Expression of the UCP1 analogue UCP3 is induced by thyroid hormones, β_3-adrenergic agonists and leptin, stimulating thermogenesis in muscles and BAT[81].

Several plant compounds, including capsaicin and catechins such as EGCG, activate TRP channels on neurons, thereby promoting BAT thermogenesis[82] (FIG. 2). Treatment of HFD-fed rats with an ethanolic extract of a variant of *Solanum tuberosum* (potato), at 100–500 mg/kg for 4–6 weeks, activates UCP3 expression in BAT and the liver, reducing body weight and fat deposition, relative to HFD-only controls[83]. Plant compounds such as berberine, an alkaloid found in Berberis plants (FIG. 1), not only induce UCP1 expression in BAT, but also promote the differentiation of WAT into BAT, thereby further contributing to thermogenesis and weight loss[84].

Another strategy to enhance energy expenditure is to target AMP-activated protein kinase (AMPK), an enzyme that acts as a sensor of energy levels[85,86]. AMPK is activated by AMP and ADP, which are produced by the hydrolysis of ATP. Activation of AMPK in skeletal muscle contributes to cellular energy availability by inhibiting anabolic pathways and activating catabolic pathways, such as fatty-acid oxidation, which produces ATP and reduces lipid storage. AMPK also sensitizes muscle cells to insulin, which is beneficial against T2DM. Various phytochemicals, including berberine[87] and genistein[88], activate AMPK in adipose tissues, muscles and the liver (FIG. 2). Activation of AMPK in WAT by compounds such as resveratrol also leads to differentiation into BAT[89].

Enterohepatic circulation
Circulation of bile acids from the liver to the small intestine, followed by absorption by enterocytes and transport back to the liver via the blood.

β-Oxidation
Catabolic process occurring in eukaryotic cells in which fatty acids are broken down to produce ATP and cellular metabolites.

Adipokines
Hormones secreted by adipocytes.

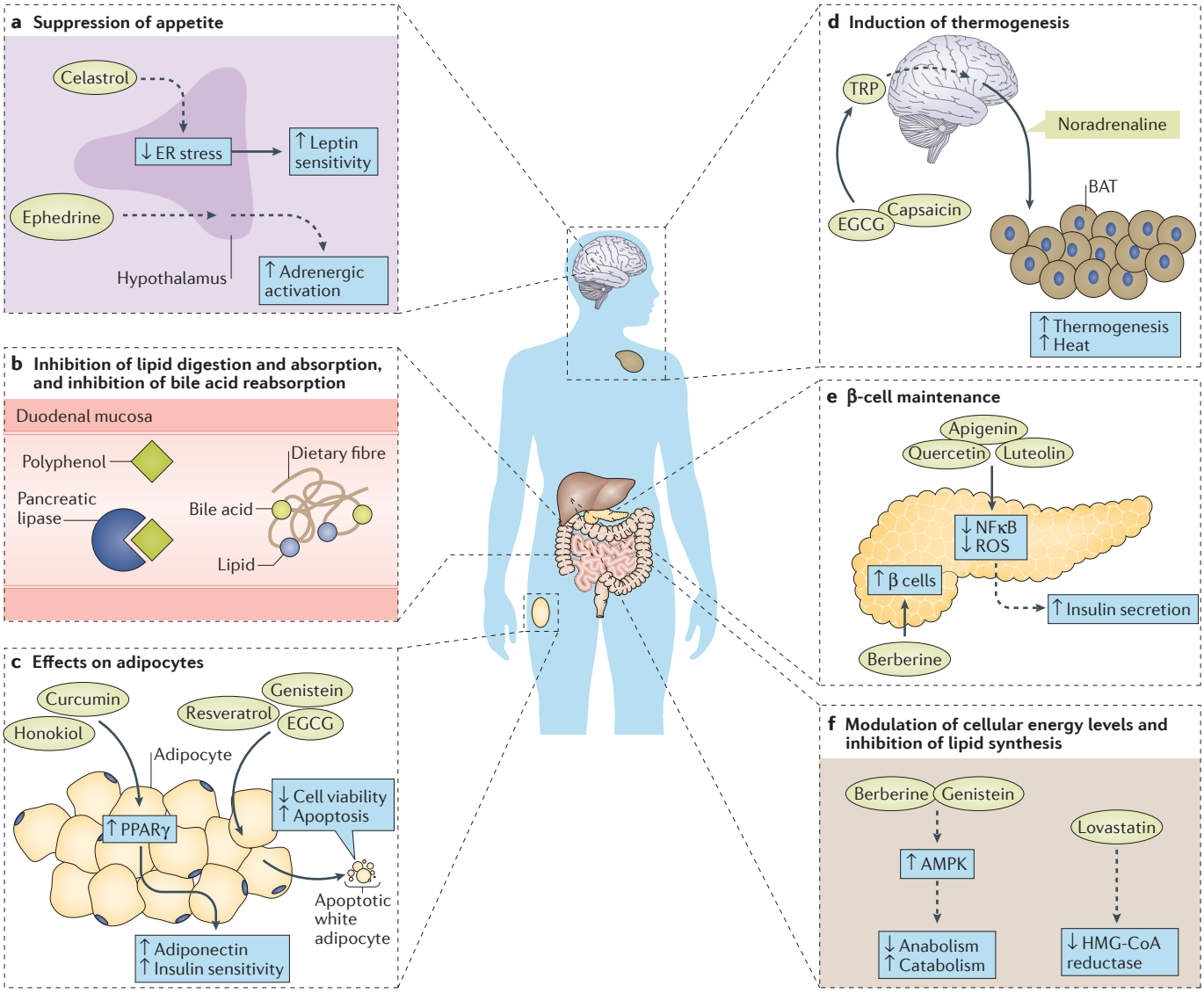

Figure 2 | **Molecular mechanisms of the antidiabetic and anti-obesogenic effects of plants and mushrooms.** **a** | Plant compounds such as celastrol reduce body weight by inhibiting endoplasmic reticulum (ER) stress in the hypothalamus, thereby increasing leptin sensitivity and suppressing appetite. Ephedrine reduces appetite by activating adrenergic receptors in the hypothalamus. **b** | Plant polyphenols inhibit pancreatic lipase activity in the duodenum and prevent the release (and subsequent absorption) of fatty acids from dietary triglycerides. In addition, dietary fibre binds to lipids and bile acids, thereby reducing lipid absorption and bile acid reabsorption, respectively. **c** | Phytochemicals including epigallocatechin gallate (EGCG), resveratrol and genistein inhibit lipid accumulation by inducing apoptosis in adipocytes. Furthermore, honokiol and curcumin activate peroxisome proliferator-activated receptor γ (PPARγ), leading to secretion of adiponectin, which enhances insulin sensitivity. **d** | Capsaicin and EGCG activate transient receptor potential (TRP) channels on sensory nerves, inducing the release of noradrenaline by sympathetic nerves, which activates uncoupling proteins in the mitochondria of brown adipose tissue (BAT), producing heat instead of ATP. **e** | Apigenin, quercetin and luteolin have antioxidant effects that protect pancreatic β cells from reactive oxygen species (ROS) and activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), helping to maintain insulin secretion in response to glucose intake. In addition, berberine induces β-cell proliferation, thereby maintaining pancreatic function and glucose homeostasis. **f** | Berberine and genistein activate AMP-activated protein kinase (AMPK) in the liver and other tissues. AMPK activation reduces energy storage by inhibition of anabolic pathways. AMPK activation also enhances energy expenditure by inducing catabolism and ATP production. Furthermore, lovastatin, a compound found in mushrooms and pu-erh tea, inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the liver, thereby reducing cholesterol synthesis. Modified with permission from Nature Publishing Group © Dietrich, M. O. and Horvath, T. L. *Nat. Rev. Drug Discov.* **11**, 675–691 (2012).

Inhibition of lipid synthesis is another potential anti-obesogenic strategy. Statins are cholesterol-lowering drugs that were first isolated from fungi, and inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), an important enzyme in the cholesterol biosynthesis pathway. Statins also have beneficial effects on the blood lipid profile, and reduce the risk of cardiovascular events, compared with placebo[90]. Lovastatin, which was first isolated from the mould *Aspergillus terreus*, is found in various mushrooms,

including in the fruiting bodies or mycelia of *Agaricus*, *Antrodia*, *Ganoderma*, *Ophiocordyceps* and *Pleurotus* species[91,92], as well as in Chinese fermented pu-erh tea (FIG. 1,2)[93]. Compounds such as EGCG also inhibit HMG-CoA reductase activity *in vitro*[94], and might contribute to the reduction of hyperlipidaemia and lipid deposition *in vivo*.

β cells and insulin sensitivity

Pancreatic β cells secrete insulin in response to food intake. The release of pro-inflammatory cytokines by hypertrophied adipocytes leads to β-cell dysfunction, apoptosis and necrosis, which affects insulin secretion[95]. A number of phytochemicals, including the flavonoids apigenin, quercetin and luteolin, protect pancreatic β cells from pro-inflammatory cytokines *in vitro* by reducing activation of the transcription factor nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) (FIG. 2), relative to the level in the absence of flavonoids[96]. Berberine, curcumin (found in the spice turmeric) and catechins also increase the number of β cells in animal models of T2DM (FIG. 2)[97], although the mechanisms underlying this regenerative process remains unclear. Similarly, extracts prepared from *Allium sativum* (garlic), *Momordica charantia* (bitter melon) and *Crocus sativus* (saffron) protect β cells in animal models of T2DM[97].

Pancreatic β cells have poor antioxidant capacity and are, therefore, susceptible to oxidative stress[98]. Phytochemicals might protect β cells by preventing oxidative damage caused by various stimuli, including glucotoxicity. Plant polyphenols and flavonoids, for example, are known to have antioxidant effects[99,100]. Some phytochemicals also inhibit the expression of enzymes that produce reactive oxygen species, including nitric oxide synthase[101].

Insulin induces glucose uptake by skeletal muscle and adipocytes, promoting energy storage, in addition to inhibiting glucose production by the liver. Hormones such as adiponectin and GLP-1 sensitize the body to the action of insulin[95,102,103]. Mice with intraperitoneal injection of 20 mg/kg resveratrol daily for 7 weeks have higher levels of GLP-1 in the blood than controls[104]. Similarly, individuals with T2DM who consume 500 mg of green tea extract three times a day for 16 weeks have higher levels of GLP-1 in the blood and improved insulin sensitivity compared with placebo-treated controls[105]. Treatment of intestinal endocrine cells *in vitro* with 200 μg/ml chitosan for 2 h results in a 1.6-fold increase in secretion of GLP-1, compared with untreated cells[106]. Dietary supplementation with chitosan also induces accumulation of GLP-1 in the blood of diabetic rats, leading to enhancement of insulin sensitivity[107]. Compared with no treatment, glycyrrhizin from liquorice root (FIG. 1) improves insulin sensitivity and reduces oxidative stress in diabetic rats; the effects are comparable with those of the antidiabetic drug glibenclamide[108]. Cinnamon extract has a dose-dependent effect on insulin signalling in diabetic mice[109]. Other herbs, seeds and roots that contain substances with possible insulin-sensitizing effects include tarragon, fenugreek, bitter melon and ginseng[110,111]. The mechanisms of action of these extracts and phytochemicals require further characterization.

Effects on the gut microbiota

The gut microbiota of an individual contains trillions of microorganisms that participate in various physiological functions, including vitamin production, maintenance of intestinal cells, development of the immune system and neutralization of pathogens, drugs and toxins[112]. The gut microbiota also has an important role in extracting energy from food and could be involved in the development of obesity and T2DM[113,114]. In obese mice, the gut microbiota extracts more energy from food than in lean mice[115]. In humans with obesity, treatment with vancomycin for 1 week modulates the gut microbiota and reduces insulin sensitivity, compared with baseline levels[116]. Transfer of the gut microbiota from lean individuals to those with obesity improves insulin sensitivity in the recipients[117]. These results suggest that modulation of the gut microbiota could have beneficial effects on obesity and T2DM.

An aqueous extract of the TCM mushroom *Ganoderma lucidum* has anti-obesogenic effects through modulation of the composition of the gut microbiota[41,118,119]. Compared with water, the extract not only reduces body weight and fat accumulation in HFD-fed mice, but also reduces the expression and secretion of the pro-inflammatory cytokines TNF, IL-1β and IL-6 (REF. 41). In HFD-fed animals, levels of proteins responsible for maintaining intestinal tight junctions (occludin and zona occludens protein 1) are lower than levels in chow-fed animals[41]. Supplementation with *G. lucidum* extract restores the levels of these proteins, which maintains intestinal integrity and prevents translocation of pro-inflammatory endotoxins (such as lipopolysaccharide) from gut bacteria to the blood. Compared with water alone, the *G. lucidum* extract also improves glucose tolerance and insulin sensitivity. Notably, the weight-loss effects induced by *G. lucidum* are transmissible via horizontal transfer of faeces from *G. lucidum*-treated mice to HFD-fed mice, indicating that these effects are mediated by the gut microbiota[41].

The active compounds responsible for the anti-obesogenic effects of *G. lucidum* extract are present in a fraction that contains high-molecular-weight polysaccharides (>300 kDa) (FIG. 1)[41]. Fungal polysaccharides are not digested in the stomach or small intestine, but they can be digested by bacteria in the large intestine to produce short-chain fatty acids (SCFAs), which induce the secretion of GLP-1 by intestinal cells[103,120]. GLP-1 and SCFAs enter the blood and have effects on the brain, muscles, adipose tissues and liver, delaying gastric emptying and leading to reductions in appetite, lipid deposition, insulin resistance and inflammation (FIG. 3). Moreover, GLP-1 promotes proliferation and inhibits apoptosis in β cells[121]. Evidence suggests that proteins released by intestinal *Escherichia coli* also stimulate production of GLP-1 and peptide YY and induce satiety and meal termination[122].

Glucotoxicity
Structural and functional damage to pancreatic β cells and the target tissues of insulin caused by chronic hyperglycaemia.

Intestinal tight junctions
Connections between two adjacent intestinal cells that limits the space between them and the passage of material from the intestinal lumen to the gut mucosa.

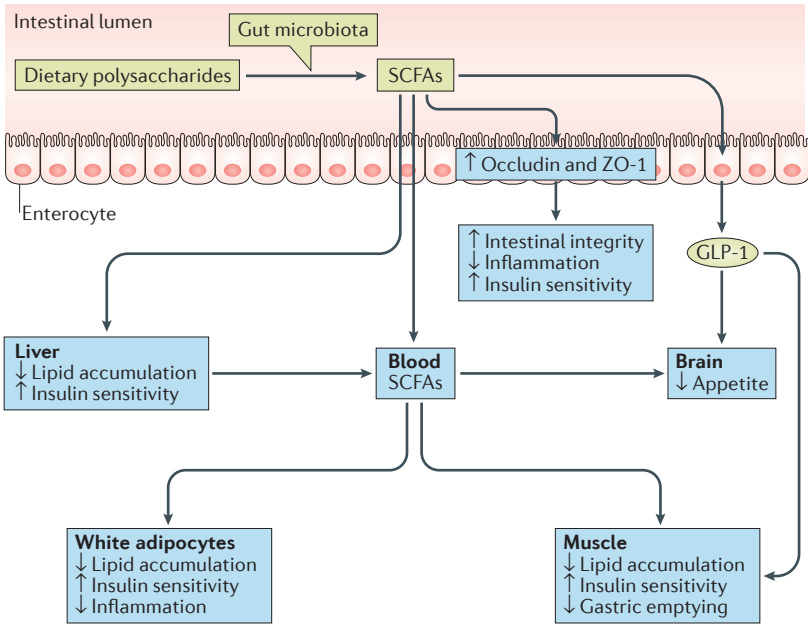

Figure 3 | **Polysaccharides from plants and mushrooms have antidiabetic and anti-obesogenic effects via the gut microbiota.** Dietary polysaccharides are not digested in the duodenum because of the absence of suitable enzymes. Polysaccharides reach the large intestine, where they are digested by the gut microbiota to short-chain fatty acids (SCFAs), which induce the secretion of glucagon-like peptide 1 (GLP-1) by intestinal cells. SCFAs and GLP-1 reach the blood circulation and have direct and indirect anti-obesogenic and antidiabetic effects on the human body, notably acting in the brain to reduce appetite and in muscles, adipocytes and the liver to enhance insulin sensitivity. In addition, SCFAs and GLP-1 reduce lipid accumulation, which in turn reduces inflammation. Polysaccharides also induce occludin and zonula occludens protein 1 (ZO-1) expression in intestinal cells, maintaining intestinal integrity and preventing the release of pro-inflammatory bacterial endotoxins into the bloodstream. Modified with permission from Nature Publishing Group © Canfora, E. E. *et al. Nat. Rev. Endocrinol.* **11**, 577–591 (2015).

Mushrooms such as button mushroom (*Agaricus bisporus*) and shiitake (*Lentinula edodes*) that are rich in polysaccharides have been shown to induce the growth of beneficial gut bacteria[123]. *Hirsutella sinensis*, the anamorph (asexual reproductive form) of *O. sinensis*, also modifies the composition of the gut microbiota and has anti-obesogenic, antidiabetic and anti-inflammatory effects in HFD-fed mice (Wu, T. R. *et al.*, unpublished work). Several substances, such as fibre and polysaccharides, can have beneficial effects on the human body via the gut microbiota without being directly assimilated by the body[124]. These substances can have roles as prebiotics, and are candidates for the development of antidiabetic and anti-obesogenic treatments.

Epidemiological and clinical evidence

The anti-obesogenic effects of several phytochemicals, including celastrol, EGCG, capsaicin and fungal polysaccharides, have been demonstrated in laboratory animals[40,41,125,126]. Resveratrol reduces fat levels in rodents[127], but it remains unclear whether similar results will be observed in humans[128,129]. The results of epidemiological studies indicate that, compared with consumption of foods containing animal products, consumption of plant-based foods is associated with reduced incidence of obesity and T2DM in humans[32,130]. In a prospective study[131] involving 124,086 individuals, who were studied for up to 24 years, the level of consumption of plant and fruit flavonoids (such as anthocyanins, flavonoid polymers and flavonols) was negatively associated with body weight, after adjustment for diet, cigarette smoking and physical activity. In addition, several randomized controlled trials (RCTs) have been performed to examine the anti-obesogenic effects of TCM plant remedies and nutraceuticals (TABLE 1). For instance, a mixture of *Ephedra sinica*, kola nut and white willow bark given daily for 3 months has been shown to reduce body weight by 1.5 kg compared with placebo[132]. According to meta-analyses and RCTs, green tea[133], green coffee extract[134] and green tea extract[135] significantly reduce body weight compared with placebo (TABLE 1). These results suggest that some TCM herbal remedies and nutraceuticals can help to control body weight in individuals with overweight or obesity.

Most clinical studies in this field have been small, limited in duration and have not followed standardized methodologies. Compared with drugs in clinical trials, plants and mushrooms are consumed in relatively large quantities, in different combinations and for extended periods of time in the normal diet. To demonstrate the effectiveness of the consumption of plants, mushrooms and their extracts against diabetes and obesity will require appropriately designed epidemiological and clinical trials. However, few serious adverse effects have been reported so far, with the exceptions of formulations containing *Ephedra sinica* (which produces psychiatric, gastrointestinal, autonomic and cardiovascular adverse effects)[52] and *Garcinia* extract (which is associated with gastrointestinal problems)[136]. Comparisons are required of the effects of whole functional foods and complex extracts with the effects of pure compounds isolated from the same foods. Whole functional foods have the advantages of wide availability, ease of preparation and low adverse effects, whereas purified active compounds are likely to have higher anti-obesogenic and antidiabetic activities. Whole functional foods might be best suited for the prevention of obesity and T2DM, whereas purified active compounds might be preferable as pharmaceutical drugs for the treatment of severe symptoms.

Targeting multiple pathways

Some plants, fungi and their extracts contain substances that affect multiple cellular targets and physiological pathways involved in energy regulation and development of obesity and T2DM. For instance, catechins might have anti-obesogenic effects via modulation of adipogenesis, energy expenditure, lipid digestion and metabolism[66,67,82,94], whereas polysaccharides could reduce body weight and fat deposition by maintenance of intestinal integrity and inhibition of dietary fat absorption[41,59]. By targeting multiple pathways, combinations of agents derived from plants and mushrooms could have synergistic effects. A combination of resveratrol and quercetin has pro-apoptotic effects

Prebiotics
Foods that are not digestible by humans, but promote the growth of beneficial microorganisms in the intestines.

Table 1 | **Clinical studies of the weight-loss effects of plants and mushrooms**

Material	Study population	Treatment dose and duration	Effect on body weight (BW)	Refs
Plants and plant extracts				
Caralluma fimbriata (cactus)	Overweight adults ($n = 50$)	1 g per day for 60 days	BW NS −1.0 kg ($P > 0.05$)	140*
Crocus sativus extract (saffron)	Overweight women ($n = 60$)	176.5 mg per day for 8 weeks	BW −1.0 kg ($P < 0.01$)	141*
Ephedra, ephedrine, caffeine	MA, 52 studies	Variable doses	BW −0.9 kg per month ($P < 0.05$)	52‡
Ephedra sinica, guarana, caffeine	Overweight adults ($n = 48$)	312 mg extract per day for 8 weeks	BW −3.2 kg, FM −2.3% ($P < 0.006$)	142*
Fenugreek (seed)	Overweight males ($n = 39$)	1,176 mg per day for 6 weeks	BW NS ($P > 0.05$)	143*
Garcinia atroviridis (fruit)	Women with obesity ($n = 42$)	3.5 g per day for 8 weeks	BW −1.4 kg ($P < 0.05$)	144*
Garcinia extract	MA, 12 studies ($n = 706$)	Variable doses for ≥2 weeks	BW −0.9 kg ($P = 0.05$)	136‡
Green coffee extract	MA, three studies	Variable doses	BW −2.5 kg ($P = 0.006$)	134‡
Herbal mixture (*E. sinica*)	Overweight adults ($n = 86$)	~2.9 g per day for 12 weeks	BW −1.5 kg ($P = 0.002$)	132*
Herbal mixture	Overweight women ($n = 28$)	750 mg per day for 6 weeks	BW −1.5 kg ($P = 0.89$)	145*
Herbal mixture	Overweight adults ($n = 72$)	500 mg per day for 10 weeks	BW −9.8% ($P < 0.05$); BF −16.1% ($P < 0.05$)	146*
Hoodia gordonii extract	Overweight women ($n = 41$)	2,220 mg per day for 15 days	BW NS +0.1 kg ($P > 0.05$)	147*
Phaseolus vulgaris extract (bean)	MA, six studies	Variable doses	BW NS −1.8 kg ($P = 0.1$); BF −1.9 kg ($P = 0.02$)	148‡
Phytochemicals				
Capsinoids	Overweight individuals ($n = 67$)	6 mg per day for 12 weeks	BW NS −0.4 kg ($P = 0.86$); AF −0.9% ($P = 0.049$)	149*
EGCG	Women with obesity ($n = 83$)	300 mg per day for 12 weeks	BW NS −0.3 kg ($P = 0.84$), FM NS −0.7 kg ($P = 0.22$)	150*
Glucomannans	MA, nine studies	Variable doses	BW NS −0.2 kg ($P = 0.3$)	151‡
Phytochemical mixture	Adults with obesity ($n = 45$)	~2 g per day for 8 weeks	BW −1.5% ($P < 0.01$); FM −5.0% ($P < 0.001$)	152*
Quercetin	Overweight individuals ($n = 93$)	150 mg per day for 6 weeks	BW, FM NS ($P > 0.05$)	153*
Tea				
Camellia sinensis (green tea)	Individuals with obesity ($n = 35$)	Four cups per day for 8 weeks	BW NS −2.4 kg ($P = 0.28$)	154§
Green tea (catechin and caffeine)	Overweight individuals ($n = 182$)	~2,200 mg per day for 90 days	BW −1.2 kg ($P < 0.05$)	155*
Green tea (EGCG–caffeine mixture)	MA, 11 studies	Variable doses for ≥12 weeks	BW −1.3 kg ($P < 0.001$)	133‡
Green tea extract (catechins)	Adults with obesity ($n = 240$)	583 mg per day for 12 weeks	BW −1.6 kg ($P < 0.05$); FM −1.8 kg ($P < 0.05$)	156*
Green tea extract	Individuals with obesity ($n = 100$)	300 mg per day for 90 days	BW −9.0 kg ($P < 0.001$)	135‖
Pu-erh tea extract	Overweight individuals ($n = 36$)	999 mg per day for 12 weeks	BW −1.2 kg ($P < 0.05$)	157*
Mushrooms				
Mushrooms (to replace red meat)	Adults with obesity ($n = 73$)	Three meals per week for 6 months	BW NS −2.2 kg ($P = 0.281$)	158§

The mean body weight loss or gain in the placebo group was subtracted from that of the treatment group. AF, abdominal fat; BF, body fat; EGCG, epigallocatechin gallate; FM, fat mass; NS, nonsignificant. *Double-blind, randomized, controlled trial. ‡Meta-analysis (MA). §Single-blind design. ‖No information about blinding.

on mature adipocytes that are greater than the sum of the effects with individual treatments[68]. Similarly, treatment with EGCG and resveratrol for 3 days synergistically enhances energy expenditure in individuals who are overweight[137]. Targeting multiple pathways could enhance the effectiveness of treatments and prevent the development of resistance to a single therapeutic agent. Herbal remedies used in TCM often consist of a combination of several plants and mushrooms whose compounds can synergize to produce anti-obesogenic and antidiabetic effects. Combining TCM-based remedies and conventional pharmaceutical drugs is another strategy that remains to be investigated in clinical trials.

Quality control

Medicinal plants and mushrooms generally have few adverse effects, are inexpensive and are widely available. However, some products sold as TCM plant extracts or neutraceuticals have reduced amounts of active compounds, compared with the information provided on the label[132]. DNA sequencing of TCM products has demonstrated the presence of material from plant and animal species not listed on product labels[138]. Potentially toxic substances have also been found, such as aristolochic acid, which has been implicated in the development of urothelial cancer[139]. Correct species identification, optimal growth conditions and extract preparation, prevention of product alteration, standardization of extract composition and safety evaluation are required to enable the widespread use of TCM products and neutraceuticals.

Conclusions

Obesity and T2DM are complex conditions, and current approaches to prevention and treatment involve a combination of factors, such as diet modifications and regular exercise. Pharmaceutical approaches to treatment of these conditions require further development. Several plant and mushroom species, including a number that have uses in TCM, have now been shown to have anti-obesogenic and/or antidiabetic effects.

Only a fraction of the medically active substances available in plants and mushrooms have been identified, and the unidentified natural products have great potential. Modern technologies enable the detailed analysis of herbal and fungal extracts to identify active substances. These phytochemicals, in the form of the plants and mushrooms themselves, extracts or purified components, can be combined with existing treatments to reduce the prevalence of obesity and its complications.

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Author contributions
J.M. and D.M.O. researched data for the article. J.M., D.M.O. and J.D.Y. wrote the article. All authors contributed to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests statement
Y.F.K. is President of Chang Gung Biotechnology Corporation. J.D.Y. is Chairman of the Board of Chang Gung Biotechnology Corporation. The authors (with the exception of S.F.T.) have filed patent applications related to the anti-obesogenic and antidiabetic effects of mushroom polysaccharides.

Review criteria
PubMed was searched with the terms "obesity", "diabetes", "plants", "plant extracts", "mushrooms", "traditional Chinese medicine", "nutraceuticals", "phytonutrients", "phytochemicals", "herbal remedies", "hormones" and "gut microbiota", without time constraints on publication. Only articles written in English were included. Additional studies were identified from the bibliographies of the retrieved articles

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