Review

Mechanisms of action for the anti-obesogenic activities of phytochemicals

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Abstract

The prevalence of obesity is increasing rapidly globally and has recently reached pandemic proportions. It is a multifactorial disorder linked to a number of non-communicable diseases such as type-2 diabetes, cardiovascular disease, and cancer. Over-nutrition and a sedentary lifestyle are considered the most significant causes of obesity; a healthy lifestyle and behavioural interventions are the most powerful ways to achieve successful weight loss, but to maintain this in the long term can prove difficult for many individuals, without medical intervention. Various pharmacological anti-obesogenic drugs have been tested and marketed in the past and have been moderately successful in the management of obesity, but their adverse effects on human health often outweigh the benefits. Natural products from plants, either in the form of crude extracts or purified phytochemicals, have been shown to have anti-obesogenic properties and are generally considered as nontoxic and cost-effective compared to synthetic alternatives. These plant products combat obesity by targeting the various pathways and/or regulatory functions intricately linked to obesity. Their mechanisms of action include inhibition of pancreatic lipase activities, an increase in energy expenditure, appetite regulation, lipolytic effects, and inhibition of white adipose tissue development. In this review, we discuss the distinct anti-obesogenic properties of recently reported plant extracts and specific bioactive compounds, along with their molecular mechanisms of action. This review will provide a common platform for understanding the different causes of obesity and the possible approaches to using plant products in tackling this worldwide health issue.

Keywords: Anti-obesogenic; Phytochemicals; Pancreatic lipase; Adipose tissue; Leptin/ghrelin

Nomenclature

ACC	Acetyl-coenzyme A carboxylase
ACSL1	Long-chain-fatty-acid-CoA ligase 1
AMPK	Adenosine monophosphate activated protein kinase
ATGL	Adipocytes triglycerides lipase
C/EBP-α	CCAAT/Enhancer binding protein-alpha
C/EBP-β	CCAAT/Enhancer binding protein-beta
Cited 1	Cbp/p300-interacting trans activator 1
CPT1	Carnitine palmitoyl transferase 1
DGAT1	Diacylglycerol O-acyltransferase 1
FAS	Fatty acid synthase

FATP4 Fatty acid transport protein 4
FFAs Free fatty acids
GLUT4 Glucose transporter 4
GSK-3β Glycogen synthase kinase-3 beta
HMGR HMG-CoA reductase
hMSC human Mesenchymal stem cells
HSL Hormone sensitive lipase
iWAT Inguinal white adipose
tissue LPL Lipoprotein lipase
MAGL Monoacylglycerol lipase
p-ACC Phosphorylated acetyl-CoA carboxylase
pAMPK phosphorylated Adenosine monophosphate activated protein kinase
PGC-1α Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PLIN Perilipin
PPAR-γ Peroxisome proliferator activated receptor–Gamma
PRDM-16 PR Domain containing 16
Sirt 1 Sirtuin 1
SREBP Sterol regulatory element binding protein
sWAT Subcutaneous white adipose tissue
Tbx1 T-box transcription factor 1
TG Triglycerides
TMEM 26 Transmembrane protein 26
UCP1 Uncoupling protein1

1 Introduction

Obesity can be defined as a body mass index (BMI; weight in kg/square of the body height in metres) of over 30 kg/m^2 (Khalilpourfarshbafi et al., 2018). Obesity is an international issue and a risk factor for other diseases including cardiovascular diseases, cancer, type-2 diabetes, asthma, atherosclerosis, and non-alcoholic fatty liver disease (NAFLD) (Corrêa and Rogero, 2019; Peters et al., 2018; Unamuno et al., 2018). Obesity and being overweight are the fifth leading causes of death globally (Chandrasekaran et al., 2012). According to one estimation, approximately 921 million people were obese or overweight throughout the world in 1980 and by 2013 this number had increased to 2.1 billion (Castillo et al., 2019; Ng et al., 2014) – increasing from approximately 20%–30% of the global population. It is now widely acknowledged that the imbalance between the intake and expenditure of energy results in obesity (Ahmad et al., 2020; Parray et al., 2018).

Sedentary lifestyles and other environmental risk factors are considered major causes of obesity (Fig. 1) but they are not entirely responsible: genetic mutations can also lead to the condition (Choquet and Meyre, 2011). Mutations in genes such as Leptin (LEP), leptin receptor (LEPR), prohormone convertase 1 (PCSK1), melanocortin receptor (*MC4R*), proopiomelanocortin (*POMC*), single-minded homolog 1 (SIM), and brain-derived neurotrophic factor (BDNF) have been reported to be associated with obesity (Choquet and Meyre, 2011; Farooqi and O'rahilly, 2008).

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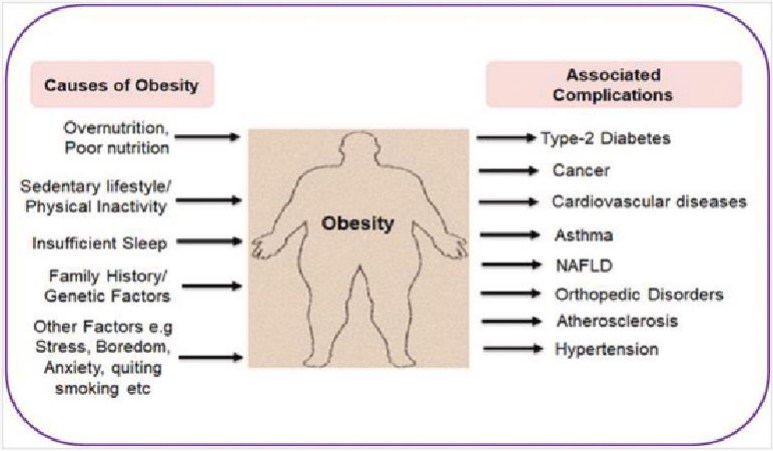
Fig. 1



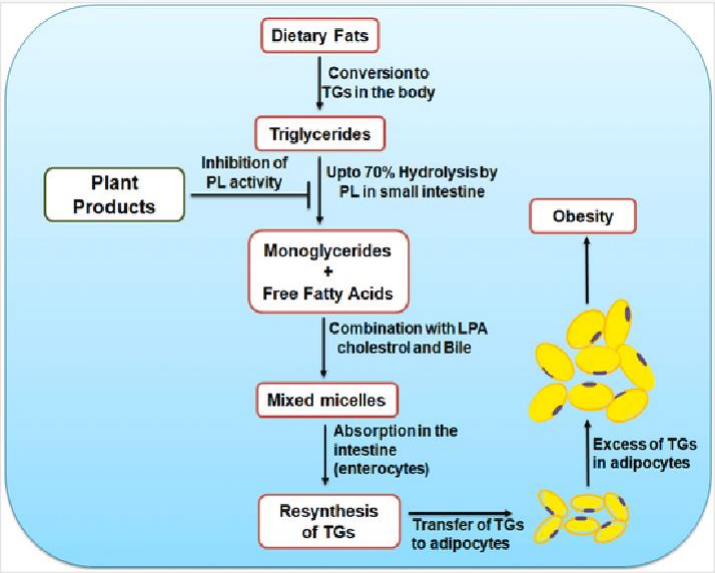
Major causes of obesity and associated complications.

There are a number of options for the treatment of obesity. These focus on changes in lifestyle, such as control of diet, physical exercise, weight-loss medications, and weight-loss surgeries (Chandrasekaran et al., 2012; Sun et al., 2016). Physiological interventions such as exercise and dieting are the preferred ways to reverse weight gain, but due to the modern lifestyle, these activities seem to be challenging to practice and maintain in the modern world. This has therefore created a need for pharmacological interventions. Demand for anti-obesogenic drugs and weigh loss therapies has accelerated the development of these interventions within the global pharmaceutical industry (Sun et al., 2016). Pharmacological interventions can aid the management of weight loss by altering processes such as absorption of calories, altering appetite, preventing or altering the development of adipose tissue, and regulating the metabolism of the body. However, related adverse effects hinder their usage and limit their beneficial effects (Chandrasekaran et al., 2012). A significant example of this is Meridia (sibutramine), which acts as an appetite suppressant by inhibiting neurotransmitters within the brain and was withdrawn in 2010 from the US and Canadian markets due to adverse effects on the cardiovascular system, resulting in heart attacks and strokes. In the same year, Xenical (orlistat), another weight loss drug, underwent revised labeling due to reported adverse effects on the liver (Sun et al., 2016). Some other commercially available pharmacological drugs, including metformin, exenatide, rimonabant, and pramlintide have also been reported to cause abdominal pain, sleeplessness, restlessness, cardiovascular problems, and incontinence (Bond, 2006; DeFronzo et al., 2005; Herrmann et al., 2016; Hollander et al., 2003; Mukherjee et al., 2015; Pi-Sunyer et al., 2006; Sam et al., 2011; DPPR Diabetes Prevention Program Research Group, 2012; Siavash et al., 2017; Wang et al., 2017). Due to these adverse effects, natural products are now often preferred over pharmacological drugs, in the management of weight loss. Furthermore, many natural products have been consumed for this purpose for hundreds of years and are often considered as nontoxic and more effective than pharmacological drugs (Park et al., 2011). An ideal anti-obesity drug should be able to control weight gain, with little or no side effects (Rodgers et al., 2012) and pharmacological anti-obesogenic drugs should be prescribed only if their beneficial effects outweigh the adverse effects. As a result, there is a growing emphasis on the development of drugs from natural plant products due to their perceived effectiveness and minimal or absent side effects. In addition, plant-based products, either as standardized extracts or pure compounds, have historically provided innumerable opportunities for the discovery of drugs, due to their lack of adverse effects and wide chemical diversity (Sasidharan et al., 2011).

This review will comprehensively outline the anti-obesogenic mechanisms of action of plant products. Their mechanisms of action include: inhibitory effects on the activity of lipases such as pancreatic lipase, increase in the expenditure of energy via processes such as brown adipogenesis, appetite suppression through control of leptin and ghrelin levels, enhancing the expression of lipolytic proteins such as hormone-sensitive lipase (HSL) and adipocytes triglycerides lipase (ATGL), and the inhibition of white adipose tissue (WAT) development.

2 Inhibition of pancreatic lipase (PL) activity

Lipids are essential to all living organisms: they are the building blocks of cellular membranes, can act as thermal isolators, and serve as a source of stored energy in the body. Nonetheless, excessive long-term intake of dietary lipids is one of the major causes in the development of obesity and is linked with other significant co-morbidities. Inhibition of dietary lipid digestion is an important approach in combating obesity, and a logical target for many anti-obesogenic pharmaceutical agents. Interference with the hydrolysis of lipids results in the reduction of the utilization of ingested lipids. Therefore, inhibition of lipases, responsible for the digestion and absorption of lipids, results in the decreased absorption of fats (Conforti et al., 2012). Consequently, one of the strategies for the screening and discovery of potential anti-obesogenic products is to investigate their inhibitory effects upon lipases. (Marrelli et al., 2013). A key example is pancreatic lipase (PL, also known as triacylglycerol acyl hydrolase), the principal enzyme of pancreatic juice, synthesized and secreted by the pancreas, and associated with absorption of dietary fats (Kim et al., 2016a,b). Dietary fats are usually consumed as a collection of triglycerides (TGs) that before absorption in the gastrointestinal tract, undergo a series of biochemical reactions (Lunagariya et al., 2014). Ninety percent of dietary fat consists of TGs and they must be hydrolyzed prior to absorption. The products of TG hydrolysis are monoglycerides, and free fatty acids (FFAs); these form mixed micelles with cholesterol, lysophosphatidic acid, and bile salts. The micelles are then absorbed into enterocytes where TGs are resynthesized and then stored in mature adipocytes as an energy source (Birari and Bhutani, 2007). An excess of these TGs in adipocytes is directly linked to obesity (Fig. 2). PL plays a crucial role in the hydrolysis of TGs and is responsible for the processing of 50–70% of total dietary fat (Birari and Bhutani, 2007). Inhibition of this enzyme is therefore one of the approaches used to combat obesity.



Absorption of lipids in the body and physiological role of Pancreatic Lipase (PL). Plants products inhibit the activity of PL, thus preventing the hydrolysis of triglycerides (TGs) into monoglycerides (MGs) and free fatty acids (FFAs). Arrows indicate activation or further processing while bar indicates inhibition.

PL inhibition is being widely studied to evaluate the potential of natural products to inhibit dietary fat absorption (Jamous et al., 2018; G.N. Kim et al., 2016; Marrelli et al., 2013). The blockbuster drug, orlistat, sold under the trade name Xenical, acts through the inhibition of pancreatic lipase and is used commercially as an anti-obesogenic drug. Orlistat is synthesized from the natural product lipstatin, a known lipase inhibitor (Lunagariya et al., 2014). Many plant extracts and their specific isolated bioactive compounds identified through their anti-obesogenic effects demonstrate inhibition of

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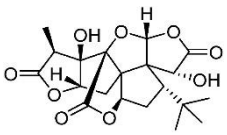
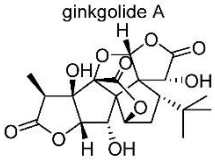
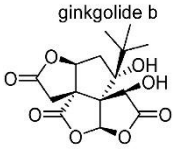
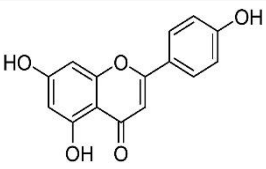
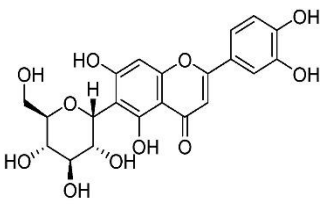
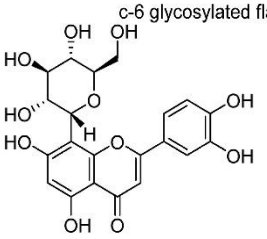
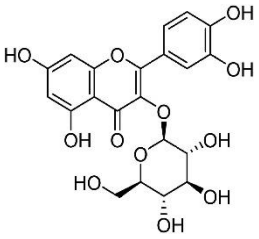
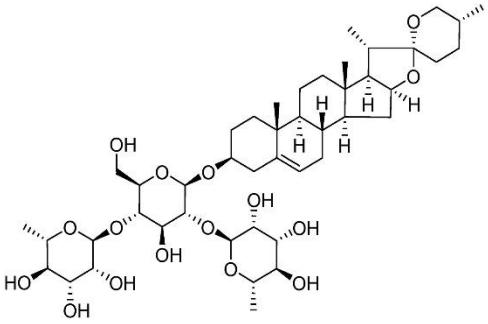
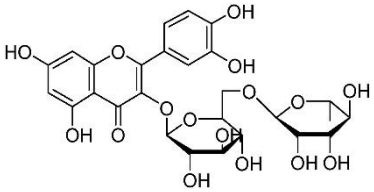
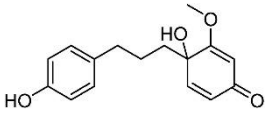
Table 1

The effect of selected phytochemicals on the *in vitro* enzyme activity of Porcine Pancreatic Lipase.

Phytochemical	Structure	IC_{50} Values	Reference
Trilactone terpenes (ginkgolides A, B and bilobalide)	 ginkgolide A  ginkgolide b  bilobalide	56, 212, and 186 μM	Bustanji et al. (2011)
Apigenin		0.8 mM	Guo et al. (2016)
Quercetin		4.9 mM	Li et al. (2011)

C-glycosylated flavones (C-6, C-8 glycosylation of luteolin skeleton)	 c-6 glycosylated flavone  c-8 glycosylated flavone	18.5–50.5 µM	Lee et al. (2010)
Isoquercetin		2.1 mM	Li et al. (2011)
Dioscin	 dioscin	23 µM	Birari and Bhutani (2007)
Rutin		1.8 mM	Li et al. (2011)
Broussonone A		28.4 µM	Ahn et al. (2012)

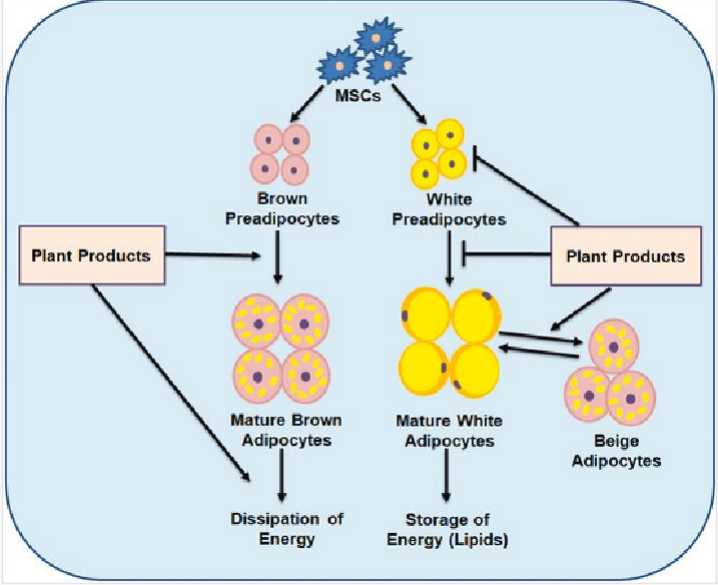
Jamous et al. (2018) screened 90 plant extracts for their inhibitory effects on the activity of crude porcine PL *in vitro*. Among those, the most active plants with the lowest IC_{50} values were *Camellia sinensis* (0.45 mg/mL), *Ceratonia siliqua* (leaves) (0.76 mg/mL), *Curcuma longa* (0.82 mg/mL), *Sarcopoterium spinosum* (1.2 mg/mL) and *Mentha spicata* (1.2 mg/mL). Similarly, Ong et al. (2014) screened 32 medicinal plants found in Malaysia for their anti-porcine PL activity *in vitro*. Among those, the extracts of four plants (*Eleusine indica*, *Myristica fragrans*, *Melastoma candidum* and *Phyla nodiflora*) showed the highest inhibitory effects (31.3%, 20.3%, 19.720% and 18.2% inhibition of PL activity at 100 µg/mL respectively). Recently, Tiamyom et al. (2019) reported the porcine PL inhibitory effects of *Gymnema inodorum* extract. The extract inhibited the activity of PL in a dose-dependent manner with IC_{50} value of 982 µg/mL. Another study by Kim et al., (2016) reported the inhibitory effects of *Diospyros kaki* fruit, and *Citrus unshiu* peel mixture extract (PCM) on porcine PL activity *in vitro*. The same group also then evaluated the anti-obesogenic effects of this mixture *in vivo* in high fat-diet (HFD) mice. The IC_{50} value against the PL activity levels found for PCM was 0.5 mg/mL. In addition, total cholesterol levels, serum triacylglycerol and visceral fat weight were significantly reduced when compared to the control HFD mice, which suggested that the administration of PCM might have reduced the absorption of fats by inhibiting the activity of PL. Similarly, Adnyana et al. (2014) showed porcine PL inhibitory effects of the ethanolic extracts of pomegranate leaves, it was observed that the extract inhibited the activity of PL in a dose-dependent manner.

In addition to plant crude extracts, specific bioactive compounds from plants have also been shown to possess inhibitory effects on PL activity. Bustanji et al. (2011) documented the porcine PL inhibitory effects of trilactone terpenes, including ginkgolides and bilobalide. The results revealed that ginkgolides A & B and bilobalide inhibited the activity of PL with IC_{50} values of 22.9, 90.0, and 60.1 µg/mL, respectively. Apigenin has been shown to have activity against porcine PL, with inhibition rates exceeding 50% at a concentration of 0.8 mM (Guo et al., 2016). Similarly,

quercetin, its monoglycoside and diglycoside forms, isoquercetin and rutin, inhibited the activity of porcine PL (IC_{50}) at concentrations of 1.49, 0.97 and 1.1 mg/mL (Li et al., 2011). C-glycosidic flavones are also reported to inhibit porcine PL activity with IC_{50} values ranging from 18.5 ± 2.6 to 50.5 ± 3.9 μM (Lee et al., 2010). Glycosyl groups at positions 6 and 8 of the A ring showed maximum inhibitory effects on the activities of PL (Lee et al., 2010). Two other hydroxylated methoxy flavones, 3,7-dihydroxy-4′methoxyflavone and 3,7,3′-trihydroxy-4′-methoxyflavone have also been shown to inhibit the activity of porcine PL (Ahn et al., 2012). These two compounds inhibited the activity of PL by 21.8 and 24.8% respectively at a concentration of 100 μM. Dioscin, isolated from methanol extract of *Dioscorea nipponica* powder, also inhibited PL activity (IC_{50}) at 20 μg/mL (Birari and Bhutani, 2007; Szewczyk and Sternbach, 2005). Ahn et al. (2012) showed the inhibitory effects of various bioactive compounds isolated from *Broussonetia kanzinoki*. Among those, broussonone A showed a non-competitive inhibitory effect on the activity of porcine PL with an IC_{50} value of 28.4 μM.

3 Increase in energy expenditure

Adipose tissue in mammals has classically been characterized into two types based on morphology, functions, and anatomical locations: white adipose tissue (WAT), and brown adipose tissue (BAT) (Ahmad et al., 2020). WAT and BAT, both originate from mesenchymal stem cells (MSCs) (Unser et al., 2015) through a well-orchestrated process known as adipogenesis (Fig. 3). Both of these tissues store energy in the form of lipids, whilst BAT contributes to dissipation of the stored energy in the form of heat (Velickovic et al., 2018). WAT is mainly responsible for the storage of energy in the form of TGs. BAT supports control of core body temperature by a specialized process known as adaptive or non-shivering thermogenesis, in which chemical energy is transformed into heat (Azhar et al., 2016). Correspondingly, BAT protects against obesity due to its ability to dissipate calories as heat (Gill and La Merrill, 2017). BAT activity is inversely related to the occurrence of obesity (Ahmad et al., 2020). BAT releases heat from the available nutrients via a process that is uncoupled from the production of ATP by uncoupling protein 1 (UCP1) (Kaisanlahti and Glumoff, 2018). UCP1 is the central activator of the thermogenic effect and induction of its expression by natural anti-obesogenic plant products is one route to reduceing obesity (Kajimura and Saito, 2014; Sun et al., 2016). The expression of UCP1 in WAT has also been reported in recent years (Dempersmier et al., 2015). Over-expression of UCP1 causes 'browning' of WAT, thus known as brite or beige adipose tissue. Browning is usually induced by hormonal stimulation and cold exposure. Brite or beige adipocytes are similar to BAT adipocytes in that they also generate heat by utilizing the available lipids in the body (Bi et al., 2014). Peroxisome proliferator-activated receptor γ 1 coactivator (PGC-1) regulates the expression of UCP1 during the development of brown fat or exposure to external stimuli such as cold or diet (Cooper et al., 2008; Gill and La Merrill, 2017). PGC-1α is considered the founding member of the PGC-1 family. It increases mitochondrial biogenesis and is a critical regulator of BAT thermogenesis (Gill and La Merrill, 2017). Similarly, sirtuin 1 (SIRT1) is also known to play a key role in stimulating and activating brown adipogenesis, activating browning of WAT, and retarding the expansion of WAT (Sudhakar et al., 2018). Interest in the prevention of obesity by regulation of non-shivering thermogenesis in BAT and brite adipose tissue through phytochemicals has been rapidly increasing, due to their potential for minimal side effects.



Differentiation of white, brown, and beige adipocytes. Plant products (Extracts and specific phytochemicals) inhibit white adipogenesis and activate brown adipogenesis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

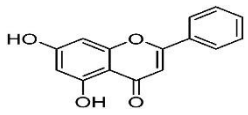
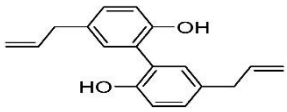
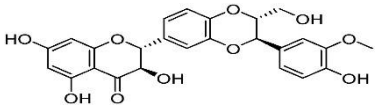
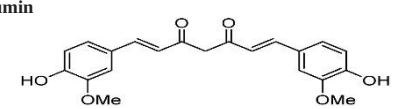
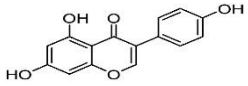
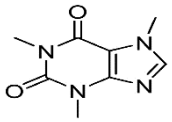
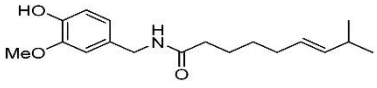
Various phytochemicals (Table 2 A and B) have previously been reported to activate browning of WAT and brown adipogenesis. For example, genistein upregulates the expression of PGC1-α and UCP1 (Aziz et al., 2017), hence promoting brown adipogenesis. Similarly, Formononetin, capsaicin, and myricetin have been shown to induce the browning of WAT by upregulating the genes, and transcriptional factors specifically expressed in BAT (Gautam et al., 2017; Hu et al., 2018). Capsaicin has been reported to activate the genes responsible for browning of WAT, including UCP1 and bone morphogenetic protein 8b (BMP8b) in WAT. Moreover, it also activates the energy sensor protein of the body, AMP-activated protein kinase (AMPK), SIRT-1 and PGC-1 α (Baboota et al., 2014; Baskaran et al., 2016). AMPK is obligatory for the proper functioning of BAT (Day et al., 2017), and its activation correspondingly increases during brown adipogenesis (Bijland et al., 2013). Barbagallo et al. (2016) reported the anti-adipogenic and thermogenic effects of silibinin. Silibinin (a natural flavonoligan and the main active constituent of *Silybum marianum*, also known as milk thistle) at a concentration of 10 μM increased the gene expressions of UCPs (UCP1, 2 and 3), PGC-1α, PPAR-α and SIRT-1. Moreover, it also decreased the expression of key adipogenic genes, PPAR-γ, fatty acid-binding protein- 4 (FABP4) and fatty acid synthase (FAS). Likewise, phyllodulcin, a natural sweetener found in certain types of *Hydrangea*, also activates the browning of WAT by enhancing the expression of thermogenic genes in subcutaneous WAT (E. Kim et al., 2017). Cinnamaldehyde and thymol are also reported to act as browning agents. Cinnamaldehyde is one of the most abundant phytochemicals found in cinnamon and has been used for various medicinal purposes since medieval times (Azhar et al., 2016). Cinnamaldehyde decreased the accumulation of visceral fat in a dose-dependent manner; in part by stimulating the interscapular BAT. It also increased the expression levels of UCP1 in high fat and high sucrose diet-fed mice (Azhar et al., 2016; Tamura et al., 2012). Thymol is a monoterpene phenolic compound and raises the expression of brown fat-specific markers and protein levels, i.e. PGC-1α, hormone sensitive lipase (HSL), UCP1, and carnitine palmitoyl transferase 1 (CPT1). Moreover, it also leads to increased phosphorylation of AMPK and acetyl-CoA carboxylase (ACC) (Choi et al., 2017). Arias et al. (2017) showed the synergistic effect of quercetin and resveratrol on WAT in rats. The combination of these two compounds significantly induced browning in the perirenal WAT of rats. Moreover, it also induced the protein expression of UCP1 in the interscapular BAT. Apigenin and naringenin have also been shown to cause elevated expression of UCP1 in BAT in a dose-dependent manner (Thaiss et al., 2016). Similarly, the prenylated flavonoid xanthohumol obtained from the hop plant (*Humulus lupulus*), activates the thermogenic program of adipose tissue (Azhar et al., 2016). Xanthohumol has been shown to increase the energy expenditure in various types of tissues including WAT and BAT, and its administration inhibits ATP synthase, increases the consumption level of oxygen and reactive oxygen species (ROS), leading to activation of AMPK and PGC-1α (Azhar et al., 2016; Kirkwood et al., 2013). Luteolin was shown to upregulate thermogenic genes and enhance energy expenditure in subcutaneous and brown adipose tissue (Zhang et al., 2019). It increased UCP1 expression and activated AMPK/PGC-1α signaling in C57BL/6 mice (Zhang et al., 2016). The inhibition of AMPK reversed the thermogenic effects of luteolin confirming its interaction with AMPK/PGC-1α signaling (Zhang et al., 2016). Chrysin (Choi and Yun, 2016) and magnolol (Parray et al., 2018) were also shown to have the same effect.

They upregulated the expression of genes and proteins involved in the regulation of brown adipogenesis such as UCP1, PGC-1α and PR-domain containing 16 (PRDM-16) in 3T3-L1adipocytes. PRDM-16 is an essential transcriptional factor involved in the differentiation of brown adipocytes (Park, 2014). Caffeine also induces brown adipogenesis (Clark et al., 2019; Rebollo-hernanz et al., 2019; Velickovic et al., 2019), and hence increases thermogenesis. Exposure of mouse-derived mesenchymal stem cells (MMSCs) to caffeine, induced the expression of UCP1 and enhanced cell metabolism and oxygen consumption. Additionally, caffeine also increased the expression of PGC-1α and mitochondrial biogenesis together with other BAT and beige specific gene markers (Velickovic et al., 2019). A polyphenolic compound, resveratrol has also been shown to induce the formation of brown-like adipocytes in WAT (Wang et al., 2015). It significantly increased the mRNA and protein expression of brown adipocyte marker genes such as UCP1 and PRDM-16 *in vitro*. Moreover, treatment with resveratrol also markedly increased the phosphorylation of AMPKα1 subunit. The browning-inducing effect of resveratrol was reversed in cells lacking AMPKα1 subunit, demonstrating that resveratrol induces brown-like adipocytes through activation of AMPK α1 (Wang et al., 2015). Other phytochemicals such as curcumin (Lone et al., 2016), sudachitin (Tsutsumi et al., 2014), genicetin (Aziz et al., 2017), myricetin (Hu et al., 2018) and berberine (Zhang et al., 2014) also enhance brown adipogenesis. They either enhance the thermogenic activity of BAT by increasing the expression of BAT specific genes and transcriptional factors or enhance the browning of WAT by specifically expressing the genes and proteins involved in the process.

alt-text: Table 2A

Table 2A

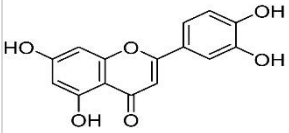
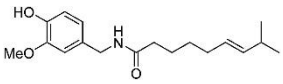
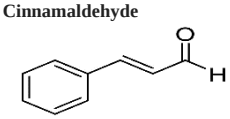
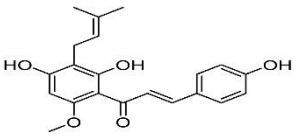
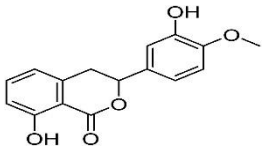
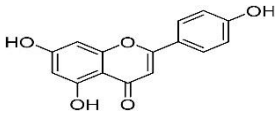
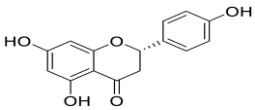
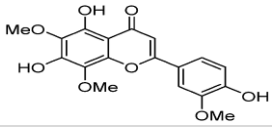
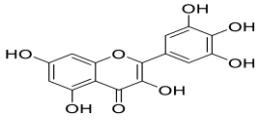
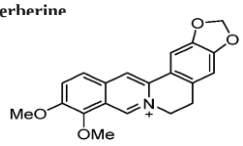
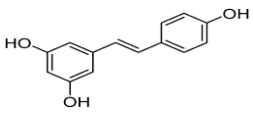
Thermogenic effects of phytochemicals (Cell Studies).

Phytochemical	Cell Type	Molecular Mechanism	Reference
Chrysin 	3T3-L1 cells	Increased the expression of Tmem26, cited 1 and Tbx1. Upregulated the genes involved in the regulation of brown adipogenesis (UCP1and Prdm-16, PGC-1 α)	Choi and Yun (2016)
Magnolol 	3T3-L1 adipocytes	Increased UCP1, PRDM-16, Cd137, Tbx1 genes, and UCP1, PGC-1 α and PRDM-16 protein expression. Enhanced the expression of lipolytic and FAs oxidation markers CPT1, PLIN, SIRT1 and ACSL1.	Parray et al. (2018)
Silibinin 	Human adipose tissue derived MSCs	Increased the expression of thermogenic genes, UCPs (UCP1, 2 and 3), PGC-1α, SIRT 1 and PPAR-α.	Barbagallo et al. (2016)
Curcumin 	3T3-L1 cells	Induced browning of 3T3-L1 primary white adipocytes. Increased protein level of p-ACC and HSL. Increased the expression of UCP1 and other browning inducing specific markers through activation of AMPK.	Lone et al. (2016)
Genistein 	3T3-L1 cells	Upregulated the expression of PGC1-α, UCP1, Sirt1. Increased the consumption level of oxygen	Aziz et al. (2017)
Caffeine 	Mouse derived MSCs	Promoted thermogenesis, brown adipogenesis. Increased the expression of brown-selective genes UCP1, PRDM-16 and PGC-1 α. Increased mitochondrial biogenesis and oxygen consumption	(Clark et al., 2019; Rebollo-hernanz et al., 2019; Velickovic et al., 2019)
Capsaicin 	3T3-L1 cells	Increased the expression of brown adipocytes-specific marker genes e.g UCP1, PGC-1α, PRDM-16, PPAR-α etc	(Baboota et al., 2014)

alt-text: Table 2B

Table 2B

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Phytochemical	Animal Model	Molecular Mechanism	Reference
Luteolin 	male C57BL/6 mice	Increased oxygen consumption, carbon dioxide production and respiratory exchange ratio. Increased thermogenesis by enhancing the expression UCP1 through activation of AMPK/PGC-1 α signaling	(Zhang et al., 2016)
Capsaicin 	WT and TRPV1 $^{-/-}$ mice	Activated the brown adipogenic markers i-e UCP1, AMPK, SIRT, PRDM-16 and PGC-1α	Baskaran et al. (2016)
Cinnamaldehyde 	male C57BL/6 Cr mice	Diminished visceral fat deposition. Activated interscapular BAT and increased the expression of UCP1	Tamura et al. (2012)
Xanthohumol 	Zucker obese fa/fa male and female mice	Inhibited ATP synthase, increased the oxygen consumption levels. Activated AMPK and PGC-1α	(Azhar et al., 2016; Kirkwood et al., 2013)
Phyllodulcin 	C57BL/6 mice	Significantly increased the expression of fat-browning related genes, UCP1, PRDM-16 and PGC-1α in scWAT. Decreased the expression of lipogenesis-related genes	Kim et al. (2017)
Apigenin  **Naringenin** 	Male C57BL/6 mice	Elevated the expression of UCP1 in BAT in a dose-dependent manner	Thaiss et al. (2016)
Sudachitin 	C57BL/6J mice and db/db mice	Increased O_2 consumption, energy expenditure and UCP1 expression in sWAT	Tsutsumi et al. (2014)
Myricetin 	db/db mice	Increased the body's temperature and consumption of oxygen. Enhanced the browning of iWAT by enhancing the expression of PGC-1α and UCP1. Moreover, it also enhanced mitochondrial biogenesis by increasing the copy number of mitochondrial DNA (mtDNA).	Hu et al. (2018)
Berberine 	Obese C57BLKS/J-Lepr Db (db/db) male mice	Increased UCP1 and thermogenic genes expressions in BAT, WAT and primary adipocytes	Zhang et al. (2014)
Resveratrol 	HFD CD1 female mice	Significantly increased the protein and mRNA expression of brown adipogenic markers-UCP1, PGC-1α, PRDM-16 etc. Also induced beige adipogenesis by increasing fatty acid oxidation, multilocular lipid droplets, and activation and phosphorylation of AMPK in iWAT.	Wang et al. (2015)

4 Appetite suppressors

High-calorie intake is the root cause of obesity. Various kinds of dietary supplements, marketed as appetite suppressors are already targeting a desperate overweight and obese population (Yimam et al., 2019). The search for natural and safe appetite-suppressing agents has sparked special interest in industry and the general population throughout the world (van Heerden, 2008). The regulation of body weight and control of appetite is a multifactorial problem. Various hormonal and neurological signals regulate the state of satiety in human bodies (Yun, 2010). Neural signal peptides, for instance, dopamine, histamine and serotonin and their associated receptors are correlated with the state of satiety, and these may be the targets of specific phytochemicals/plants crude extracts in the treatment of obesity (Yun, 2010). Plant products that give a perceived enhancement of satiety through an increase in adrenaline level and activation of the sympathetic nervous system are considered beneficial for controlling weight gain (Belza et al., 2007; Morton et al., 2014). Hormones associated with adiposity are thought to be the main communicators of body energy status to the central nervous system (Chandrasekaran et al., 2012). Two prominent and well-known hormones associated with hunger and food intake are leptin and ghrelin (Klok et al., 2007). They regulate food intake, hunger, energy homeostasis, and promote satiety by interacting with the hypothalamus in the brain (Singh, 2014) and are known to have a major impact on the balance of energy. Leptin mediates long term regulation of energy balance whereas ghrelin is known to be a fast-acting hormone, and it seems to play a role in meal initiation (Klok et al., 2007).

4.1 Leptin

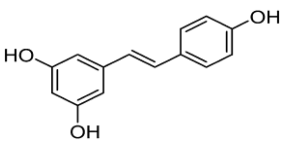
Leptin is mainly produced by mature adipocytes in white adipose tissue, but its effects extend across the body, targeting for example the heart, kidneys, and sympathetic nervous system (González-Castejón and Rodriguez-Casado, 2011). Leptin is a peptide hormone that mediates its effects through leptin receptors (*LEPR*) located primarily in the hypothalamus of brain. Activation of these receptors can regulate food intake, promote satiety and energy homeostasis by initiating different signaling cascades (Ford et al., 2013; Klok et al., 2007; Singh, 2014; Van Der Klaauw and Farooqi, 2015). Primarily, leptin acts as an energy sensor and causes reduction of appetite via signaling through the hypothalamus (Mukherjee et al., 2015), but in obesogenic conditions, leptin signaling is impaired, resulting in an excessive drive to eat, a condition known as hyperphagia (Van Der Klaauw and Farooqi, 2015). Overexpression of leptin genes and the resultant increased levels of leptin in the blood are known to cause leptin-resistance as the hypothalamus of the brain becomes less sensitive due to over activation of receptors. Synthesis and secretion of leptin are dependent on various factors such as growth hormone, insulin, steroid hormone and glucose levels (Szkudelska et al., 2009). Targeting these factors, or leptin synthesis and secretion directly with plant products is a potential approach to combat obesity.

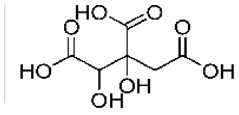
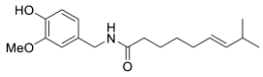
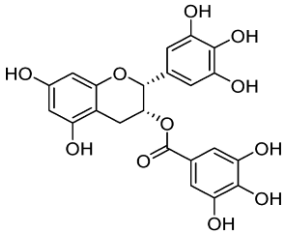
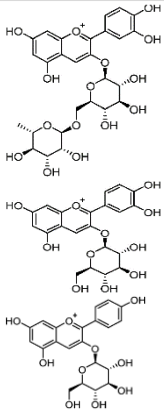
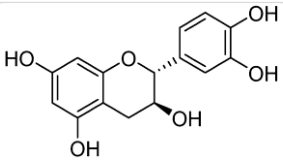
In the past, different plant products had been tested for their appetite suppressive effects and the treatment of obesity (Table 3). Resveratrol decreased the secretion of leptin in rat adipocytes, and orally administered resveratrol significantly reduced the blood leptin concentration in mice exhibiting hyperleptinemia (Baur et al., 2006). In another study, resveratrol directly decreased the level of leptin secretion in isolated rat adipocytes, when treated with insulin and glucose (Szkudelska et al., 2009). Similarly, administration of 2800 mg/day of hydroxy citric acid (HCA), an extract from *G. Cambogia*, resulted in a reduction in food intake, serum leptin level, and baseline body weight in humans (Preuss et al., 2004; Tucci, 2010). And in the same vein, purified anthocyanins (cyanidin-3-rutinoside, cyanidin-3- glucoside and pelargonidin-3-glucoside) from *Morus australis Poir* significantly decreased the leptin secretion levels, alongside other factors such as adipocyte size, lipid accumulation and weight gain in HFD C57BL/6 mice (Azzini et al., 2017; Wu et al., 2013a). Catechin is also thought to have inhibitory effects on the excess secretion of leptin. It has been shown in clinical trials that the administration of catechin ranging from 270 to 1200 mg/day resulted in reduced body weight and lowering of serum leptin levels (Rains et al., 2011; Sun et al., 2016). Epigallocatechin 3 Gallate (EGCG) and capsaicin are also known to have appetite suppressing effects and increase the sensation of fullness, and decrease the desire to eat (Janssens et al., 2014; Fernandes et al., 2018).

alt-text: Table 3

Table 3

List of selected phytochemicals with known appetite suppressing effects.

Phytochemical	Structure	Animal Model and Human	Reference
Resveratrol		male C57BL/6NIA mice	Baur et al. (2006)
Hydroxy citric acid		Human	(Preuss et al., 2004;

			
Capsaicin		Human	Janssens et al. (2014)
Epigallocatechin 3 gallate (EGCG)		Human	Fernandes et al. (2018)
Cyanidin-3-rutinoside, Cyanidin-3-glucoside and Pelargonidin-3-glucoside		HFD C57BL/6 mice	(Azzini et al., 2017; Wu et al., 2013a)
Catechin		Human	(Rains et al., 2011; Sun et al., 2016)

In addition to the aforementioned bioactive compounds, plant extracts (*Prunus mume* and *Lithospermum erythrorhizon*) synergistically prevent the impairment of energy, glucose, and lipid regulation, through potentiating hypothalamic leptin and insulin signaling in rats (Ko et al., 2013). Likewise, Wu et al. (2013b) reported the effects of blueberry and mulberry juice on the secretion of leptin in high fat-diet (HFD) obese mice. The juice significantly reduced serum leptin levels when compared to control HFD mice.

4.2 Ghrelin

Ghrelin is a 28 amino acid peptide acetylated on serine 3, which is synthesized in the stomach but it has also been identified in other tissues such as the pancreas, gastrointestinal tract, adrenal cortex and ovary (Klok et al., 2007). It binds to and activates the growth hormone secretagogue receptor (GHS-R), leading to stimulation of food uptake, fat deposition and growth hormone release (Pradhan et al., 2013; Singh, 2014). The hypothalamus modifies the energy status of the body by sensing peripheral ghrelin levels (Singh, 2014). Lowering the secretion of ghrelin is therefore another strategy for fighting weight gain. Numerous plant products have been shown to inhibit the abnormal secretion of ghrelin. Celestino et al. (2017) showed that a combination of South American herbal extracts reduced food intake through gastrointestinal hormone modulation in obese and overweight women. They showed that these combined extracts decreased acylated ghrelin levels, an active isoform of ghrelin, after mealtimes, indicating the appetite suppressing effects of these extracts. Similarly, Sengupta et al. (2012) reported that *Dolichos biflorus* and *Piper betle* extracts (herbal formulation LI10903F) significantly reduced serum ghrelin levels in 50 human subjects after eight weeks of supplementation. Extracts of *Phaseolus vulgaris* have also been shown to control appetite in human subjects when given as supplements with mixed meals to 12 volunteers. Three hours after meal consumption, the extracts of *P. vulgaris* suppressed secretion of ghrelin and effected the sensation of satiety, inducing a lower desire to eat (Spadafranca et al., 2013). A compound known as P57, isolated from a South African succulent of the Hoodia family has been shown to act as a prominent appetite suppressor in preclinical trials (Gooda Sahib et al., 2012). It has been used in preclinical studies and shown to have a good safety profile and significantly promoted weight loss in dogs, mice and rats (Habeck, 2002). Similarly, other extracts and herbal supplements such as *Citrus aurantium*, ephedra and hydroxy citric acid also exhibit appetite suppressing properties (Rezaie et al., 2015). Based on these studies, it can be concluded that plant products show promise for use as appetite regulating agents in obesogenic conditions.

5 Regulation of lipid metabolism

A key step in the metabolism of lipids from stored fat is lipolysis (Luglio et al., 2015). Control of lipolysis has significant potential for the development of anti-obesogenic products (Sun et al., 2016). Lipolysis is the breakdown of

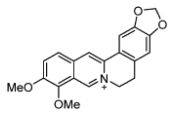
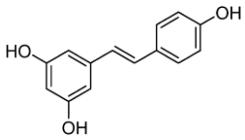
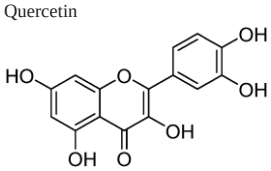
TGs to form monoglycerides and free fatty acids, which can be used by other tissues. Adipose tissue is the only tissue that has the ability to hydrolyze stored TGs and mobilize fatty acids into the bloodstream (Chaves et al., 2011). Lipolysis is a key step in the absorption and accumulation of fats in mature adipocytes. Initially, it was thought that the most important enzyme in the process of lipolysis is HSL, but, with the advancement of knowledge, it was revealed that two other enzymes, ATGL and monoacylglycerol lipase (MAGL) are also involved in the breakdown of lipids to free fatty acids (Luglio et al., 2015). Therefore, complete hydrolysis of TGs into fatty acids in adipose tissue is dependent on the activities of ATGL, HSL, and MAGL (O'Neill et al., 2013). HSL is mostly found in both brown and white adipose tissue (Luglio et al., 2015). HSL and ATGL are known to be the main lipases in WAT, and the mobilization of fatty acids by WAT is dependent on the activity of these two lipases. Together they are also considered to be responsible for 95% of the total hydrolysis of TGs in adipocytes (Chaves et al., 2011; Schweiger et al., 2006). ATGL is primarily responsible for the hydrolysis of TGs, while HSL is known to preferentially hydrolyze diglycerides (DGs), with a tenfold higher effect than on TGs (Chaves et al., 2011). AMPK is also known to be involved in lipid metabolism (lipolysis), and increased activity levels can be achieved by administering plant products such as berberine and resveratrol (O'Neill et al., 2013). Similarly, β-adrenergic receptor activation is also known to cause lipolysis in white adipocytes (Bordicchia et al., 2014), illustrating that altering the expression of key regulatory enzymes involved in lipolysis can prove advantageous in the fight against obesity.

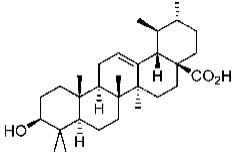
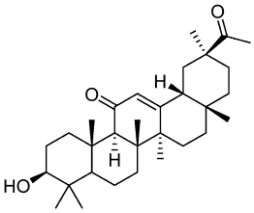
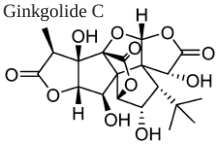
There are a number of reports evidencing the lipolytic effects of plant products or specific phytochemicals (Table 4). Gómez-Zorita et al. (2013) showed the lipolytic effect of resveratrol. Resveratrol significantly stimulated the expression of HSL but not ATGL in genetically obese rats. In another study, Lasa et al. (2012) reported the lipolytic effects of resveratrol through ATGL management. Resveratrol enhanced the gene and protein level of ATGL in adipose tissue, and it was concluded that lipolytic effects regulated by resveratrol in human and murine adipocytes are through mainly changes in ATGL levels. 18β-Glycyrrhetinic acid and Ginkgolide C are also reported to enhance lipolysis. 18β-Glycyrrhetinic enhances lipolysis, and enhances the mRNA level of HSL and ATGL (Moon et al., 2012). Ginkgolide C increases the production of lipolytic proteins (ATGL and HSL) and activates AMPK (Liou et al., 2015). Similarly, the flavonoid quercetin has also been shown to induce lipolysis. In OP9 cells, which were induced to differentiate into mature adipocytes, quercetin dose-dependently induced lipolysis in these cells by enhancing the expression of both HSL (>2-fold) and ATGL (>4-fold) (Seo et al., 2015). Jiang et al. (2016) showed the lipolytic effects of berberine in 3T3-L1 adipocytes. Berberine extracted from *Coptis chinensis* increased the expression of ATGL and phosphorylated HSL (p-HSL) in a time-dependent manner, and reduced TG level by 10% in 3T3-L1 adipocytes. Moreover, it was also revealed that AMPK was involved in the enhanced expression of p-HSL and ATGL after treatment with berberine in 3T3-L1 adipocytes. Likewise, ursolic acid (a pentacyclic triterpenoid) stimulated lipolysis in primary-cultured rat adipocytes (Li et al., 2010). It was shown that ursolic acid increased lipolysis by translocating the HSL to the lipid droplet from the cytosol and inhibiting perilipin A expression. It was also observed that ursolic acid upregulated the expression of ATGL.

alt-text: Table 4

Table 4

Lipolytic effects of phytochemicals (Cell and Animal Studies).

Phytochemical	Experimental Model	Molecular Mechanism	References
Berberine 	3T3-L1 cells	Reduced TG level by 10% and increased the expression of ATGL and phosphorylated HSL (p-HSL) in a time-dependent manner.	Jiang et al. (2016)
Resveratrol 	Male Zucker (fa/fa) rats	Enhanced the expression HSL and reduced the activities of glucose-6-P-dehydrogenase, ACC and expression of LPL	Gómez-Zorita et al. (2013)
Quercetin 	OP9 cells	Enhanced the expression of HSL (>2-fold) and ATGL (>4-fold)	Seo et al. (2015)
Ursolic Acid	Primary-cultured rat	Enhanced the expression of ATGL and HSL. Moreover inhibited the expression of perilipin A	Li et al. (2010)

	adipocytes		
18β-Glycyrrhetinic acid 	3T3-L1 cells	Increased lipolysis, and enhanced the mRNA level of HSL and ATGL. Moreover, it also induced the phosphorylation of HSL	Moon et al. (2012)
Ginkgolide C 	3T3-L1 cells	Increased the production of lipolytic proteins (ATGL and HSL). Moreover activated AMPK which resulted in decreased activity of ACC	Liou et al. (2015)

Apart from specific phytochemicals, crude plant extracts also exhibit lipolytic effects. Black soybean (Glycine max (L.) Merr.) is rich in anthocyanins. Its ethanolic extract was shown to enhance the activity of AMPK, HSL, and lipoprotein lipase (LPL) in mesenteric fat of C57BL/6N mice (S.Y. Kim et al., 2015). Extract of *Vigna angularis* (Black adzuki bean) also showed anti-obesogenic and lipolytic effects. The extract significantly decreased the accumulation of TGs in a dose-dependent manner and enhanced the expression of prominent lipolytic genes for HSL to 457%, at 1 mg/mL concentration. Similarly, the mRNA expression of ATGL was enhanced to 303% at 1 mg/mL and 427% at 2 mg/mL (M. Kim et al., 2015). Chen et al. (2014) reported the anti-obesogenic and lipolytic effects of methanolic extract of black garlic. The extract significantly enhanced lipolysis and increased the expression of ATGL and HSL along with other anti-adipogenic genes.

Based on these reports, it is clear that plant products either in the form of crude extracts or specific phytochemicals have latent lipolysis regulating effects. Further investigation is needed for these compounds to be used as anti-obesogenic agents after successful clinical trials.

6 Adipocyte differentiation

Adipose tissue controls energy balance and the homeostasis of lipids. Excessive calorie intake and low energy expenditure can result in hypertrophy and hyperplasia of adipocytes (Tang and Lane, 2012), two of the primary detrimental conditions, which relate to adipose tissue. Hyperplasia is the recruitment of mesenchymal stem cells (MSCs) to the adipogenic lineage, resulting in an increase in the number of adipocytes in WAT (Tang and Lane, 2012). Similarly, hypertrophy refers to the expansion in the size of mature WAT adipocytes due to increased calorie intake and lipid accumulation. Mature WAT adipocytes store TGs and release them when necessary, in response to energy demands. Blocking of the principal factors that influence the development of new adipocytes, by natural products may prove effective in the development of anti-obesity therapies (Sun et al., 2016; Xiao et al., 2010). The development of WAT from pre-adipocytes is a well-defined process, known as white adipogenesis, which is regulated by a cascade of positive and negative regulators (Ahmad et al., 2020). PPAR- γ is a critical pro-adipogenic transcription factor that positively regulates the differentiation of preadipocytes to mature adipocytes (Sarjeant and Stephens, 2012). Positive regulators of adipogenesis have been shown to induce the activation of PPAR-γ mRNA. Members of CCCAAT/enhancer binding protein family (C/EBPs), some of the kruppel like factors (KLFs) (Sarjeant and Stephens, 2012) and early beta-cell factors 1 and 2 (EBF 1 and 2) (Jimenez et al., 2007) are inducers of PPAR-γ mRNA, hence promote adipocyte differentiation. Repressors of adipogenesis include members of the KLFs family such as KLF 2, 3, 7, 16 (Jang et al., 2016,b; Jiang et al., 2015; Pollak et al., 2018; Sue et al., 2008), GATA-binding factors 2 and 3 (GATA 2,3) (Tong et al., 2000), Wnt /β- catenin signaling (T. Chen et al., 2018), and the Hh signaling pathway (Fontaine et al., 2008; Moseti et al., 2016).

It has been shown that plant products can inhibit the differentiation of preadipocytes into mature white adipocytes through up- or downregulation of these negative and positive adipogenic factors (Table 5 A and B). For example, 6- gingerol, found in ginger, inhibits adipogenic differentiation through activation of the Wnt/β-catenin signaling pathway (Li and Zhou, 2015). This compound was shown to lower the mRNA levels of key adipogenic and lipogenic factors in 3T3-L1 cells such as mRNA levels of C/EBP-α, PPAR-γ, and protein expression of FAS and ACC through the activation of Wnt/β-catenin signaling pathway. Similarly, toosendanin, a triterpenoid, has also been shown recently to inhibit adipogenesis through the Wnt/β-catenin dependent pathway (Chen et al., 2018,b). Toosendanin significantly reduces the expression of central adipogenic factors C/EBP-α and PPAR-γ, FAS, and ACC through activation of the Wnt/β-catenin dependent pathway in 3T3-L1 cells and *in vivo* in male C57 BL/C6 mice (T. Chen et al., 2018). Loganic acid (oral administration with 10 and 50 mg/kg/day) significantly inhibits total fat increase, fatty hepatocyte deposition in the liver, body weight gain, and adipocyte enlargement in the abdominal visceral fat tissues in ovariectomized mice and also inhibits the expression of positive regulators of adipogenesis in 3T3-L1 cells (Park et al., 2018). In another study, the administration of isobavachalcone isolated from the Japanese *Angelica keiskei* plant resulted in decreased adipocyte proliferation by 38.6% at day 2 (D2) and 31.0% at day 8 (D8). It also reduced intracellular lipid contents by 75% and decreased the protein levels of PPAR-γ and C/EBP-α. Levels of sterol regulatory element-binding protein -1c (SREBP-1c), ACC1, and FAS mRNA in 3T3-L1 pre-adipocytes were also lowered (Lee et al., 2018). Caffeic acid and hydroxytyrosol have also been reported to have anti-adipogenic properties and suppress the protein expression levels of PPAR-γ (Lutfi et al., 2017). Recently an anthocyanin, Delphinidin-3-O-β- glucoside (D3G) has also been shown to inhibit the differentiation of pre-adipocytes, reduce lipid accumulation, and downregulate key lipogenic and adipogenic markers, SREBP-1, PPAR-γ, C/EBP-α and FAS in 3T3-L1 adipocytes (Park et al., 2019). Kumkarnjana et al. (2018) reported the anti-adipogenic effects of four flavonoids (kaempferide, pectolinarigenin, dillenetin and 4,2′-dihydroxy-4′,5′,6′-trimethoxychalcone) extracted from the leaves of Chromolaena odorata. These flavonoids dose-dependently inhibited the accumulation of lipids in differentiating 3T3-L1 adipocytes of which 2′-dihydroxy-4′,5′,6′-trimethoxychalcone was the most potent one. It inhibited cellular lipid accumulation by 75%–90% in a dose-dependent manner. Similarly two other flavonoids (flavones), 5,7-dimethoxyflavone (Song et al., 2016) and 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (Wang et al., 2016) have also been shown to attenuate white adipogenesis in 3T3-L1 cells and HFD-induced obese mice. Pterostilbene has also been shown to have anti-adipogenic effects (Seo et al., 2017). It reduces the accumulation of lipids and suppresses the expression of positive central

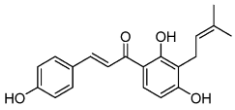
regulators of adipogenesis i-e PPAR-γ, C/EBP-α, adipocyte protein 2 (aP2) and C/EBP-β (Seo et al., 2017). Tangeretin, nobiletin and hesperetin also show the same effect. They reduce triglyceride levels and downregulate the expression level of PPAR-γ in differentiating 3T3-L1 adipocytes (J. Chen et al., 2018). Similarly, anthocyanins from *Vitis coignetiae* enhance AMPK activation, decrease the number of lipid droplets, reduce TG level and inhibit the expression of PPAR-γ, C/EBP-α,- β and REBP-1c in 3T3-L1 adipocytes (Han et al., 2018). Oxyresveratrol and cyanomaclurin also show the same effect: they reduce TG contents in differentiating 3T3-L1 cells (Tan et al., 2015). Moreover, they also inhibits cell proliferation, induce cell cycle arrest, and down-regulate the expression of PPAR-γ and C/EBP-α (Tan et al., 2015). Kaempferol-3-O-rutinoside from *Solidago virgaurea* also inhibits the differentiation of pre-adipocytes through suppression of PPAR-γ and C/EBP-α expression (Y.S. Jang et al., 2016). Tricin, a hydroxylated methoxyflavone, inhibits the lipid accumulation in 3T3-L1 adipocytes by 37% at 6 μg/mL and significantly decreases the mRNA level of PPAR-γ, CEBPs/and SREBP-1

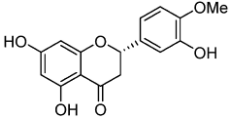
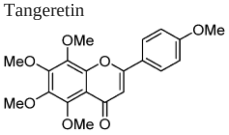
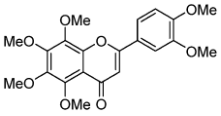
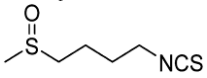
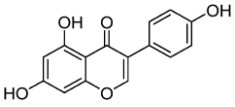
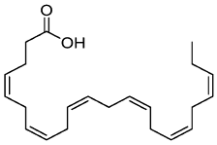
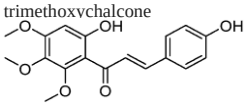
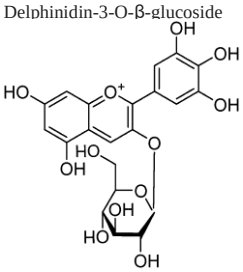
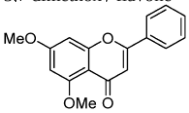
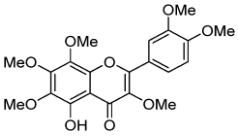
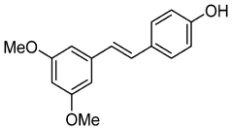
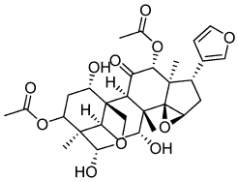
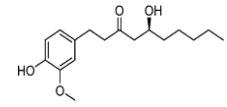
at 1.5 μg/mL concentration (Lee et al., 2015). Recently purpurin has also been reported to reduce blood glucose, cholesterol, and triglycerides levels in Male C57BL/6 mice and inhibit differentiation of 3T3-L1 adipocytes apparently by activation of AMPK (Nam et al., 2019).

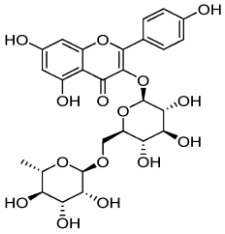
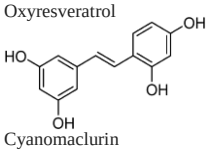
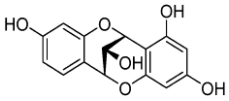
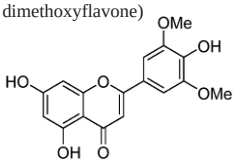
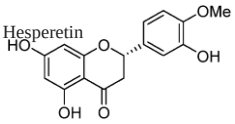
alt-text: Table 5A

Table 5A

Anti-Adipogenic effects of bioactive compounds from plants (Cell Studies).

Phytochemicals	Cell line	Molecular mechanism of action	Reference
Isobavachalcone (IBC) 	3T3-L1 pre-adipocytes	Decreased cell proliferation by 38.6% at day 2 (D2) and 31.0% at day 8 (D8). Reduced intracellular lipids contents by 75%. Decreased protein level of PPAR-γ and C/EBP-α by 85.5% and 97.3%. Decreased the expression of SREBP-1c, adiponectin, ACC1, and FAS mRNAs levels	Lee et al. (2018)
Hesperetin	3T3-L1 adipocytes	Reduced TG level by 16.08, 23.10 and 45.67% at 50 μmol concentration. Downregulated the expression level of central adipogenic factor PPAR-γ.	(J. Chen et al., 2018)

 Tangeretin  Nobiletin 			
Sulforaphane  Genistein  Docosahexaenoic acid 	3T3-L1 murine pre-adipocytes	Reduced accumulation of lipids in differentiating adipocytes. Also inhibited adipocyte differentiation through C/EBP-α, PPAR-γ1, PPAR-γ2, and GLUT4 mRNA downregulations	Valli et al. (2018)
4,2′-dihydroxy-4′,5′,6′-trimethoxychalcone 	3T3-L1 adipocytes	Inhibited lipid accumulation up to 75% and 90% at a concentration of 30 and 50 μmol/L	Kumkarnjana et al. (2018)
Delphinidin-3-O-β-glucoside 	3T3-L1 adipocytes	Reduced lipid accumulation. Down regulated the expression of PPAR-γ, C/EBP-α, SREBP1 and FAS.	Park et al. (2019)
5.7 dimethoxy flavone 	3T3-L1 adipocytes and HFD C57/BL6j mice	Down regulated C/EBP- α, PPAR- γ, FAS, LPL, HMG-CoA, SREBP-1c and ACC.	Song et al. (2016)
5-hydroxy-3,6,7,8,3′,4′-Hexamethoxyflavone 	3T3-L1 cells	Inhibited lipid accumulation by 55–60% in a dose-dependent manner. Downregulated key adipogenic transcriptional factors, C/EBPs, PPAR- γ, FAS and ACC.	Wang et al. (2016)
Pterostilbene 	3T3-L1 cells	Reduced lipid accumulation, suppressed expression of PPAR-γ by (78%), C/EBP-α (68%), aP2 (84%), C/EBP-β (51%). Decreased expression of TG synthesis-associated proteins DGAT1 (37.5%) and Lipin1 (63.8%).	Seo et al. (2017)
Toosendanin 	3T3-L1 pre-adipocytes and male C57BL/C6 mice	Attenuated accumulation of lipids in a dose-dependent manner in differentiating 3T3-L1 adipocytes. Reduced the expression of positive regulators of adipogenesis such as PPAR-γ, C/EBP-α, ACC and FAS through Wnt/β-catenin dependent pathway	(T. Chen et al., 2018)
6-Gingerol 	3T3-L1 adipocytes	Inhibited adipogenesis by attenuating the mRNA expression of various adipogenic and lipogenic genes i-e C/EBP-α, PPAR-γ, ACC, and FAS through activation of Wnt/β-catenin signalling. It promoted phosphorylation of GSK-3β and translocation of β catenin to the nucleus.	Li and Zhou (2015)

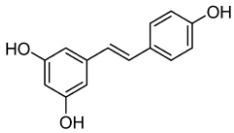
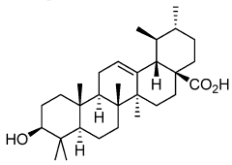
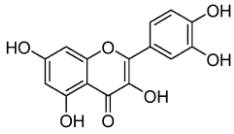
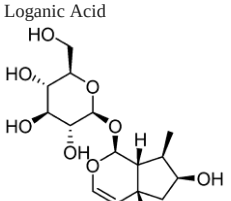
Kaempferol-3-O-rutinoside from *Solidago virgaurea* 	3T3-L1 fibroblasts	Inhibited the differentiation of pre-adipocytes through suppression of PPAR-γ and C/EBP-α expression	(Y. S. Jang et al., 2016)
Oxyresveratrol  Cyanomaclurin 	3T3-L1 cells	Reduced TG contents to 68% and 41% of control with 100 and 600 μM concentrations. Inhibited cell proliferation by 45% and 67%. Induced cell cycle arrest and down-regulated the expression of PPAR-γ and C/EBP-α	Tan et al. (2015)
Tricin (5,7,4′ trihydroxy-3′,5′-dimethoxyflavone) 	3T3-L1 pre-adipocytes	Reduced lipid accumulation by 37% at 6 μg/ml. Significantly decreased the mRNA level of PPAR-γ, CEBP-α and SREBP-1 at 1.5 μg/ml concentration	Lee et al. (2015)
Hesperetin 	Human Mesenchymal Stem cells (hMSCs)	Decreased lipid contents to 42.6 and 67.82% in a concentration-dependent manner. Almost completely suppressed the differentiation of hMSCs to pre-adipocytes. Decreased 1.79 and 1.63 folds the expression level of PPAR- and C/EBP-β	Subash-Babu and Alshatwi (2015)

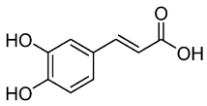
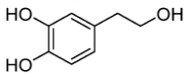
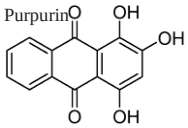
γ β

alt-text: Table 5B

Table 5B

Anti-Adipogenic effects of bioactive compounds from plants (Animal Studies)

Phytochemical	Animal Model	Molecular Mechanism	References
Resveratrol 	HFD induced Kumming mice	Downregulated mRNA level of ACC -1, PPAR- γ LPL and FAS	Qiao et al. (2014)
Triterpenoid (Ursolic Acid) 	HFD induced Sprague-Dawley Rats	Enhanced activation of AMPK and increased β-oxidation of FFAs. Reduced insulin resistance and body weight (45g average weight loss) Decreased HFD/Body ratio by 17%	Chu et al. (2015)
Quercetin-rich supplement 	HFD induced Wister male rats	Reduced lipid accumulation and size of adipocytes. Downregulated the adipogenic genes, FAS, LPL, aP2, FATP1 etc. Moreover, it upregulated the expression of negative regulators of adipogenesis i-e AMPK, CPT1, HSL, ATGL and PPAR-α.	Ting et al. (2017)
Loganic Acid 	Ovariectomized mice	Oral administration (10 and 50 mg/kg/day) of loganic acid inhibited total fat increase, body weight gain, adipocyte enlargement in the abdominal visceral fat tissues and fatty hepatocyte deposition in the liver	Park et al. (2018)

Caffeic acid  Hydroxytyrosol 	Zebrafish and Rainbow Trout	Supressed the protein expression of PPAR-γ and lipid accumulation in primary-cultured rainbow trout adipocytes. Hydroxytyrosol significantly reduced the amount of triacylglycerol and the *FASN* gene mRNA levels in rainbow trout.	Lutfi et al. (2017)
Purpurin 	Male C57BL/6 mice	Oral administration of purpurin (40 mg/kg and 80 mg/kg) reduced weight gain by 34 and 55%. Moreover, the increased blood glucose, cholesterol, and triglycerides levels caused by HFD, were reduced by purpurin treatments (40 and 80 mg/kg) by 24 and 78%, 27 and 76%, and 64 and 123%.	Nam et al. (2019)

Again, besides the specific bioactive compounds of plants, crude extracts can also have anti-adipogenic effects. Combined extracts of green coffee, cinnamon, and ginger significantly decrease the level of low-density lipoprotein (LDL), TGs, and total lipids in obese Sprague-Dawley rats (Raoof et al., 2017). Gyeongshingangjeehwan 18 (GGEx18), a herbal composition from *Rheum palmatum* L, *Laminaria japonica* Aresch and *Ephedra sinica* reduces lipid accumulation in 3T3-L1 adipocytes by 41%, 54% and 70% at 0.1, 1 and 10 μg/mL concentrations respectively. It also decreases visceral adipose tissue weight by 46% and 24% at 250 and 500 mg/kg doses in HFD C57BL/6J mice (Oh et al., 2015). Similarly, *Curcuma longa* L extracts also showed anti-adipogenic effects in Sprague Dawely rats (J.H. Kim et al., 2016). The extract suppressed adipocyte differentiation and lipogenesis, decreased mRNA expression of FAS, ACC, aP-2 and lipoprotein lipase (LPL) (J. H. Kim et al., 2016). *Camellia sinensis* extract reduces the expression of pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor α (TNF- α) genes, serum leptin level and inhibits the absorption of fatty acids, resulting in reduce body weight and fat accumulation in HFD rats (Xu et al., 2015). Extracts of *Tropaeolum majus* have also been shown to reduce triglyceride level up to 25.8%–54.7%, decrease PPAR-γ expression level by 23.0%–90.4% and C/EBP-α by 45.8% and 71.9% at different concentrations in 3T3-L1 cells (G.C. Kim et al., 2017).

7 Summary and outlook

Obesity is a common disorder caused by the interaction of behavioural, environmental, genetic and nutritional factors, and its prevalence is accelerating worldwide. Excessive consumption of calorific foods, and increasingly sedentary lifestyles are the predominant causative factors for this rise in obesity. Returning to healthy lifestyles, for example, daily exercise and reducing excessive calorific intake is the surest route to successful weight loss, but for many, it is extremely challenging to maintain. For decades, synthetic chemicals have been developed as anti-obesogenic drugs. Despite generating positive results, they have also caused adverse effects that muted their benefits. Traditionally used medicinal plants, which contain a wide range of natural chemicals, have been used for the treatment of many infectious as well as chronic disorders including obesity. These natural products from plants may play a supportive role in combating obesity by helping obese people to lose weight. There is also potential for synergistic activity, conferred by the combination of multiple natural products to increase their anti-obesogenic activities and mode of action on multiple targets, which may prove to be advantageous over other chemical treatments. Previously published results regarding anti-obesogenic compounds, are either based on *in vitro* (cell) studies or mouse models and therefore do not guarantee the same results in humans. Additional preclinical development followed by appropriate clinical trials must therefore be performed to evaluate the effectiveness of bioactive compounds to understand their safety, bioavailability, pharmacokinetics and efficacy. Clinical trials should be planned carefully to evaluate both immediate and long-term side effects of these bioactive compounds. An investigation into promising targets and identification of unique regulators of both WATand BAT development are still needed for formulating appropriate natural products as drugs against obesity. In conclusion, natural products derived from medicinal plants, have the potential if developed appropriately, to deliver anti-obesogenic drugs that could play a central role in the management of obesity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phytochem.2020.112513.

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Biography

1. Bilal Ahmad. Bilal Ahmad did his MSc in Biotechnology from IZTECH, Turkey. He is currently a PhD candidate in the School of Biosciences at Taylor's University Malaysia. His research interests include extraction and characterization of phytochemials and determination of their therapeutic effects. He is currently doing research on the anti-obesogenic effects of flavones at Taylor's University Malaysia under the supervision of Associate Prof. Dr Eng Hwa Wong. 

2. Emily P. Friar. Emily Friar achieved her MChem in Chemistry with Medicinal Chemistry with International Placement from University of Warwick, UK in 2019. This included work in the Sadler group and a placement in the Paterson group at Monash University, Australia. She is now a PhD student working under the joint supervision of Dr. Serpell and Professor Garrett at University of Kent, UK. Her interdisciplinary research focuses on identifying cellular targets of flavone molecules in colorectal cancer cells. 

3. M Sufyan Vohra. Muhammad Sufyan Vohra graduated his Masters in Industrial Biotechnology from National University of Science and Technology, Pakistan. He is currently a PhD scholar in the School of Medicine at Taylor's University, Malaysia. His research interests include determination of antibiotic resistance and evalution of anti-obesogenic therapies. His research project for PhD is focused on the obesogenic effects of the brain and the anti-obesogenic effects of flavones under the supervision of Associate Prof. Dr Eng Hwa Wong. 

4. Michelle D. Garrett. Michelle Garrett is Professor of Cancer Therapeutics at the University of Kent, UK. Her PhD research was at The Institute of Cancer Research (ICR), London, followed by post-doctoral research at Yale University, USA. She then undertook small molecule cancer drug discovery in industry (Onyx Pharmaceuticals, USA, 1994–99) and academia (ICR, 1999–2014), before joining University of Kent in 2014. She has three cancer drugs in clinical development. Current research interests are cancer drug discovery and drug resistance. 

5. Christopher J. Serpell. Dr. Serpell achieved his DPhil with Prof. Paul Beer at the University of Oxford in 2010. He then moved to Prof. Hanadi Sleiman's group at McGill University, on a Tomlinson, and then a Banting Fellowship. He returned to Oxford in 2014 to work with Prof. Ben Davis. He was appointed as a Lecturer in Chemistry at the University of Kent in 2015, and his research interests encompass biomolecular, supramolecular, and macromolecular chemistry. 

6. Isabel Lim Fong. Dr Isabel is a Senior Lecturer in the Department of Paraclinical Sciences, at Universiti Malaysia Sarawak (UNIMAS) since 2005. She did her PhD from University of Leicester, United Kingdom. Her research focuses on discovery of phytochemicals as antimicrobial and anti-cancer therapeutics. She also offers her molecular genetics expertise to the field of Cardiology in collaboration with Sarawak Heart Centre, searching for circulating microRNA biomarkers as a prognostic tool to assess tissue healing in patients of anterior myocardial infarction. Her collaboration networks include University of Kent (UK),

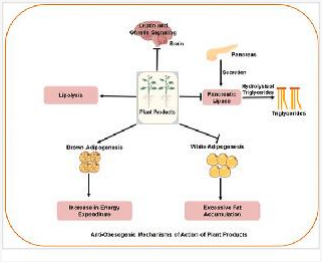
University of Tripoli, (Libya), Universiti Teknologi Malaysia (Sarawak), Taylor's University (Malaysia), SEGi College (Malaysia) and Sarawak Biodiversity Centre.

7. Eng Hwa Wong. Dr. Eng Hwa Wong is an Associate Professor at Taylor's University Lakeside Campus, Malaysia. She did her PhD in Medical Microbiology from University of Malaya, Malaysia. She has held the post of Associate Dean of Research, and Programme Director of Postgraduate studies, in the School of Medicine Taylor's University. Moreover, she is a life member of The Malaysian Biosafety and Biosecurity Association (MBBA), and a member of American Society of Microbiology (ASM since year 2013). Her research intersts include “exploring the usage of new technologies in combating antimicrobial resistance, investigation of

Graphical abstract

Plant products tackle obesity through various mechanisms of action. These include inhibition of pancreatic lipase activities, increase in energy expenditure, appetite regulation, lipolysis, and inhibition of white adipose tissue development.

alt-text: Image 1



Highlights

- Obesity results due to imbalance between intake and expenditure of energy
- In obesogenic conditions the excessive fats are accumulated in white adipocytes
- Brown and Beige adipose tissues utilize the stored fats to generate heat through non-shivering thermogenesis
- Plant products promote brown adipogenesis and inhibit white adipogenesis
- Plant products prevent the excessive accumulation of fats in white adipocytes through various molecular mechanisms