RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW



Cite this: *RSC Med. Chem.*, 2023, **14**, 1429

# Recent advancements in pharmacological strategies to modulate energy balance for combating obesity

Benudhara Pati,[a] Satyabrata Sendh,[a] Bijayashree Sahu,[a] Sunil Pani,[a] Nivedita Jena[b] and Naresh Chandra Bal *[a]

Received 6th March 2023,
Accepted 6th June 2023

DOI: 10.1039/d3md00107e

rsc.li/medchem

The prevalence of obesity along with its related metabolic diseases has increased globally in recent decades. Obesity originates from a heterogeneous physiological state, which is further complicated by the influence of factors such as genetic, behavioural, and environmental. Lifestyle interventions including exercise and diet have limited success, necessitating the development of pharmacological approaches. Mechanistically, strategies target either reducing energy intake or increasing consumption through metabolism boosting. Current drugs lower energy intake *via* inducing satiety or inhibiting substrate absorption, while targeting mitochondria or cytosolic energy sensors has shown limited success due to toxicity. Nonshivering thermogenesis (NST) has provided hope for activating these processes selectively without significant side effects. The internet-based marketing of plant-based formulations for enhancing metabolism has surged. This review compiles scientific articles, magazines, newspapers, and online resources on anti-obesity drug development. Combination therapy of metabolic boosters and established anti-obesity compounds appears to be a promising future approach that requires further research.

## 1. Introduction

Obesity has emerged as a major chronic disease with serious health consequences that worsens the associated co-morbidity factors, including type 2 diabetes (T2D).[1] It originates from the dysregulation of energy balance (caloric intake and expenditure), which is tightly regulated by a synergistic interplay of neural, hormonal and metabolic pathways.[2] The pathogenesis of obesity is highly intertwined with metabolism of different organs, including the liver, adipose tissue, and skeletal muscle (SkM).[3,4] In the case of increased caloric intake, several pathways are turned on to dissipate energy in a process called "diet-induced thermogenesis (DIT)".[5] The DIT constitutes adaptive (futile) energy dissipation mechanisms, and has been a major area of research in the last few decades in the hope of discovering molecular targets for countering obesity.[6] The non-shivering thermogenesis (NST) has significant mechanistic overlap with DIT (as depicted in Fig. 1).[7,8] Due to this, mechanisms of NST have been considered as good targets to increase energy expenditure.

Among the NST mechanisms, the most-studied one is the uncoupling protein (UCP)1.[9] UCP1 is expressed in the inner mitochondrial membrane more preferentially in brown adipose tissue (BAT) and dissipates a proton gradient, turning the potential energy into heat.[10] Recent studies have identified a few UCP1-independent mechanisms of thermogenesis in the BAT.[11,12] In addition to BAT, SkM has been shown as an alternate site of NST. The proposed molecular mechanisms of NST in the SkM are: 1) futile $Ca^{2+}$-cycling in the sarcoplasmic reticulum (SR), 2) leakiness of mitochondrial membrane, 3) futile $Na^{+}/K^{+}$ ATPase, and 4) ATP utilization by super relaxed myosin.[13–15] Out of these potential mechanisms, the first two have been supported by research evidences and a lot of data has recently accumulated in favour of the first. The futile $Ca^{2+}$-cycling in the muscle is induced by leakage of $Ca^{2+}$ from the SR through ryanodine receptor (RyR) 1 that activates the $Ca^{2+}$-ATPase called SERCA. Interestingly, the efficiency of the SERCA-mediated ATP utilization and $Ca^{2+}$-transport can be modulated by various physiological conditions, due to which some have even termed it as a "heat pump".[16] Recent studies have provided data that a small SR-located peptide called sarcolipin (SLN) regulates the SR $Ca^{2+}$-cycling by SERCA and increases ATP usage, enhancing thermogenesis.[17,18] Some studies have provided hope that SERCA-based thermogenesis can be enhanced by pharmacological agents.[19]

Several interventions to manage obesity have been tested, such as lifestyle changes, bariatric surgery and

[a] *School of Biotechnology, KIIT University, Bhubaneswar, Odisha, 751024 India. E-mail: naresh.bal@kiitbiotech.ac.in*
[b] *Institute of Life Science, DBT ILS Bioincubator, Bhubaneswar, Odisha, 751021-India*

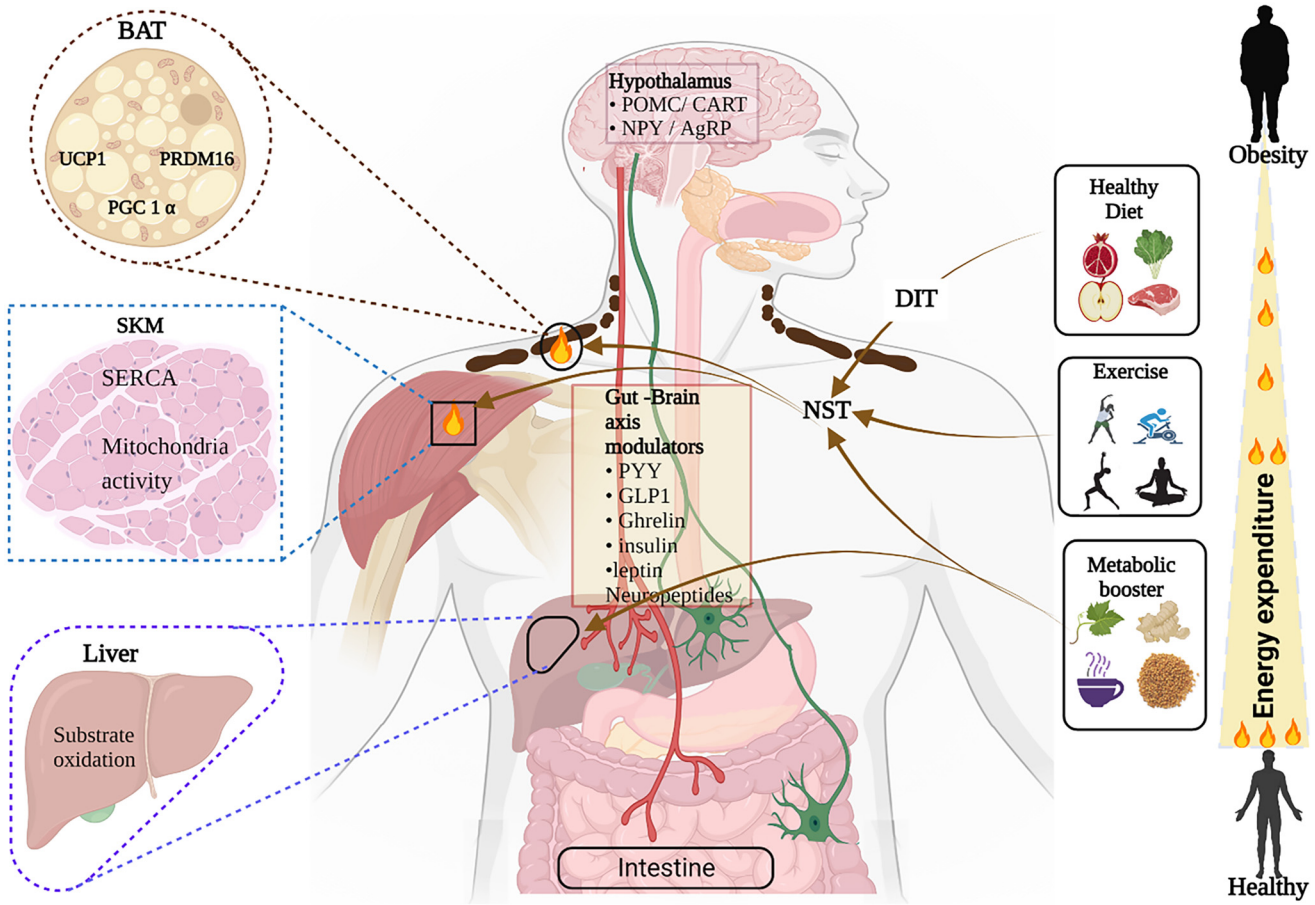


**Fig. 1** Enhancing the metabolic rate can promote healthy condition. Three major factors are known to increase energy expenditure: 1) healthy diet, 2) high physical activity and 3) metabolic boosters. A healthy diet induces an optimal DIT that can promote overall metabolism. High levels of physical activity that include aerobics, yoga, and zumba can upregulate energy consumption. DIT and NST are overlapping mechanisms that are primarily housed in two sites of adaptive thermogenesis: BAT and SkM. In the BAT, proton gradient dissipation by UCP1 and its upstream regulators like PGC1$\alpha$ and PRDM16 play critically important roles. In the SkM, SERCA-based futile $Ca^{2+}$-cycling and mitochondrial activities are known to be major factors in NST. Currently several metabolic boosting agents derived from natural sources are being considered and/or marketed to promote energy expenditure. Many of the metabolic boosters act on liver and alter substrate utilization pattern that may lead to change in overall whole-body energy balance.

pharmacotherapy.[20] The proposed lifestyle changes include exercise, yoga, and curbing irregular feeding/sleeping habits.[21,22] However, both lifestyle changes and bariatric surgery can not completely reverse the obese phenotype in most cases. By targeting the intermediators of the pathways, we might counter obesity and related comorbidity. This provides an opportunity for the development of anti-obesity agents as an intervention modality. A search for the identification of suitable targets for obesity management suggests that it can be achieved by either decreasing caloric intake/assimilation or increasing energy expenditure.[23] Here, we cover the drug development activities in the last few decades to counter obesity *via* both aspects. We have thoroughly researched the published literature from patent databases, drug-approving agencies, journal articles and non-journal (magazines, newspapers and commercial) sources. Furthermore, we have critically analysed the mode of action and side effects of once-approved but withdrawn drugs used for obesity treatment (Fig. 2).

## 2. How to target energy balance

There are multiple factors (like homeostatic, genetic, environmental and behavioural) that determine body weight.[24–26] So, weight gain leading to obesity is obviously very complex, and involves the interplay of central and peripheral pathways.[27] But, simplistically, the targets to counter obesity are lowering caloric input (including targeting the reward effect) or increasing energy expenditure.[28] Increasing energy expenditure can have many health benefits beyond weight loss. However, energy expenditure can also have side effects, such as fatigue, muscle loss, and inflammation.[29] On the other hand, targeting mechanisms that reduce caloric input are usually more efficacious. Meanwhile, the drugs targeting the reward effect modulate complex neural pathways that restrict cravings. These mechanisms also have their own side effects, like gastrointestinal disturbances, changes in taste, dry mouth, or mood alterations.[30]

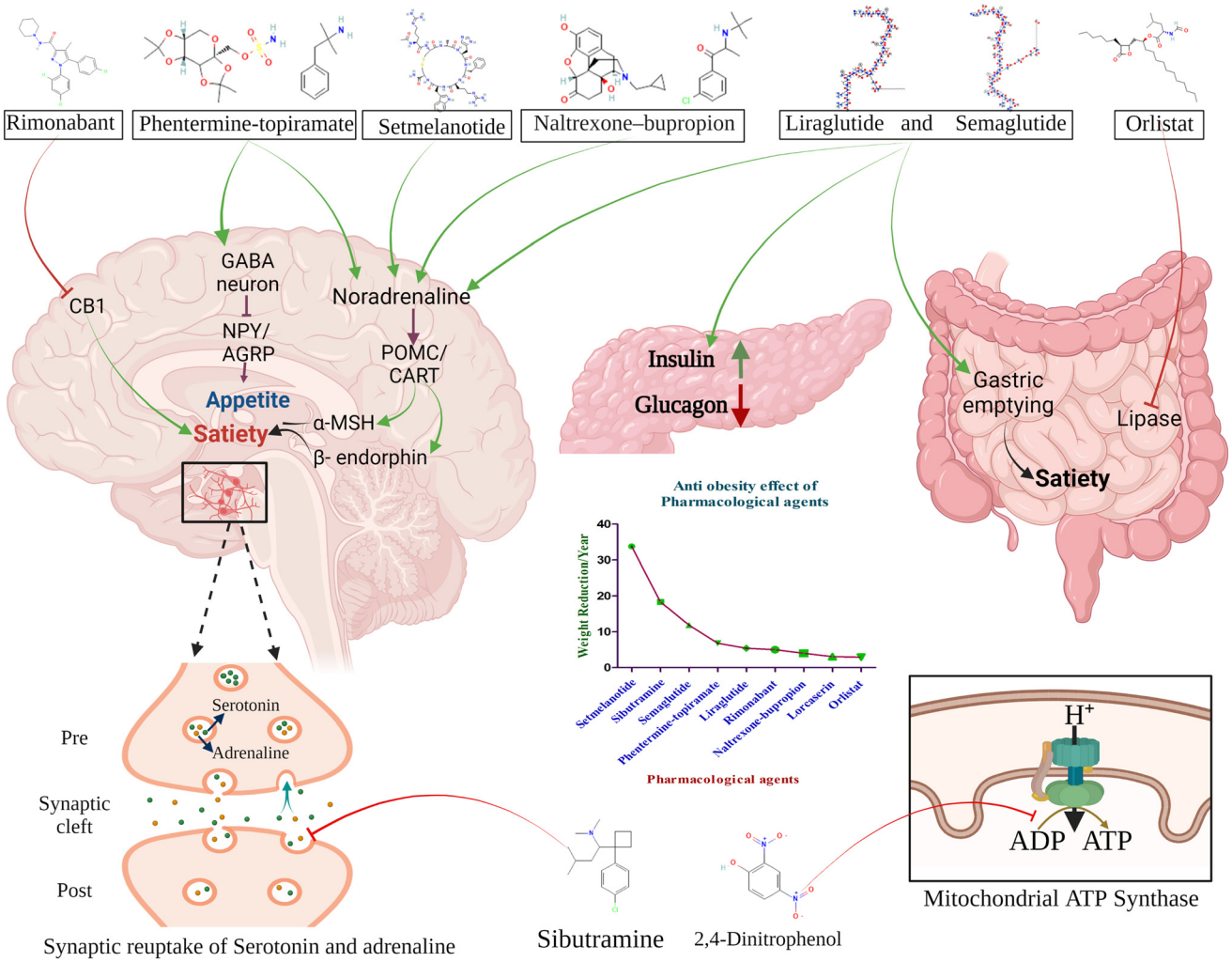


**Fig. 2** Scheme showing the mode of action for key pharmacological agents. To create a caloric deficit, there are three basic pharmacological methods. Two of them work to prevent the storage of extra calories, the first by acting on the CNS and producing an anorexic effect, and the second by preventing calorie absorption through various individual mechanisms. The third strategy is the use of that boost energy expenditure by making the body use more calories preferentially from already stored fat. The graph at the centre represents the average weight reduction by the drug reported in its respective clinical trial.

### 2.1 Reduction of energy intake (feeding) and uptake (absorption/gut)

The homeostatic regulation of feeding is regulated by the hypothalamus, specifically the arcuate nucleus (ARC), a mediobasal region of the hypothalamus in the brain. The ARC contains different types of neurons regulating various physiological processes, one of which controls the food intake and energy balance. Two key neurons involved in this regulation are pro-opiomelanocortin (POMC) neurons and neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons.[31] When the body energy balance is low, the appetite and food intake are upregulated by the activation of 'hunger' neurons, *i.e.*, orexigenic AgRP and NPY.[32] These neurons are associated with the reduction of serum levels of two hormones, insulin and leptin, that lead to the activation of hunger neurons.[33] Anorexigenic POMC/cocaine- and amphetamine-regulated transcript (CART)-expressing neurons are adjacent to the AgRP neurons, which help in decreasing the food intake.[34]

Amylin is secreted by the β pancreatic cells along with insulin, and helps in the delayed gastric emptying, which prolongs the period of satiety and fullness.[35] The hormone glucagon, which encourages the liver to produce glucose, is secreted less when the amylin level is high. This helps to control the postprandial glucose levels.[36] These hormones [amylin, insulin, leptin, peptide YY (PYY), and pancreatic polypeptide (PP)] bind with their respective receptors located in the CNS. They exhibit functional interplay to reduce food intake by either directly or indirectly stimulating the anorexigenic pathway and inhibiting the orexigenic pathway.[37–39] Thus, during negative energy balance conditions, POMC neurons are inhibited, whereas AgRP neurons are activated, which promotes food intake.[40] Interestingly, both neuronal systems are also modulated by signals from the adipose tissue, gut, pancreas and liver,

making the process of energy homeostasis a complex system.[41,42]

Ghrelin is the best known orexigenic gut peptide that stimulates the production of NPY and AgRP in the central nervous system (CNS), inducing hunger.[43] So, pharmacological antagonists of the ghrelin receptor decrease energy intake and slow down gastric emptying, thereby lowering the energy surplus.[44] Endocannabinoids, like *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) acting through cannabinoid receptors type 1 (CB1-R) expressed in the CNS, promote feeding and CB1-R antagonists have anti-obesity effects.[45] Serotonin (5-hydroxytryptamine, 5-HT) plays a vital role in modulating enteric neurotransmission and CNS signalling.[46] Various serotonin receptors are known. Upon activation, they produce hypophagia by inhibiting the release of antagonist AgRP and promoting the release of agonist α-MSH. Alternatively, lowering the intestinal nutrient absorption has also been targeted through multiple mechanisms. Inhibitors of lipase prevent the conversion of dietary triglycerides into monoglycerides by blocking the intestinal lipase enzyme activity, thereby lowering the dietary fat absorption and letting the fat go through the stool.[47] Glucose-dependent insulinotropic polypeptide (GIP), glucagon and glucagon-like peptide-1 (GLP-1) are three key hormones regulating the movement of food in the gut and absorption thereof.[48–50] GLP-1 suppresses gastric emptying by inhibiting stomach peristalsis and intestinal motility, which are essential for the optimization of nutrient digestion and absorption.[51] When glucose or fat are absorbed, duodenal endocrine K cells rapidly release GIP.[52] GIP promotes adipocytes to store ingested fat more effectively with secondary insulin resistance and hyperinsulinemia.[53] Additionally, glucagon contributes to the restriction of hepatic glucose uptake and the development of the hyperglycaemic phenotype linked to insulin resistance and insufficiency.[54,55]

### 2.2 Enhancers of energy expenditure

The sites and mechanisms of NST and/or DIT have been considered as targets of causing increased energy expenditure.[7,56] For this purpose, several chemicals and/or crude (mostly plant) extracts have been suggested, and some are already in the market for consumers to counter obesity.[57,58] Some of these agents exert similar effects as exercise and have been termed "exercise-mimetic".[59] However, the exact mechanistic details of many of the natural extracts are not available in the literature.

**2.2.1 Capsaicin.** One of the major components of red chili, called "capsaicin" has been used as a metabolic booster.[60] Oral administration of capsaicin has shown to temporarily increase metabolism by about 8% and more upon chronic administration.[61,62] It is suggested that capsaicin activates thermogenesis *via* the sympathetic nervous system through physically interacting with the transient receptor potential vanilloid 1 (TRPV1) receptor, leading to weight loss.[60,63] Capsaicin binding to the TRPV1 receptor in sympathetic neurons releases the neuropeptide calcitonin gene-related peptide (CGRP), which regulates energy metabolism.[64,65] Capsaicin has also been proven to enhance lipid oxidation and trigger thermogenesis in BAT by increasing UCP1 activity, enhancing energy expenditure and lowering body weight.[66,67] Some studies suggest that capsaicin alone or in combination with mild cold temperatures induce white-to-brown fat conversion, leading to weight loss.[68] Whether capsaicin can act on BAT and/or skeletal muscle directly has not been clearly illustrated. However, recent studies have indicated functional interplay between these two thermogenic sites, especially during cold conditions and exercise.[69,70] Capsaicin might work on thermogenic mechanisms in the skeletal muscle, as *in vitro* studies show the enhanced uncoupling of SERCA-based ATP utilization by capsaicin. It might be possible to amplify the amount of ATP utilized during exercise/cold conditions by administration of capsaicin or some of its analogs. The currently available TRPV1 agonists including capsaicin have side effects, such as tachycardia, hypertension and acid reflux.[71] Therefore, further research is needed to develop capsaicin-based molecules to target either of the targets: TRPV1 or SERCA or beiging. However, some of the common side effects of capsaicin supplements include a burning sensation throughout the digestive tract, acid reflux or heartburn.[72]

**2.2.2 Apple cider vinegar.** Some sources have claimed that apple cider vinegar has numerous health benefits, including anti-obesity, when taken orally in small quantities.[73] Apple cider vinegar is highly acidic in nature and contains several chemicals like carotenoids, phytosterols, phenolic compounds (epicatechin, gallic acid, *p*-coumaric acid, catechin, caffeic acid, chlorogenic acid), vitamins (C and E), and many organic acids.[74] However, there is little scientific information for the anti-obesity effect of apple cider vinegar, and the bioactive chemicals exerting this effect have not been delineated.[73] The major issue with apple cider vinegar is the lack of data for significant and sustainable weight loss in a diverse population.[74] Intriguingly, chronic administration of apple cider vinegar in some people causes throat irritation, adverse interaction with diuretics and insulin.[74] Furthermore, consumption of apple cider vinegar has been correlated with low serum potassium levels.[74]

**2.2.3 Hydroxycitric acid (HCA) and *Garcinia cambogia*.** Many online advertisements and dietary supplement stores have promoted a weight-loss supplement containing extracts from *Garcinia cambogia*, a tropical fruit also known as the Malabar tamarind.[75] Although not established, its fruit rind is considered to contain HCA, which might be the major active ingredient.[76] HCA is proposed to impede the process of fatty acid synthesis in the body and increase brain serotonin levels, leading to reduced appetite.[76–78] In contrast to the advertisements, there are many clinical trials of *Garcinia cambogia* showing the potential side effects from *Garcinia cambogia* extracts. The Food and Drug administration (FDA) has issued a warning against the use of weight-loss products containing *Garcinia cambogia*, as some patients that take it have developed serious liver problems.[79] Other side effects include: upset stomach or diarrhoea, dizziness, headache, and dry mouth.[80,81] Another issue

 

observed is that *Garcinia cambogia* may adversely interact with medicines for diabetes, pain and psychiatric conditions.[82] So, further studies are needed to demonstrate if HCA or extracts of *Garcinia cambogia* administration help in weight loss.

**2.2.4 Green tea.** Green tea has been a widely consumed beverage in Asia from ancient times with the belief that it bears significant health-promoting effects.[83] In recent years, several online marketing platforms sell green tea as a metabolic booster to induce weight loss and treat obesity without much scientific literature. The major constituents of green tea are caffeine, theobromine and catechins that stimulate fat cell breakdown, enhance insulin sensitivity and glucose metabolism potentially *via* the AMPK pathway.[83,84] Some suggest that the components of green tea inhibit the degradation of norepinephrine, causing increased SNS activation, leading to the elevation of energy expenditure and lipolysis.[85,86] Some sellers suggest better weight management outcome by green tea in combination with dietary modifications or exercise. Caffeine is a pharmacological activator of RyR1, causing elevated cytosolic $Ca^{2+}$ levels in the skeletal muscle. Such a condition would lead to amplification of SERCA-based ATP utilization due to physical activity, and might be the basis for a synergism between exercise and green tea.[87,88] However, green tea can cause gastrointestinal problems and hepatotoxicity, especially when consumed on an empty stomach.[89]

**2.2.5 *Gymnema sylvestre*.** *Gymnema* is known as "Meshashringi" in the Ayurvedic tradition, and has been used for treating various health conditions, including obesity and diabetes.[90] Its leaves contain gymnemic acids, which are a combination of saponins, acidic glycosides, and anthroquinones.[91] The anti-obesity property of *Gymnema* is proposed to be due to gymnemic acids and gurmarin peptide, which retards the intestinal glucose absorption.[92,93] One of the mechanisms proposed for the action of gymnemic acid is that it structurally mimics glucose and binds to the $Na^{+}$-glucose symporter in the intestine, thus preventing the absorption of glucose. Other mechanisms proposed suggest that the *Gymnema* leaf extract promotes the regeneration of islet cells in the pancreas, stimulating insulin secretion and increasing glucose utilization in insulin-dependent peripheral organs.[94] Some interpret that gymnemic acid binds to the taste receptor on the tongue, thereby reducing the taste and sugar cravings in patients with metabolic syndrome.[95] While *Gymnema* shows potential as an anti-obesity agent, further research is necessary to fully comprehend its mechanism and effects, which is essential for integrating *Gymnema* into any weight loss program with or without any dietary supplements.

# 3. FDA/EMA approved drugs for obesity

## 3.1 Gastro-intestine acting agents

**3.1.1 Orlistat (Xenical).** The active chemical of orlistat, tetrahydrolipstatin, is a lipase inhibitor with a prescribed intake of between 60–120 mg three times a day.[96] It is the only anti-obesity medication on the market that does not directly affect the mechanism of the appetite.[97,98] The use of orlistat for 1 year resulted in a weight loss of −2.9%.[30] Orlistat exerts its action by covalent binding to both pancreatic and gastric lipase most likely to a serine residue in their active site.[99,100] When administered with diets high in fat, orlistat reduces the absorption of monoacylglycerides and free fatty acids by partially inhibiting the breakdown of triglycerides.[100] Hence, orlistat increases the defecation of the unabsorbed fatty acids termed steatorrhea.[101] The major issue of orlistat is its low efficacy, and it ensures weight loss by only a small percentage. For better results, orlistat has been administered along with a low-calorie diet, low-fat diet, and exercise programs.[102] However, some literature suggests that orlistat also acts on two special lipases called mono-acyl-glycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) that are involved in appetite regulation in the brain.[103] Furthermore, administration of orlistat is suggested to have a beneficial effect on cholesterol balance by lowering the serum low density lipoprotein (LDL) while escalating the high density lipoprotein (HDL), thereby relieving obesity-associated high blood pressure.[99] Orlistat was approved by the European Medicines Agency (EMA) in 1998, and subsequently by FDA in 1999.[104] The best thing about orlistat is that it can be taken by people suffering with diabetes, hypertension and hypercholesterolemia.[105,106] In addition to steatorrhea, side effects include flatulence, fecal incontinence, stomach pain, and liver toxicity.[107] Orlistat decreases fat-soluble vitamin absorption, so multi-vitamin supplements are recommended with it.[108] The development of newer versions of orlistat with improved efficacy might be more useful, and may enter the market in the near future.

## 3.2 CNS acting agents

**3.2.1 Phentermine–topiramate (Qsymia).** Topiramate is an anti-seizure medicine used to control epilepsy that causes weight-loss as a side effect, whereas phentermine is an appetite suppressant and stimulant.[109,110] For weight-loss, the recommended intake is once daily in the morning *via* oral route.[110] After the use of phentermine–topiramate for 1 year, a weight loss of −6.8% was observed.[30] Pregnant women, people with glaucoma, people with hyperthyroidism, and people who recently used MAOIs (within 14 days) should not use phentermine–topiramate.[111] Phentermine–topiramate (trade name Qsymia) is not approved by the (EMA) for the treatment of obesity. In 2012, the FDA granted approval for a phentermine–topiramate combination, partly because of data from three clinical trials known as the CONQUER, EQUIP, and SEQUEL trials.[112] Phentermine has been licensed for immediate use in the treatment of obesity because it reduces hunger by enhancing the release of epinephrine in CNS.[113] Topiramate is a carbonic anhydrase inhibitor, glutamate antagonist and gamma aminobutyric acid agonist that is used to treat epilepsy and prevent migraines.[114,115] Its mechanism of action for treating obesity is unclear. However,

it reduces weight through increasing satiety, boosting energy expenditure, lowering calorie intake and altering taste.[116] Some of the common side effects with phentermine–topiramate co-administration include dry mouth, taste-loss, paraesthesia, constipation, sleeplessness and dizziness.[116] As we know, topiramate inhibits carbonic anhydrase, which promotes stone formation in kidneys by lowering the urine citrate excretion and raising the urinary pH. Co-administration of phentermine–topiramate also increases the risk of kidney stones in some people.[117,118] Although the exact weight-loss mechanism by phentermine is not elucidated in publications in the public domain, it is assumed that phentermine exerts its effect by acting as a sympathomimetic agent.[119,120] It is proposed that topiramate suppresses appetite, as well as increases metabolism.[110,121] Topiramate has been linked to weight loss through various pathways, including neurotransmitter-mediated appetite suppression and satiety increase.[119] The detailed analysis through which topiramate and phentermine exerts their weight loss effects is poorly defined and is not found in the public domain.

**3.2.2 Naltrexone–bupropion (Contrave).** The combination of naltrexone and bupropion was approved to be used as an anti-obesity drug in 2014 by the FDA and in 2015 by the EMA.[122,123] This combination therapy works better with elevated physical activity, and with decreased food intake and/or low calorie diet.[124] It is shown to be effective in retaining weight loss in follow up assessments in patients with a BMI $\geq$ 30 kg $m^{-2}$ (obese) or overweight ($\geq$27 kg $m^{-2}$), having comorbidities like T2D or dyslipidemia.[125,126] The recommended dose is as follows: initial dose at 8/90 mg per day for week 1, increase by 8/90 mg each week to reach 16/180 mg twice daily at week 4.[127] In trials, after around a year (56 weeks) of diet, exercise, and taking Contrave (naltrexone/bupropion), subjects dropped −4.0% their body weight.[30] This combination drug is unsafe for use during pregnancy.[111] Bupropion is a norepinephrine and dopamine reuptake inhibitor that is used to treat depression and smoking addiction. It causes the POMC neurons of the hypothalamus to release α-MSH and β-endorphin, which suppresses the appetite and reduces food intake through the reward system.[128,129] Bupropion also supplements dopamine signalling, which is usually lower among obese individuals, leading to an increase in energy expenditure. On the other hand, naltrexone works as a mu-opioid receptor antagonist that is classically used to counter alcohol and/or opioid dependence.[130,131] The appetite reducing effects of naltrexone is primarily *via* cannabinoid-1 receptor activation in the CNS, leading to an increased release of beta-endorphin that works on the satiety centre in the hypothalamus.[132,133] A synergistic effect on appetite suppression has been found by the combination of bupropion and naltrexone through regulation of the mesolimbic reward pathways and goal-oriented behaviours.[134] The reported adverse effects for naltrexone–bupropion co-treatment are nausea, constipation, headache, and dizziness.[135]

**3.2.3 Liraglutide (Saxenda).** Liraglutide belongs to the only class of molecules that are approved GLP-1 receptor agonists (RA), which have been licensed for the treatment of diabetes and obesity.[136] Liraglutide was added to lifestyle counselling for a year, and the average weight loss was −5.4% of their initial body weight.[30] It is an acyl-conjugated GLP-1 analogue having some binding affinity for serum albumin *in vivo*, thereby significantly increasing the half-life of GLP-1 from a few minutes to several hours.[137,138] GLP-1 is produced mainly by the small intestine and acts on the pancreas, causing almost 70% postprandial insulin secretion and simultaneously reducing glucagon release.[139] GLP-1 is also known to cross the blood–brain barrier acting on the hypothalamus to induce satiety, reducing food intake.[140] Some other studies indicate that GLP-1 delays gastric emptying and promotes energy expenditure by turning substrate selection in the target tissue towards fatty acid *versus* carbohydrates.[141] GLP-1 also induces insulin sensitivity in the target tissue and by collective action, it leads to an increased effect of insulin.[142] Overall, liraglutide by increasing GLP-1 action leads to reducing the glycemic status of the body.[143] Liraglutide is administered as a subcutaneous injection once daily: initiated at 0.6 mg per day for a week, then increased until the dose reaches 1.8 mg per day.[144] The FDA approved liraglutide (brand name Victoza) for the treatment of type 2 diabetes in 2010.[145,146] The EMA approved liraglutide (brand name Victoza) for the treatment of type 2 diabetes in 2009 and for chronic obesity in 2015 (brand name Saxenda).[147,148] Several adverse effects have been associated with liraglutide, including diarrhoea, hypoglycemia, fatigue, dizziness, abdominal cramps, and nausea.[149] It has been shown to cause pancreatitis, and increased lipase production and acute renal failure in some patients.[150,151] Most of the GLP-1-RA undergoing clinical trials have been shown to be effective in lowering weight and glucose in people with T2D.[152] Several GLP-1-RA are available in the US and European market, liraglutide (Victoza, Novo Nordisk), which is administered once daily, was released in 2010 and increased patient convenience and acceptance.[149]

**3.2.4 Semaglutide.** Another novel variant of glutide called semaglutide was developed by Novo Nordisk as a treatment option to reverse obesity under the brand name "Wegovy".[153] Administration of semaglutide at 2.4 mg per week for 68 weeks was found to cause weight loss of 14.9% more than the placebo.[154] It also elicits its effect through the GLP-1 receptor and got approval from the FDA in June 2021 for chronic weight management of obese or overweight individuals.[155,156] Wegovy was not approved by the (EMA) for the treatment of obesity. Wegovy comes as a 2.4 mg per week subcutaneous injection, thereby reducing discomfort.[153] In double-blind, randomised, placebo-controlled trials, about 2600 enrolled subjects were used to demonstrate the efficacy and safety of semaglutide.[157] It has multiple aspects of reducing appetite and food cravings, increasing feelings of fullness, and improving glycemic control in patients with type 2 diabetes.[158] Minimal side effects were reported, with

 

the common ones being nausea, diarrhoea, vomiting, constipation, abdominal pain, and headache.[159] So far, Wegovy is the best anti-obesity FDA approved drug in the market, as it causes ~15% body weight loss with a single weekly dose being patient-friendly.[155] However, the high cost (~$1400 in a month) can be a barrier to long-term use.

**3.2.5 Setmelanotide.** Setmelanotide is sold by Rhythm Pharmaceuticals, Inc. under the brand name "Imcivree" after approval by FDA in 2020 and EMA in 2021.[160,161] Setmelanotide comes in a 1 mL multidose vial (concentration – 10 mg $mL^{-1}$), and subcutaneous injection is the preferred method of administration.[162] The initial dose is 1 mg (0.1 mL) injected daily for two weeks for children between the ages of 6–12 years old. Patients should be cautiously observed for any potential adverse effects during this time, especially gastrointestinal and hypersensitivity reactions.[162] Sustained weight loss (~13.5%) was observed over an 8-week treatment period in a nonhuman primate model upon diet-induced obesity.[163] Setmelanotide is a pro-opiomelanocortin derived peptide that is an agonist of the melanocortin 4 receptor (MC4R), which regulates satiety and food intake. It is a more potent agonist of MC4R than endogenous α-melanocyte stimulating hormone. By directly agonizing MC4R, setmelanotide decreases food intake and promotes weight loss. Setmelanotide is an atypical bitopic ligand that interacts with both the orthosteric and putative allosteric binding sites of MC4R, allowing for both high affinity and specificity.[164] The medication has been used in patients who have certain genetic conditions, including pro-opiomelanocortin, proprotein subtilisin/kexin type 1, or leptin receptor deficiencies, which are characterized by severe and uncontrolled hunger (hyperphagia) and early-onset obesity that is difficult to manage with lifestyle interventions alone.[165,166] However, several side effects of setmelanotide have also been observed during the clinical trials. Some of the common adverse effects include injection site reactions, skin hyperpigmentation, and gastrointestinal symptoms, such as nausea, vomiting, and diarrhea.[167] Other less common side effects include spontaneous penile erections and spontaneous female arousal, depression and suicidal thoughts.[168]

**3.2.6 Phendimetrazine.** Phendimetrazine is a prescription weight loss medication sold under several brand names like Bontril, Adipost, Melfiat, Obezine *etc.* The FDA authorised its use as an appetite suppressant for the management of obesity as part of a short-term weight-loss plan, often with a low calorie diet.[169] Phendimetrazine is typically prescribed in doses of 105 mg once daily in the morning, although this may change depending on the patient's response to the drug and the doctor's recommendations.[170] Phendimetrazine causes an increase in metabolism by activating the alpha-adrenergic system, and some classify it as a stimulant. The medication also functions as a norepinephrine–dopamine releasing agent (NDRA) that suppresses the appetite and reduces caloric intake, which eventually leads to weight loss.[171] For better results, phendimetrazine has been used in conjunction with a balanced diet and regular exercise, although individual outcomes of weight loss differ. Common side effects of phendimetrazine include coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension, hyperthyroidism and glaucoma.[170] Therefore, the individual efficacy and side effects need to be weighed before use of phendimetrazine for an anti-obesity treatment regimen.

# 4. Market withdrawn drugs for obesity

## 4.1 Lorcaserin

The US-FDA approved lorcaserin hydrochloride as a long-term weight-loss drug for obese people and morbidly obese individuals in 2012.[172,173] It was introduced as two different formulations; 10 mg twice-daily or 20 mg once-daily.[174] It was recommended not to be used by pregnant women and children.[175] Lorcaserin was added to lifestyle counselling for a year, and the average weight loss was −3.1% of their initial body weight.[30] Lorcaserin exerts the anti-obesity effects by its serotonin agonist action on POMC receptors in the arcuate nucleus of the hypothalamus.[176,177] It is suggested that lorcaserin is highly selective for 5-$HT_{2c}$ receptor (158-fold and 100-fold greater binding affinity than 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors, respectively).[178,179] This selective action of lorcaserin on the hypothalamus leads to suppression of the appetite without triggering pulmonary hypertension or hallucination, which are usually associated with non-specific serotonin agonists like fenfluramine and dexfenfluramine.[177,179] Studies suggest that lorcaserin can reduce craving, impulsivity and hunger, while enhancing satiety, which contributes to weight loss.[180] Three randomized controlled trials (RCTs) have demonstrated the efficacy of lorcaserin for the treatment of obesity by promoting weight loss.[181] One of these RCT published in 2018 showed no significant difference in the occurrence of cardiovascular diseases and cancer between lorcaserin treatment and control (placebo) groups.[182] However, a long-term follow-up study by US-FDA reported a possible increase in the risk of cancer (especially lung, colon, and pancreas) in those treated with lorcaserin in January 2020.[183] Based on this observation, the US-FDA called for the withdrawal of lorcaserin from the market in February 2020.[183] The lorcaserin treatment in non-diabetic individuals causes common side-effects like headache, dizziness, nausea, constipation, dry mouth, and fatigue. In patients having T2D, backpain, fatigue, headache and cough have been observed. In some cases, lorcaserin treatment leads to psychological disturbance, and such individuals need to be closely monitored for depression and/or suicidal tendency.[111] In spite of being highly selective, the side-effects of lorcaserin may arise from the target effects especially on 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors, which show expression in organs, including the lung, colon, CNS and pancreas.[104] In spite of its ban in several countries, it is still marketed in many countries, including India under the brand name "Alfence" by Sun Pharmaceutical Industries, Ltd.[184]

## 4.2 Sibutramine

One of the early medications introduced for weight loss, sibutramine acts as an inhibitor of adrenaline and serotonin

reuptake in the hypothalamus, thereby enhancing satiety.[185] Since its approval by the US-FDA in 1997, sibutramine has been used for both short-term and long-term treatment of obesity with body mass index (BMI) ≥ 30.[186] There have been several clinical trials using sibutramine; the eminent ones being the Sibutramine Trial of Obesity Reduction and Maintenance (STROM) and Sibutramine Cardiovascular Outcomes (SCOUTS).[187] Sibutramine at 30 mg per day results in an average weight loss of 9.4% after 6 months of treatment.[188] The STORM trial showed that out of the sibutramine treated group, 80% participants retained their initial weight loss over a period.[189] In spite of this excellent effect, sibutramine was withdrawn from the market by the US-FDA in 2010 because of its side effects on the cardiovascular system.[190,191] Since then, it has been removed from the market in USA, Europe and many other countries. However, it continues to be marketed in several countries, including India, with brand names as obestat (Cipla, Ltd.) and leptos (Abbott India, Ltd.).[192,193] SCOUT assessed the long term safety of sibutramine in individuals with pre-existing cardiovascular disease (nonfatal myocardial infection [MI], stroke, cardiovascular resuscitation after cardiac arrest, or cardiovascular death).[194] This study showed that sibutramine users are at 16% increased risk of cardiac issues compared to the control group.[195] Surprisingly, reanalysis of data from the SCOUT revealed that patients with sibutramine-mediated weight loss were protected from cardiovascular events, whereas an increase in cardiovascular risk was high in those patients who did not lose weight due to the medication.[196] This may suggest that sibutramine may not be strongly associated with cardiovascular risk.[196] So, patient taking sibutramine needs to be closely monitored for an increase in heart rate (≥10 bpm), blood pressure (≥10 mmHg), dyspnoea, chest pain and ankle oedema.[197,198] The cardiac effect of sibutramine might be due to its action on the sympathetic nervous system (SNS) in the heart. SNS controls the heart by releasing adrenaline, which needs to be reabsorbed quickly after action. However, sibutramine prolongs adrenaline action on the cardiac muscle that may create an imbalance in the heart rhythm, thereby increasing the risk towards cardiovascular diseases.[196,199]

### 4.3 Rimonabant

Rimonabant was approved and introduced in Europe by EMA in 2006, although it has never been approved by the US-FDA.[200,201] Rimonabant acts selectively on CB1 and not CB2, causing downregulation of hunger, leading to decreased food intake.[202] However, CB1 is expressed in various tissues, including the hypothalamus, CNS, GI tract, liver, and adipose tissues, which indicate that its role goes beyond satiety only.[203] Treatment of rimonabant at a dose of 20 mg per day for one year was shown to cause a weight loss of ~5%.[204] In mid 2007, the US Endocrine and Metabolic Drugs Advisory Committee raised concern against the use of rimonabant to treat obesity in the USA due to its association with altered mental health.[205] EMA followed suit in October 2008 and suspended the production of rimonabant, prohibiting its marketing in Europe due to psychiatric risk factors.[206] Clinical trials have shown that rimonabant administration is associated with an increased occurrence of psychiatric episodes, such as depression, anxiety and suicidal ideation.[207] The use and marketing of rimonabant has been banned in India since 2010 after the decision by the Indian Health Ministry, following advice by the Drug Coordination Committee of Drug Controller General of India (DCGI). As CB1 shows a wide distribution, its inhibition by rimonabant can be expected to modulate organ functions other than the satiety centre in the hypothalamus.[208] CB1 in other parts of the CNS is the source for the psychiatric side effects of rimonabant.[209] Although the side effects are serious, rimonabant has not be properly tested for its efficacy (on a large number of participants) in obese individuals with no known history of psychiatric illnesses.[210] It is obvious that rimonabant and other CB1-antagonists should not be administered on people with pre-existing mental disorders.

### 4.4 Dinitrophenol

The first anti-obesity medication, 2-4-dinitrophenol (DNP), was introduced in early 1930s with the observation of significant weight loss in factory workers where DNP was in use. Studies showed that oral or topical application of DNP can cause loss of weight up to 1.5 kg per week.[211] Molecular investigations using animal models and human samples indicated that DNP works on the mitochondrial inner membrane (probably irrespective of the organ target) and causes a proton gradient dissipation, leading to dangerously high body temperatures that may develop into heatstroke.[212] This unusual increase in the basal metabolic rate (BMR) results in elevation (mild to moderate) of body temperature.[213] However, chronic administration of DNP was reported to have several adverse effects, such as hyperthermia, diaphoresis, tachycardia, tachypnoea, and death in some cases.[211] As few deaths were clearly associated with DNP administration in 1930s, the US-FDA issued a ban on its human consumption in 1938.[211,214] Due to the emergence of obesity in the USA in the 1970s and 80s, some physicians started prescribing DNP under the trade name 'Mitcal', suggesting intracellular hyperthermia therapy as the mechanism of action.[211] With the emergence of internet marketing, DNP use increased in the 2000s under various names, such as 'Dinosan', 'Dnoc', 'Solfo Black', 'Nitrophen', 'Aldifen' and 'Chemox'. Up to 15 deaths were reported in the early 2000s due to the use of non-prescribed DNP from internet sources.[215] Due to this, several drug agencies like the US-FDA released guidelines suggesting DNP as 'extremely dangerous and not fit for human consumption'.[216] As DNP is non-selective, it can bring out its effects in any organ that it reaches. The induced hyperthermia due to DNP can cause additional problems intracellularly in various organs, leading to widespread physiological sequelae, like increases in heart

 

rate, respiratory rate, confusion, dizziness, delirium, nausea, and vomiting.[217] Other side effects of DNP include muscle spasm/pain, acute renal failure, liver necrosis, pulmonary edema, peripheral neuritis, agranulocytosis, and cataracts.[218]

# 5. Drugs under research

Several agencies are working on anti-obesity drugs. Currently, many molecules are under research study. Some of such compounds are discussed below in detail, and others in advanced stages of clinical trials are listed in Table 1.

### 5.1 Serotonin–norepinephrine–dopamine-reuptake-inhibitor (SNDRI)

**5.1.1 Tesofensine.** It works as an inhibitor for the reuptake of three neurotransmitters found mainly in the CNS, called serotonin–norepinephrine–dopamine-reuptake-inhibitor (SNDRI).[219] Tesofensine was initially developed by NeuroSearch for the treatment of neurological disorders like Alzheimer's and Parkinson's disease, but was later reported to cause significant weight loss.[220,221] Although not fully defined, tesofensine administration (both in mice and in human) is shown to suppress the appetite, while having a minor effect on energy expenditure.[222] Various phase 2 and 3 studies have been published to show the significant efficacy of tesofensine at different doses and in combination with other pharmacological agents to counter obesity.[221] After 24 weeks of tesofensine administration at doses of 0.25 mg, 0.5 mg, and 1.0 mg on 161 participants, weight losses of 4.5 kg, 9.2 kg, and 10.6 kg were observed, respectively, compared to the placebo.[223] At the higher doses, especially 1.0 mg exhibited only a minor enhancement in blood pressure and heart rate, while lower doses were safer.[223] Interestingly, tesofensine administration had a modest effect on HbA1C, with its improved lipid profile reducing the total cholesterol and triglycerides.[224] At doses of 0.25 and 0.5 mg of tesofensine, no significant elevation in systolic or diastolic BP was observed after 24 weeks.[225] However, the doses of 0.5 mg tesofensine ($p$ = 0.0001) showed an increase in heart rate by 7.4 beats per minute.[226] Tesofensine can have certain adverse effects like drying of the mouth, vomiting, diarrhoea, constipation and sleeping disorders.[223] Although few anti-obesity drugs have been approved, tesofensine is a promising drug that effectively reduces the weight of obese people.[227] In 2014, NeuroSearch handed over tesofensine rights to Saniona.[228] Saniona followed a combined approach of tesofensine with metoprolol (an antihypertension drug), and found that this combination can induce weight loss without increasing BP.[224,229] Saniona is currently pursuing entry into phase 3/4 clinical trials with the national regulatory agencies of different countries like Mexico.[230] In the meantime, tesofensine is already available for online purchase in various countries, including India.[231]

### 5.2 Lipase inhibitor

**5.2.1 Cetilistat.** After the discovery of orlistat as a gastrointestinal lipase inhibitor, this class of molecules became an active area for anti-obesity drug development.[232] Cetilistat is a novel type of gastrointestinal lipase inhibitor that prevents the digestion and absorption of fat, which lowers calorie consumption and promotes weight loss.[233] A clinical trial of cetilistat using a randomized, double-blind strategy demonstrated the efficacy of cetilistat (120 mg tid) to cause significant weight loss compared to a placebo within a 3-month period.[234] The compound remains in the gastrointestinal tract and inhibits pancreatic lipase release into the intestine, blocking fat digestion and leading to the release of most fat to pass through the faeces.[233] Several clinical trials showed a 3-to-7 fold increase in fecal fat in a dose (cetilistat)-dependent manner.[235] By the end of 2018, it was under a phase III trial and a specific dosage has not yet been assigned. It has shown similar weight loss results to orlistat in human studies, but it also had similar adverse effects, including oily, loose stools, faecal incontinence, frequent bowel movements, and gas.[233,234] In 2012, Alizyme in collaboration with Takeda Pharmaceutical submitted a NDA application for cetilistat under the trade name "Oblean".[233] However, a statement on the Takeda Pharmaceutical website dated 13 October, 2018 announced the termination of the license for the development,

**Table 1** Drugs under research

| Mechanism of action | Drug name | Company | Status | Reference |
|---|---|---|---|---|
| GLP1 and glucagon dual agonists | MED10382 | AstraZeneca and MedImmune | Phase II | NCT03235050 |
| GLP1 and glucagon dual agonists | SAR425899 | Sanofi | Phase I | NCT02411825 |
| GLP1R agonists | Rybelsus | University of Colorado, Denver | Phase III | NCT03919929 |
| GLP1R agonists | Danuglipron (PF-06882961) | Pfizer | Phase II | NCT04707313 |
| Leptin sensitizers | Extract of *Cinnamomum cassia* (CC) and *Withania somnifera* (WS) (300 mg + 150 mg, respectively) | University of Roma La Sapienza and Nutrintech Ltd., London, UK | Not applicable | NCT05210218 |
| Y2R agonists | NNC0165-1562 and Semaglutide | Novo Nordisk A/S | Phase I | NCT03574584 |
| Y2R agonists | NNC01651875 + semaglutide | Novo Nordisk A/S | Phase II | NCT04969939 |
| Amylin analogues | Cagrilintide | Novo Nordisk A/S | Phase II | NCT04940078 |
| 5-HT2C receptor agonist | ATHX-105 | Athersys, INC and Syneos Health | Phase II | NCT00735683 |
| Other appetite suppressants | LY-3463251 | Eli Lilly and Company | Phase I | NCT03764774 |
| Other appetite suppressants | Long-acting GDF15 | Novo Nordisk | Phase I | 261 |

manufacture and sale in Japan of OBLEAN.[236] Clinical trial plans in other countries have not been announced publicly so far, although cetilistat is sold in some countries (including India) under brand names like "Kilfat" and "Cetislim" by Akumentis Healthcare, Ltd.[237]

**5.2.2 GT 389-255.** A new type of lipase inhibitor has been designed and termed "GT 389-255" by Peptimmune, Inc., a privately held biotechnology company engaged in the development of novel therapeutics.[238] GT 389-255 is a fat binding hydrogel polymer conjugate that is proposed to prevent fat digestion and lower (~30%) fat absorption in the intestine.[239] As it is retained in the gastrointestinal tract, it does not cause systemic exposure and hence has lower side-effects. Small single and multiple ascending dose (SAD and MAD) Phase I trials have already been conducted and results seem promising.[239]

### 5.3 PYY and pancreatic polypeptide dual receptor agonist

**5.3.1 Obinepitide (TM 30338).** Obinepitide is being developed by 7TM Pharma and probably is in phase II clinical trial.[240] It is structurally a small polypeptide and suggested to work as a dual agonist of receptors for two hormones, PYY and PP.[240] These hormones usually released after meal are associated with inducing satiety by binding to their receptors in the hypothalamus.[241] Pre-clinical studies on diet-induced obese mice and a phase I small group clinical trial suggest that oral administration of obinepitide is effective in causing long term body weight reduction.[241] Although the final doses are not available in the public domain, obinepitide and similar compounds are available online in some websites.

### 5.4 Serotonin/5-HT6 receptor antagonist

**5.4.1 PRX-07034.** It is a novel investigational small molecule that acts as a selective serotonin receptor antagonist. It was initially developed by Epix Pharmaceuticals, USA, for the treatment of obesity and cognitive impairment associated with Alzheimer's disease and schizophrenia[242,243] Although the mode of action has not been described in detail, it has been observed on mice models that PRX-07034 reduces food intake, thereby restricting body weight. With closure of Epix Pharmaceuticals in 2009, the development of PRX-07034 has been halted. However, it is available from many companies for research as a specialty chemical, but not for human consumption.[242,243]

### 5.5 Glucagon/GLP1 receptor dual agonist

**5.5.1 BI 456906.** It is a glucagon/GLP1 receptor dual agonist drugs sponsored by Boehringer Ingelheim. A randomized study of phase I and II clinical trials was performed on 413 participants during the time period of 2020 to 2022.[244] The participants of this study were T2D individuals who were non-responsive to metformin treatment and had high blood sugar. There were two main purposes of the study: to find out the best dose of BI 456906 that reduces blood sugar and check whether BI 456906 helps in weight loss. In the study, participants were enrolled for about 23 weeks with about 13 visits to the study centre. The participants were divided into 7 groups, and those in groups 1 through 6 received weekly injections of BI 456906 at varying doses, while those in group 7 received weekly injections of semaglutide, another medication for people with T2D. With the observation that the drug is well tolerated and lowers blood sugar levels, the company recently started another trial to test its ability to reduce body weight in obese individuals.[244] The BI 456906 administration significantly reduced fat mass in a dose-dependent manner with major efficacy observed on liver fat.[245]

### 5.6 GIP/GLP1 dual agonists

**5.6.1 Tirzepatide (LY3298176).** It is a novel-new 39-amino acid synthetic peptide that is based on the native GIP sequence and functions as a dual GLP1/GIP receptor agonist. Tirzepatide, a medication developed by Eli Lilly and Company, has been demonstrated in pre-clinical studies, phase 1 and phase 2 clinical trials, and other studies to have potent glucose lowering and weight loss effects with little side effects.[246] Clinical trials showed only limited side effects. Efficacy and safety of subcutaneous tirzepatide administration in a weekly manner was demonstrated by phase I trial by the company on participants with obesity or overweight with related comorbidities in the period of 2016 through 2017. The next study by Eli Lilly and Company had two phases: a main phase and an extension phase. Participants with prediabetes stayed in the extension for an additional two years after the main phase, which lasted 72 weeks and required 14 visits. The company has reported an enrollment of 2539 participants in this study, where the drug was given in a randomized manner. An actual study of this drug will be completed on May 24, 2024.[246] In a 72-week phase 3 research study, participants taking tirzepatide could have lost up to 22.5% of weight.[247] As the first and only GLP1/GIP receptor agonist for the treatment of adults with type 2 diabetes, the FDA has approved Lilly's Mounjaro™ (tirzepatide) injection.[248]

### 5.7 Others

**5.7.1 Bupropion/zonisamide.** As discussed before, bupropion is an antidepressant medication working on the CNS. On the other hand, zonisamide is a sodium/calcium channel blocker with weak carbonic anhydrase activity that is used as an anticonvulsant agent.[249] Double-blinded clinical studies showed the effectiveness of each individual drug in inducing weight loss, but they had a high rate of adverse effects. Interestingly, a phase II clinical trial conducted by Orexigen Therapeutics demonstrated better weight loss ability of the combination therapy of bupropion and zonisamide with lesser side effects.[249–251] The dose was optimized in a randomized, double-blinded trial enrolling 623 uncomplicated (without other metabolic disease) obese individuals to 300 mg bupropion + 400 mg zonisamide orally,

 

along with low-intensity exercise and healthy eating habits.[252,253] However, the company could not take it to the next level due to lack of funds. The current status of this combination is not available in the public domain, and is also not available for purchase online.

**5.7.2 AICAR (Acadesine).** Initially developed by PeriCor Therapeutics for the treatment of acute lymphoblastic leukemia (ALL) and reperfusion injury, 5-aminoimidazole-4-carboxamide riboside (AICAR) is a purine nucleoside analogous to adenosine monophosphate (AMP). So, it can mimic AMP activating AMPK, thereby modulating homeostatic metabolic processes in several types of tissues.[254,255] AMPK activation in general has been considered as an intracellular energy sensor that inhibits energy-conserving processes and enhances catabolic pathways.[256] AICAR-induced AMPK activation enhances expression of PPAR-γ and its co-activator PGC-1α, leading to increased energy expenditure that decreases visceral and subcutaneous adipose tissue.[257] Studies on various animal models of insulin resistance suggest that AICAR administration affects skeletal muscle metabolism and promotes exercise-mediated health benefits, such as increased glucose uptake/disposal, reduced triglyceride accumulation and improved insulin sensitivity.[258,259] Clinical trials showed poor oral bioavailability of AICAR, while systemic administration enhanced skeletal muscle glucose uptake, thus having antidiabetic effects.[260] However, infusion of a drug-like property (oral bioavailability being the most prominent) to AICAR is desirable in the case of metabolic disorders where frequent administration is required.

# 6. Conclusion

According to our survey presented above, the currently marketed or under research anti-obesity pharmacological agents are only targeting either food intake or caloric absorption. Out of the pharmacological agents analyzed, the level of anti-obesity effects can be organized as follows: sibutramine (~18.4%) > semaglutide (~11.9%) > phentermine–topiramate (6.8%) > liraglutide (5.4%) > rimonabant (5%) > naltrexone–bupropion (4.0%) > lorcaserin (3.1%) > orlistat (2.9%) by one-year administration. Interestingly, sibutramine shows the best anti-obesity activity. However, it has been withdrawn from the market because of its high cardiovascular toxicity. Structure–function analysis of sibutramine–analogs to reduce side effects while preserving anti-obesity activity should be taken up. Testing of co-administration of sibutramine with any other anti-obesity agents may also help in keeping sibutramine dose at low-levels that reduce side effects. The most popular orlistat is having a low rank in terms of weight-reduction capacity. The effect of orlistat can be enhanced either by synergistic combination with any other anti-obesity agents or analog optimization. Such approach of analog functionalization has already been applied on GLP1-RA, and various glutides are under investigation. Surprisingly, a study of pharmacological agents that can enhance energy expenditure is still in the back bench, while several natural product-extracts with metabolic boosting capacity are already available in the market. The effect of these metabolic boosters in combination with established anti-obesity compounds may also be a feasible approach for future research.

Pharmacological strategies to increase energy expenditure (*via* up-regulation of NST) are not yet available in the market as an option to cause weight loss in spite of its proposition more than two decades ago. Targeting skeletal muscle-based NST is emerging recently as a lucrative strategy to cause weight loss. Enhancing the uncoupling of SERCA *via* small molecules to increase ATP utilization is evolving as a method to activate muscle NST and mimic the benefits of exercise. After the discovery of SLN, it is obvious to think that SERCA-SLN interaction can be stabilized by pharmacological means, leading to increased ATP usage and energy expenditure. Enhancing UCP1-mediated and independent mechanisms in adipose tissues are also being tested at laboratory scales, and may be translated in the future to a larger population. Future research will develop pharmacological agents to target and activate NST, causing up-regulation of the metabolic rate, reducing the energy surplus, and thereby curbing weight gain and obesity.

# Author contributions

The idea was conceived by BP and NCB. The manuscript has been written, edited and critically analysed by the combined effort of all the authors. S. P. and B. P. have prepared the figures and tables.

# Conflicts of interest

The authors declare no conflict of interest.

# Acknowledgements

This work has been partly funded by the Science and Engineering Research Board (SERB), DST, India (grant no. ECR/2016/001247) and Department of Biotechnology (DBT), India (grant no. BT/RLF/Re-entry/41/2014 and BT/PR28935/MED/30/2035/2018) to N. C. B. B. P. and S. P. and are recipients of Research Fellowships from Indian Council of Medical Research (ICMR) vide grant no. 45/17/2022-PHA/BMS and 45/3/2019/PHY/BMS respectively. B. S. has received a research Fellowship from Council of Scientific and Industrial Research (CSIR), India vide File no. 09/1035 (0011)/2017-EMR-I. We would like to thank Punyadhara Pani, Gourabmani Swalsingh and Unmod Senapati for constructive critical suggestions and discussions that helped us to shape this manuscript.

# References

1 I. Kyrou, H. S. Randeva, C. Tsigos, G. Kaltsas and M. O. Weickert, in *Endotext*, ed. K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, W. W. de Herder, K. Dhatariya, K. Dungan, J. M. Hershman, J. Hofland, S. Kalra, G. Kaltsas,

C. Koch, P. Kopp, M. Korbonits, C. S. Kovacs, W. Kuohung, B. Laferrère, M. Levy, E. A. McGee, R. McLachlan, J. E. Morley, M. New, J. Purnell, R. Sahay, F. Singer, M. A. Sperling, C. A. Stratakis, D. L. Trence and D. P. Wilson, MDText.com, Inc., Copyright © 2000–2022, South Dartmouth, MA, 2000.
2 L. Rui, *Rev. Endocr. Metab. Disord.*, 2013, **14**, 387–407.
3 M. Longo, F. Zatterale, J. Naderi, L. Parrillo, P. Formisano, G. A. Raciti, F. Beguinot and C. Miele, *Int. J. Mol. Sci.*, 2019, **20**, 2358.
4 A. M. Mengeste, A. C. Rustan and J. Lund, *Obesity*, 2021, **29**, 1582–1595.
5 K. R. Westerterp, *Nutr. Metab.*, 2004, **1**, 5.
6 S. L. Wijers, W. H. Saris and W. D. van Marken Lichtenbelt, *Obes. Rev.*, 2009, **10**, 218–226.
7 M. Periasamy, J. L. Herrera and F. C. G. Reis, *Diabetes Metab. J.*, 2017, **41**, 327–336.
8 B. M. Spiegelman and J. S. Flier, *Cell*, 2001, **104**, 531–543.
9 A. M. Cypess and C. R. Kahn, *Curr. Opin. Endocrinol., Diabetes Obes.*, 2010, **17**, 143–149.
10 A. Fedorenko, P. V. Lishko and Y. Kirichok, *Cell*, 2012, **151**, 400–413.
11 A. Roesler and L. Kazak, *Biochem. J.*, 2020, **477**, 709–725.
12 K. Ikeda and T. Yamada, *Front. Endocrinol.*, 2020, **11**, 498.
13 N. C. Bal and M. Periasamy, *Philos. Trans. R. Soc., B*, 2020, **375**, 20190135.
14 H. Li, C. Wang, L. Li and L. Li, *Life Sci.*, 2021, **269**, 119024.
15 P. Pani and N. C. Bal, *Biol. Rev. Cambridge Philos. Soc.*, 2022, **97**, 2106–2126.
16 S. Kjelstrup, L. De Meis, D. Bedeaux and J.-M. Simon, *Eur. Biophys. J.*, 2008, **38**, 59–67.
17 D. Gamu, E. S. Juracic, K. J. Hall and A. R. Tupling, *Appl. Physiol., Nutr., Metab.*, 2020, **45**, 1–10.
18 N. C. Bal, S. K. Maurya, D. H. Sopariwala, S. K. Sahoo, S. C. Gupta, S. A. Shaikh, M. Pant, L. A. Rowland, E. Bombardier, S. A. Goonasekera, A. R. Tupling, J. D. Molkentin and M. Periasamy, *Nat. Med.*, 2012, **18**, 1575–1579.
19 Y. A. Mahmmoud, *J. Biol. Chem.*, 2008, **283**, 21418–21426.
20 L. E. Burke and J. Wang, *J. Nurs. Scholarsh.*, 2011, **43**, 368–375.
21 A. M. Bernstein, J. Bar, J. P. Ehrman, M. Golubic and M. F. Roizen, *Am. J. Lifestyle Med.*, 2014, **8**, 33–41.
22 J. R. Ryder, C. K. Fox and A. S. Kelly, *Obesity*, 2018, **26**, 951–960.
23 A. Basolo, S. Bechi Genzano, P. Piaggi, J. Krakoff and F. Santini, *Nutrients*, 2021, **13**, 3276.
24 M. J. Müller, C. Geisler, S. B. Heymsfield and A. Bosy-Westphal, *F1000Research*, 2018, **7**, 1025.
25 J. O. Hill and J. C. Peters, *Science*, 1998, **280**, 1371–1374.
26 L. Dubois, A. P. Farmer, M. Girard and K. Peterson, *Eur. J. Clin. Nutr.*, 2007, **61**, 846–855.
27 T. J. Atkinson, *Obes. Rev.*, 2008, **9**, 108–120.
28 J. O. Hill, H. R. Wyatt and J. C. Peters, *Circulation*, 2012, **126**, 126–132.
29 S. K. Powers, G. S. Lynch, K. T. Murphy, M. B. Reid and I. Zijdewind, *Med. Sci. Sports Exercise*, 2016, **48**, 2307–2319.
30 Y. J. Tak and S. Y. Lee, *World J. Men's Health*, 2021, **39**, 208–221.
31 H. W. Korf and M. Møller, *Handb Clin Neurol*, 2021, vol. 180, pp. 227–251.
32 N. Luo, G. Marcelin, S. M. Liu, G. Schwartz and S. Chua, Jr., *Endocrinology*, 2011, **152**, 883–889.
33 R. S. Ahima and D. A. Antwi, *Endocrinol. Metab. Clin. North Am.*, 2008, **37**, 811–823.
34 M. S. Vohra, K. Benchoula, C. J. Serpell and W. E. Hwa, *Eur. J. Pharmacol.*, 2022, **915**, 174611.
35 B. Dehestani, N. R. Stratford and C. W. le Roux, *J. Obes. Metab. Syndr.*, 2021, **30**, 320–325.
36 E. G. Mietlicki-Baase, *Physiol. Behav.*, 2016, **162**, 130–140.
37 T. A. Lutz, B. Coester, L. Whiting, A. A. Dunn-Meynell, C. N. Boyle, S. G. Bouret, B. E. Levin and C. Le Foll, *Diabetes*, 2018, **67**, 805–817.
38 M. A. Cowley, J. L. Smart, M. Rubinstein, M. G. Cerdán, S. Diano, T. L. Horvath, R. D. Cone and M. J. Low, *Nature*, 2001, **411**, 480–484.
39 P. Holzer, F. Reichmann and A. Farzi, *Neuropeptides*, 2012, **46**, 261–274.
40 Y. Chen and Z. A. Knight, *BioEssays*, 2016, **38**, 316–324.
41 M. K. Badman and J. S. Flier, *Science*, 2005, **307**, 1909–1914.
42 A. Nadal, I. Quesada, E. Tudurí, R. Nogueiras and P. Alonso-Magdalena, *Nat. Rev. Endocrinol.*, 2017, **13**, 536–546.
43 A. Inui, *Nat. Rev. Neurosci.*, 2001, **2**, 551–560.
44 A. Inui, A. Asakawa, C. Y. Bowers, G. Mantovani, A. Laylano, M. M. Meguid and M. Fujimiya, *FASEB J.*, 2004, **18**, 439–456.
45 V. K. Vemuri, D. R. Janero and A. Makriyannis, *Physiol. Behav.*, 2008, **93**, 671–686.
46 L. K. Burke and L. K. Heisler, *J. Neuroendocrinol.*, 2015, **27**, 389–398.
47 L. Rajan, D. Palaniswamy and S. K. Mohankumar, *Pharmacol. Res.*, 2020, **155**, 104681.
48 J. J. Holst and M. M. Rosenkilde, *J. Clin. Endocrinol. Metab.*, 2020, **105**, e2710–e2716.
49 D. E. O. A. Perez-Montes, S. Pellitero and M. Puig-Domingo, *Minerva Endocrinol.*, 2021, **46**, 168–176.
50 J. H. Stern, G. I. Smith, S. Chen, R. H. Unger, S. Klein and P. E. Scherer, *J. Endocrinol.*, 2019, **243**, 149–160.
51 M. J. Dailey and T. H. Moran, *Trends Endocrinol. Metab.*, 2013, **24**, 85–91.
52 W. S. Dhillo and S. R. Bloom, *Horm. Metab. Res.*, 2004, **36**, 846–851.
53 L. Busetto, M. Rossato and R. Vettor, in *Encyclopedia of Endocrine Diseases*, ed. I. Huhtaniemi and L. Martini, Academic Press, Oxford, 2nd edn, 2019, pp. 398–405, DOI: **10.1016/B978-0-12-801238-3.66106-8**.
54 J. A. Martyn, M. Kaneki and S. Yasuhara, *Anesthesiology*, 2008, **109**, 137–148.
55 R. Prager, P. Wallace and J. M. Olefsky, *Diabetes*, 1987, **36**, 607–611.
56 W. D. van Marken Lichtenbelt and P. Schrauwen, *Am. J. Physiol.*, 2011, **301**, R285–R296.
57 N. N. Sun, T. Y. Wu and C. F. Chau, *Molecules*, 2016, **21**, 1351.

 

58 K. M. Wasan and N. A. Looije, *J. Pharm. Pharm. Sci.*, 2005, **8**, 259–271.
59 A. L. Carey and B. A. Kingwell, *Diabetologia*, 2009, **52**, 2015–2026.
60 M. F. McCarty, J. J. DiNicolantonio and J. H. O'Keefe, *Open Heart*, 2015, **2**, e000262.
61 Y. Masuda, S. Haramizu, K. Oki, K. Ohnuki, T. Watanabe, S. Yazawa, T. Kawada, S. Hashizume and T. Fushiki, *J. Appl. Physiol.*, 2003, **95**, 2408–2415.
62 P. Anand and K. Bley, *Br. J. Anaesth.*, 2011, **107**, 490–502.
63 F. Wang, Y. Xue, L. Fu, Y. Wang, M. He, L. Zhao and X. Liao, *Crit. Rev. Food Sci. Nutr.*, 2021, 1–29, DOI: **10.1080/10408398.2021.1884840**.
64 M. Nakanishi, K. Hata, T. Nagayama, T. Sakurai, T. Nishisho, H. Wakabayashi, T. Hiraga, S. Ebisu and T. Yoneda, *Mol. Biol. Cell*, 2010, **21**, 2568–2577.
65 W. G. Lima, G. H. Marques-Oliveira, T. M. da Silva and V. E. Chaves, *Endocrine*, 2017, **58**, 3–13.
66 M. J. Ludy, G. E. Moore and R. D. Mattes, *Chem. Senses*, 2012, **37**, 103–121.
67 T. Yoneshiro, S. Aita, Y. Kawai, T. Iwanaga and M. Saito, *Am. J. Clin. Nutr.*, 2012, **95**, 845–850.
68 H. El Hadi, A. Di Vincenzo, R. Vettor and M. Rossato, *Front. Physiol.*, 2018, **9**, 1954.
69 C. Peres Valgas da Silva, D. Hernández-Saavedra, J. D. White and K. I. Stanford, *Biology*, 2019, **8**, 9.
70 N. C. Bal, S. K. Maurya, S. Pani, C. Sethy, A. Banerjee, S. Das, S. Patnaik and C. N. Kundu, *Biosci. Rep.*, 2017, **37**, 206–212.
71 D. H. Wang, *Acta Pharmacol. Sin.*, 2005, **26**, 286–294.
72 F. W. Leung, *Prog. Drug Res.*, 2014, **68**, 171–179.
73 R. Singh, **https://pharmeasy.in/blog/ayurveda-uses-benefits-side-effects-of-apple-cider-vinegar/)**.
74 R. L. Fahey, *Web page*, 2017, vol. 20, **https://www.reliasmedia.com/articles/140790-health-benefits-of-apple-cider-vinegar-and-other-common-vinegars-a-review**.
75 S. L. Haber, O. Awwad, A. Phillips, A. E. Park and T. M. Pham, *The Bulletin of the American Society of Hospital Pharmacists*, 2018, vol. 75, pp. 17–22.
76 R. B. Semwal, D. K. Semwal, I. Vermaak and A. Viljoen, *Fitoterapia*, 2015, **102**, 134–148.
77 B. S. Jena, G. K. Jayaprakasha, R. P. Singh and K. K. Sakariah, *J. Agric. Food Chem.*, 2002, **50**, 10–22.
78 L. O. Chuah, W. Y. Ho, B. K. Beh and S. K. Yeap, *Evidence-Based Complementary Altern. Med.*, 2013, **2013**, 751658.
79 G. Crescioli, N. Lombardi, A. Bettiol, E. Marconi, F. Risaliti, M. Bertoni, F. Menniti Ippolito, V. Maggini, E. Gallo, F. Firenzuoli and A. Vannacci, *Intern. Emerg. Med.*, 2018, **13**, 857–872.
80 S. L. Haber, O. Awwad, A. Phillips, A. E. Park and T. M. Pham, *Am. J. Health-Syst. Pharm.*, 2018, **75**, 17–22.
81 J. H. Zothantluanga, H. S. Lalnunpuii, H. R. Bhat and A. Shakya, *Sci. Vis*, 2019, **19**, 120–133.
82 C. Der Sarkissian, I. M. Velsko, A. K. Fotakis, Å. J. Vågene, A. Hübner and J. A. Fellows Yates, *mSystems*, 2021, **6**, e0131521.
83 S. M. Chacko, P. T. Thambi, R. Kuttan and I. Nishigaki, *Chin. Med.*, 2010, **5**, 13.
84 C. S. Yang, J. Zhang, L. Zhang, J. Huang and Y. Wang, *Mol. Nutr. Food Res.*, 2016, **60**, 160–174.
85 R. T. Borchardt and J. A. Huber, *J. Med. Chem.*, 1975, **18**, 120–122.
86 T. M. Rains, S. Agarwal and K. C. Maki, *J. Nutr. Biochem.*, 2011, **22**, 1–7.
87 H. Kong, P. P. Jones, A. Koop, L. Zhang, H. J. Duff and S. R. Chen, *Biochem. J.*, 2008, **414**, 441–452.
88 A. Meizoso-Huesca, L. Pearce, C. J. Barclay and B. S. Launikonis, *Proc. Natl. Acad. Sci. U. S. A.*, 2022, **119**, e2119203119.
89 Z. Bedrood, M. Rameshrad and H. Hosseinzadeh, *Phytother. Res.*, 2018, **32**, 1163–1180.
90 J. M. Bokelmann, in *Medicinal Herbs in Primary Care*, ed. J. M. Bokelmann, Elsevier, 2022, pp. 415–419, DOI: **10.1016/B978-0-323-84676-9.00051-9**.
91 R. Pothuraju, R. K. Sharma, J. Chagalamarri, S. Jangra and P. Kumar Kavadi, *J. Sci. Food Agric.*, 2014, **94**, 834–840.
92 K. Yoshikawa, Y. Kondo, S. Arihara and K. Matsuura, *Chem. Pharm. Bull.*, 1993, **41**, 1730–1732.
93 S. Sharma, S. K. Dwivedi and D. Swarup, *Indian J. Exp. Biol.*, 1996, **34**, 372–374.
94 R. Pothuraju, R. K. Sharma, J. Chagalamarri, S. Jangra and P. Kumar Kavadi, *J. Sci. Food Agric.*, 2014, **94**, 834–840.
95 N. P. Sahu, S. B. Mahato, S. K. Sarkar and G. Poddar, *Phytochemistry*, 1996, **41**, 1181–1185.
96 A. M. Heck, J. A. Yanovski and K. A. Calis, *Pharmacotherapy*, 2000, **20**, 270–279.
97 M. O. Dietrich and T. L. Horvath, *Nat. Rev. Drug Discovery*, 2012, **11**, 675–691.
98 J. C. Halford and J. E. Blundell, *Prog. Drug Res.*, 2000, **54**, 25–58.
99 T. T. Liu, X. T. Liu, Q. X. Chen and Y. Shi, *Biomed. Pharmacother.*, 2020, **128**, 110314.
100 R. Guerciolini, *Int. J. Obes. Relat. Metab. Disord.*, 1997, **21**(Suppl 3), S12–S23.
101 A. B. Bansal and Y. Al Khalili, in *StatPearls*, StatPearls Publishing, 2022.
102 J. Aaseth, S. Ellefsen, U. Alehagen, T. M. Sundfør and J. Alexander, *Biomed. Pharmacother.*, 2021, **140**, 111789.
103 T. Behl, S. Chadha, M. Sachdeva, A. Sehgal, A. Kumar, Dhruv, T. Venkatachalam, A. Hafeez, L. Aleya, S. Arora, G. E. Batiha, P. Nijhawan and S. Bungau, *Prostaglandins Other Lipid Mediators*, 2021, **152**, 106520.
104 Y. J. Tak and S. Y. Lee, *J. Adv. Model. Earth Syst.*, 2021, **10**, 14–30.
105 B. A. Swinburn, D. Carey, A. P. Hills, M. Hooper, S. Marks, J. Proietto, B. J. Strauss, D. Sullivan, T. A. Welborn and I. D. Caterson, *Diabetes, Obes. Metab.*, 2005, **7**, 254–262.
106 V. P. Pulipati and S. Pannain, *Clin. Obes.*, 2022, **12**, e12497.
107 S. A. Polyzos, D. G. Goulis, O. Giouleme, G. S. Germanidis and A. Goulas, *J. Adv. Model. Earth Syst.*, 2022, **14**(19), 4651.
108 K. H. Lucas and B. Kaplan-Machlis, *Ann. Pharmacother.*, 2001, **35**, 314–328.

109 Y.-F. Bai, C. Zeng, M. Jia and B. Xiao, *Seizure*, 2022, **98**, 51–56.
110 S. M. Smith, M. Meyer and K. E. Trinkley, *Ann. Pharmacother.*, 2013, **47**, 340–349.
111 A. Golden, *J. Am. Assoc. Nurse Pract.*, 2017, **29**, S43–s52.
112 X. G. Lei, J. Q. Ruan, C. Lai, Z. Sun and X. Yang, *Obesity*, 2021, **29**, 985–994.
113 D. B. Johnson and J. Quick, *Topiramate And Phentermine*, StatPearls Publishing, Treasure Island (FL), 2022.
114 R. P. Shank, J. F. Gardocki, J. L. Vaught, C. B. Davis, J. J. Schupsky, R. B. Raffa, S. J. Dodgson, S. O. Nortey and B. E. Maryanoff, *Epilepsia*, 1994, **35**, 450–460.
115 P. Czapinski, B. Blaszczyk and S. J. Czuczwar, *Curr. Top. Med. Chem.*, 2005, **5**, 3–14.
116 J. H. Shin and K. M. Gadde, *Diabetes, Metab. Syndr. Obes.*, 2013, **6**, 131–139.
117 T. Salek, I. Andel and I. Kurfurstova, *Biochem. Med.*, 2017, **27**, 404–410.
118 *clinicaltrials.gov*, 2023, **https://classic.clinicaltrials.gov/ct2/show/NCT04621929**.
119 D. J. Lonneman, Jr., J. A. Rey and B. D. McKee, *P T*, 2013, **38**, 446–452.
120 H. Ling, T. L. Lenz, T. L. Burns and D. E. Hilleman, *Pharmacotherapy*, 2013, **33**, 1308–1321.
121 D. Richard, J. Ferland, J. Lalonde, P. Samson and Y. Deshaies, *Nutrition*, 2000, **16**, 961–966.
122 A. K. Kakkar and N. Dahiya, *Eur. J. Intern. Med.*, 2015, **26**, 89–94.
123 H. L. Daneschvar, M. D. Aronson and G. W. Smetana, *Am. J. Med.*, 2016, **129**, 879, e871–876.
124 M. M. Sherman, S. Ungureanu and J. A. Rey, *P T*, 2016, **41**, 164–172.
125 C. M. Apovian, L. Aronne, D. Rubino, C. Still, H. Wyatt, C. Burns, D. Kim and E. Dunayevich, *Obesity*, 2013, **21**, 935–943.
126 T. A. Wadden, J. P. Foreyt, G. D. Foster, J. O. Hill, S. Klein, P. M. O'Neil, M. G. Perri, F. X. Pi-Sunyer, C. L. Rock, J. S. Erickson, H. N. Maier, D. D. Kim and E. Dunayevich, *Obesity*, 2011, **19**, 110–120.
127 J. Early and J. S. Whitten, *Am. Fam. Physician*, 2015, **91**, 554–556.
128 S. M. Stahl, J. F. Pradko, B. R. Haight, J. G. Modell, C. B. Rockett and S. Learned-Coughlin, *Prim. Care Companion J. Clin. Psychiatry*, 2004, **6**, 159–166.
129 S. K. Billes, P. Sinnayah and M. A. Cowley, *Pharmacol. Res.*, 2014, **84**, 1–11.
130 S. X. Luo, *Biol. Psychiatry*, 2016, **79**, e85–e86.
131 D. W. Oslin, W. H. Berrettini and C. P. O'Brien, *Addict. Biol.*, 2006, **11**, 397–403.
132 J. W. Son and S. Kim, *Diabetes Metab. J.*, 2020, **44**, 802–818.
133 D. Cota, M. H. Tschöp, T. L. Horvath and A. S. Levine, *Brain Res. Rev.*, 2006, **51**, 85–107.
134 F. L. Greenway, K. Fujioka, R. A. Plodkowski, S. Mudaliar, M. Guttadauria, J. Erickson, D. D. Kim and E. Dunayevich, *Lancet*, 2010, **376**, 595–605.
135 C. T. Makowski, K. M. Gwinn and K. M. Hurren, *Obes. Facts*, 2011, **4**, 489–494.
136 L. M. Neff and R. F. Kushner, *Diabetes, Metab. Syndr. Obes.: Targets Ther.*, 2010, 263–273.
137 V. Gupta, *Indian J. Endocrinol. Metab.*, 2013, **17**, 413–421.
138 J. Lindgren, E. Refai, S. V. Zaitsev, L. Abrahmsén, P. O. Berggren and A. E. Karlström, *Biopolymers*, 2014, **102**, 252–259.
139 P. Nadkarni, O. G. Chepurny and G. G. Holz, *Prog. Mol. Biol. Transl. Sci.*, 2014, **121**, 23–65.
140 A. Secher, J. Jelsing, A. F. Baquero, J. Hecksher-Sørensen, M. A. Cowley, L. S. Dalbøge, G. Hansen, K. L. Grove, C. Pyke and K. Raun, *J. Clin. Invest.*, 2014, **124**, 4473–4488.
141 N. Delzenne, J. Blundell, F. Brouns, K. Cunningham, K. De Graaf, A. Erkner, A. Lluch, M. Mars, H. P. Peters and M. Westerterp-Plantenga, *Obes. Rev.*, 2010, **11**, 234–250.
142 J. Y. Zhou, A. Poudel, R. Welchko, N. Mekala, P. Chandramani-Shivalingappa, M. G. Rosca and L. Li, *Eur. J. Pharmacol.*, 2019, **861**, 172594.
143 A. Secher, J. Jelsing, A. F. Baquero, J. Hecksher-Sørensen, M. A. Cowley, L. S. Dalbøge, G. Hansen, K. L. Grove, C. Pyke, K. Raun, L. Schäffer, M. Tang-Christensen, S. Verma, B. M. Witgen, N. Vrang and L. Bjerre Knudsen, *J. Clin. Invest.*, 2014, **124**, 4473–4488.
144 G. E. Peterson and R. D. Pollom, *Int. J. Clin. Pract., Suppl.*, 2010, 35–43, DOI: **10.1111/j.1742-1241.2010.02498.x**.
145 FDA, FDA approves weight management drug for patients aged 12 and older, *Government Document*, 2020, **https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-weight-management-drug-patients-aged-12-and-older**.
146 FDA, *FDA approves new treatment for pediatric patients with type 2 diabetes*, 2019, vol. 17, **https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-type-2-diabetes**.
147 EMA, Saxenda recommended for approval in weight management in adults, *Government Document*, 2015, **https://www.ema.europa.eu/en/news/saxenda-recommended-approval-weight-management-adults**.
148 EMA, Victoza, *Government Document*, 2021, **https://www.ema.europa.eu/en/medicines/human/EPAR/victoza**.
149 A. Mehta, S. P. Marso and I. J. Neeland, *Obes. Sci. Pract.*, 2017, **3**, 3–14.
150 T. D. Filippatos, T. V. Panagiotopoulou and M. S. Elisaf, *Rev. Diabet. Stud.*, 2014, **11**, 202–230.
151 W. M. Steinberg, J. B. Buse, M. L. M. Ghorbani, D. D. Ørsted and M. A. Nauck, *Diabetes Care*, 2017, **40**, 966–972.
152 M. Mirabelli, E. Chiefari, P. Caroleo, B. Arcidiacono, D. M. Corigliano, S. Giuliano, F. S. Brunetti, S. Tanyolaç, D. P. Foti and L. Puccio, *Int. J. Environ. Res. Public Health*, 2020, **17**, 207.
153 C. Patel Chavez, K. Cusi and S. Kadiyala, *J. Clin. Endocrinol. Metab.*, 2022, **107**, 29–38.
154 J. P. H. Wilding, R. L. Batterham, S. Calanna, M. Davies, L. F. Van Gaal, I. Lingvay, B. M. McGowan, J. Rosenstock, M. T. D. Tran, T. A. Wadden, S. Wharton, K. Yokote, N. Zeuthen and R. F. Kushner, *N. Engl. J. Med.*, 2021, **384**, 989–1002.

155 G. Singh, M. Krauthamer and M. Bjalme-Evans, *J. Invest. Med.*, 2022, **70**, 5–13.

156 D. Rubino, N. Abrahamsson, M. Davies, D. Hesse, F. L. Greenway, C. Jensen, I. Lingvay, O. Mosenzon, J. Rosenstock, M. A. Rubio, G. Rudofsky, S. Tadayon, T. A. Wadden and D. Dicker, *JAMA, J. Am. Med. Assoc.*, 2021, **325**, 1414–1425.

157 M. Davies, L. Færch, O. K. Jeppesen, A. Pakseresht, S. D. Pedersen, L. Perreault, J. Rosenstock, I. Shimomura, A. Viljoen, T. A. Wadden and I. Lingvay, *Lancet*, 2021, **397**, 971–984.

158 K. E. Miles and J. L. Kerr, *J. Pharm. Technol.*, 2018, **34**, 281–289.

159 A. C. Mares, S. Chatterjee and D. Mukherjee, *Curr. Opin. Cardiol.*, 2022, **37**, 350–355.

160 EMA, Imcivree, *Government Document*, 2021, **https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree**.

161 FDA, Drug Approval Package: IMCIVREE, *Government Document*, 2020, **https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000TOC.cfm**.

162 A. Hussain and K. Farzam, in *StatPearls*, StatPearls Publishing, 2023.

163 D. H. Ryan, *J. Obes. Metab. Syndr.*, 2021, **30**, 196–208.

164 Drugbank, Setmelanotide, **https://go.drugbank.com/drugs/DB11700**.

165 A. Markham, *Drugs*, 2021, **81**, 397–403.

166 D. H. Ryan, *Lancet Diabetes Endocrinol.*, 2020, **8**, 933–935.

167 H. Pressley, C. K. Cornelio and E. N. Adams, *J. Pharm. Technol.*, 2022, **38**, 368–373.

168 T. D. Müller, M. H. Tschöp and S. O'Rahilly, *Cell Metab.*, 2016, **24**, 194–195.

169 D. J. P. Cunha, FACOEP, PHENDIMETRAZINE TARTRATE SIDE EFFECTS CENTER, **https://www.rxlist.com/phendimetrazine-tartrate-side-effects-drug-center.htm**.

170 M. Merative, Phendimetrazine (Oral Route), **https://www.mayoclinic.org/drugs-supplements/phendimetrazine-oral-route/side-effects/drg-20075140?p=1**.

171 D. bank, Phendimetrazine, **https://go.drugbank.com/drugs/DB01579**.

172 B. Halpern and A. Halpern, *Expert Opin. Drug Saf.*, 2015, **14**, 305–315.

173 A. Gustafson, C. King and J. A. Rey, *P T*, 2013, **38**, 525–534.

174 J. R. Taylor, E. Dietrich and J. Powell, *Diabetes, Metab. Syndr. Obes.*, 2013, **6**, 209–216.

175 S. M. Hoy, *Drugs*, 2013, **73**, 463–473.

176 J. P. Voigt and H. Fink, *Behav. Brain Res.*, 2015, **277**, 14–31.

177 L. M. Redman and E. Ravussin, *Drugs Today*, 2010, **46**, 901–910.

178 W. J. Thomsen, A. J. Grottick, F. Menzaghi, H. Reyes-Saldana, S. Espitia, D. Yuskin, K. Whelan, M. Martin, M. Morgan and W. Chen, *J. Pharmacol. Exp. Ther.*, 2008, **325**, 577–587.

179 H. Y. Meltzer and B. L. Roth, *J. Clin. Invest.*, 2013, **123**, 4986–4991.

180 B. L. Roth, D. L. Willins, K. Kristiansen and W. K. Kroeze, *Pharmacol. Ther.*, 1998, **79**, 231–257.

181 A. K. Singh and R. Singh, *Expert Rev. Clin. Pharmacol.*, 2020, **13**, 183–190.

182 J. Sharretts, O. Galescu, S. Gomatam, E. Andraca-Carrera, C. Hampp and L. Yanoff, *N. Engl. J. Med.*, 2020, **383**, 1000–1002.

183 M. Silver Spring, U.S. Food and Drug Administration. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market, **https://www.fda.gov/drugs/drug-safety-and-availability/fdarequests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market**.

184 S. P. I. LTD, Alfence 10mg Tablet 10s, **https://www.apollopharmacy.in/medicine/alfence-10mg-tablet-10s**.

185 D. H. Ryan, *Drugs Today*, 2004, **40**, 41–54.

186 C. A. Luque and J. A. Rey, *Ann. Pharmacother.*, 1999, **33**, 968–978.

187 S. Von Haehling, M. Lainscak and S. D. Anker, *Eur. Heart J.*, 2007, **28**, 2830–2831.

188 G. A. Bray, G. L. Blackburn, J. M. Ferguson, F. L. Greenway, A. K. Jain, C. M. Mendel, J. Mendels, D. H. Ryan, S. L. Schwartz, M. L. Scheinbaum and T. B. Seaton, *Obes. Res.*, 1999, **7**, 189–198.

189 W. P. James, A. Astrup, N. Finer, J. Hilsted, P. Kopelman, S. Rössner, W. H. Saris and L. F. Van Gaal, *Lancet*, 2000, **356**, 2119–2125.

190 A. J. Scheen, *Am. J. Cardiovasc. Drugs*, 2010, **10**, 321–334.

191 G. Derosa and P. Maffioli, *Expert Opin. Drug Saf.*, 2012, **11**, 459–471.

192 Cipla, OBESTAT 10 MG CAPSULE 10S, **https://sastimedicine.com/medicine-price/11218-1312733/Obestat-10mg-Cap-10s-Price-Dosage-Side-effects-Uses-and-generic-alternatives-and-its-cost**.

193 L. 10mg, Leptos 10mg, **https://www.tabletshablet.com/product/leptos-10mg/**.

194 I. Caterson, N. Finer, W. Coutinho, L. Van Gaal, A. Maggioni, C. Torp-Pedersen, A. Sharma, U. Legler, G. Shepherd and R. Rode, *Diabetes, Obes. Metab.*, 2012, **14**, 523–530.

195 J. F. Hayes, K. Bhaskaran, R. Batterham, L. Smeeth and I. Douglas, *Int. J. Obes.*, 2015, **39**, 1359–1364.

196 A. J. Scheen, *Diabetes Care*, 2011, **34**(Suppl 2), S114–S119.

197 M. Florentin, E. Liberopoulos and M. Elisaf, *Obes. Rev.*, 2008, **9**, 378–387.

198 A. V. Chobanian, G. L. Bakris, H. R. Black, W. C. Cushman, L. A. Green, J. L. Izzo Jr, D. W. Jones, B. J. Materson, S. Oparil and J. T. Wright Jr, *Hypertension*, 2003, **42**, 1206–1252.

199 M. Esler, N. Straznicky, N. Eikelis, K. Masuo, G. Lambert and E. Lambert, *Hypertension*, 2006, **48**, 787–796.

200 R. Sherafat-Kazemzadeh, S. Z. Yanovski and J. A. Yanovski, *Int. J. Obes.*, 2013, **37**, 1–15.

201 Acomplia, Acomplia, **https://www.ema.europa.eu/en/medicines/human/EPAR/acomplia**.

202 F. Dol-Gleizes, R. Paumelle, V. Visentin, A. M. Marés, P. Desitter, N. Hennuyer, A. Gilde, B. Staels, P. Schaeffer and F. Bono, *Arterioscler., Thromb., Vasc. Biol.*, 2009, **29**, 12–18.

203 A. Nagappan, J. Shin and M. H. Jung, *Int. J. Mol. Sci.*, 2019, **20**, 2109.

204 C. Curioni and C. André, *Cochrane Database Syst. Rev.*, 2006, **2006**, Cd006162.
205 A. Samat, B. Tomlinson, S. Taheri and G. N. Thomas, *Recent Pat. Cardiovasc. Drug Discovery*, 2008, **3**, 187–193.
206 V. Di Marzo and J.-P. Després, *Nat. Rev. Endocrinol.*, 2009, **5**, 633–638.
207 F. A. Moreira and J. A. S. Crippa, *Braz. J. Psychiatry*, 2009, **31**, 145–153.
208 M. Koch, *Front. Neurosci.*, 2017, **11**, 293.
209 E. Kirilly, X. Gonda and G. Bagdy, *Acta Physiol.*, 2012, **205**, 41–60.
210 L. L. Ioannides-Demos, L. Piccenna and J. J. McNeil, *J. Obes.*, 2011, **2011**, 179674.
211 J. Grundlingh, P. I. Dargan, M. El-Zanfaly and D. M. Wood, *J. Med. Toxicol.*, 2011, **7**, 205–212.
212 F. H. Blaikie, S. E. Brown, L. M. Samuelsson, M. D. Brand, R. A. Smith and M. P. Murphy, *Biosci. Rep.*, 2006, **26**, 231–243.
213 S. M. Zin, S. Habib, N. A. Yasid and S. A. Ahmad, *Journal of Environmental Microbiology and Toxicology*, 2018, **6**, 28–33.
214 D. J. Germain, D. C. Leavey, P. M. C. Van Hout and P. J. McVeigh, *Int. J. Drug Policy*, 2021, **95**, 102987.
215 J. Grundlingh, P. I. Dargan, M. El-Zanfaly and D. M. Wood, *J. Med. Toxicol.*, 2011, **7**, 205–212.
216 E. Colman, *Regul. Toxicol. Pharmacol.*, 2007, **48**, 115–117.
217 J. Przybyla, H. Carlson-Lynch, J. M. Klotzbach and J. S. Crisman, *Toxicological profile for dinitrophenols*, U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, SRI inc., USA, p. 2021.
218 M. O. Harris and J. Corcoran, *Toxicological profile for dinitrophenols*, 1995.
219 A. A. Coulter, C. J. Rebello and F. L. Greenway, *Drugs*, 2018, **78**, 1113–1132.
220 R. A. Hauser, L. Salin, N. Juhel and V. L. Konyago, *Mov. Disord.*, 2007, **22**, 359–365.
221 A. Astrup, D. H. Meier, B. O. Mikkelsen, J. S. Villumsen and T. M. Larsen, *Obesity*, 2008, **16**, 1363–1369.
222 A. Sjödin, C. Gasteyger, A.-L. Nielsen, A. Raben, J. Mikkelsen, J. Jensen, D. Meier and A. Astrup, *Int. J. Obes.*, 2010, **34**, 1634–1643.
223 A. Astrup, S. Madsbad, L. Breum, T. J. Jensen, J. P. Kroustrup and T. M. Larsen, *Lancet*, 2008, **372**, 1906–1913.
224 A. Astrup, S. Madsbad, L. Breum, T. J. Jensen, J. P. Kroustrup and T. M. Larsen, *Lancet*, 2008, **372**, 1906–1913.
225 R. A. Hauser, L. Salin, N. Juhel and V. L. Konyago, *Mov. Disord.*, 2007, **22**, 359–365.
226 D. Al-Bazz and J. P. Wilding, *Clinical Obesity in Adults and Children*, 2022, pp. 279–296.
227 N. T. Bello and M. R. Zahner, *Curr. Opin. Invest. Drugs*, 2009, **10**, 1105–1116.
228 M. A. Subbaiah, *J. Med. Chem.*, 2017, **61**, 2133–2165.
229 L. Appel, M. Bergström, J. Buus Lassen and B. Långström, *Eur. Neuropsychopharmacol.*, 2014, **24**, 251–261.
230 A. B. Saniona, 2022, **https://www.globenewswire.com/news-release/2022/05/20/2447468/0/en/Saniona-provides-update-on-ongoing-review-of-tesofensine-in-Mexico.html**.
231 T. R. Chemicals, Tesofensine, 1mg, **https://www.biomall.in/product/tesofensine-1mg-t136500-1mg**.
232 M. O. Dietrich and T. L. Horvath, *Nat. Rev. Drug Discovery*, 2012, **11**, 675–691.
233 P. Kopelman, A. Bryson, R. Hickling, A. Rissanen, S. Rossner, S. Toubro and P. Valensi, *Int. J. Obes.*, 2007, **31**, 494–499.
234 P. Kopelman, A. Bryson, R. Hickling, A. Rissanen, S. Rossner, S. Toubro and P. Valensi, *Int. J. Obes.*, 2007, **31**, 494–499.
235 M. A. Hossain, R. Pervin, D. Debnath and M. A. Bhuiyan, in *Global Perspectives on Childhood Obesity*, ed. D. Bagchi, Academic Press, 2nd edn, 2019, pp. 377–385, DOI: **10.1016/B978-0-12-812840-4.00030-X**.
236 T. P. C. Limited, 2018, **https://www.takeda.com/newsroom/newsreleases/2018/termination-of-license-and-development-agreement-for-oblean-tablets-120mg-for-treatment-of-obesity/**.
237 A. H. Ltd, CETISLIM CAP, **https://www.medplusmart.com/product/kilfat-60mg-cap_kilf0001**, **https://www.medplusmart.com/product/cetislim-cap_ceti0015**.
238 R. F. Witkamp, *Pharm. Res.*, 2011, **28**, 1792–1818.
239 DrugBank, PubChem Substance Record for SID 347910299, GT 389-255, **https://pubchem.ncbi.nlm.nih.gov/substance/347910299**.
240 A. K. McGavigan and K. G. Murphy, *Br. J. Clin. Pharmacol.*, 2012, **74**, 911–919.
241 DB05045, Obinepitide, **https://go.drugbank.com/drugs/DB05045**.
242 DB05993, PRX-07034, **https://go.drugbank.com/drugs/DB05993**.
243 E. G. Mohler, P. M. Baker, K. S. Gannon, S. S. Jones, S. Shacham, J. A. Sweeney and M. E. Ragozzino, *Psychopharmacology*, 2012, **220**, 687–696.
244 N. Boehringer Ingelheim, *Government Document*, 2021, **https://clinicaltrials.gov/ct2/show/NCT03591718**.
245 T. Zimmermann, L. Thomas, T. Baader-Pagler, P. Haebel, E. Simon, W. Reindl, B. Bajrami, W. Rist, I. Uphues, D. J. Drucker, H. Klein, R. Santhanam, D. Hamprecht, H. Neubauer and R. Augustin, *Mol. Metab.*, 2022, **66**, 101633.
246 N. Eli Lilly and Company, *Government Document*, 2023, **https://clinicaltrials.gov/ct2/show/NCT04184622**.
247 E. L. A. Company, Lilly's tirzepatide delivered up to 22.5% weight loss in adults with obesity or overweight in SURMOUNT-1, **https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-delivered-225-weight-loss-adults-obesity-or**.
248 E. L. A. Company, FDA approves Lilly's Mounjaro™ (tirzepatide) injection, the first and only GIP and GLP-1 receptor agonist for the treatment of adults with type 2 diabetes, **https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-mounjarotm-tirzepatide-injection-first-and**.
249 Orexigen Therapeutics, Bupropion/zonisamide, *Online Multimedia*, 2013, **https://adisinsight.springer.com/drugs/800024638**.

250 L. L. Ioannides-Demos, L. Piccenna and J. J. McNeil, *J. Obes.*, 2011, **2011**, 179674.
251 R. A. Adan, *Trends Neurosci.*, 2013, **36**, 133–140.
252 Orexigen Therapeutics, *Pamphlet*, 2012, **https://www.cureus.com/posters/275-dose-ratio-optimization-with-zonisamide-sr-and-bupropion-sr-for-weight-loss**.
253 Orexigen Therapeutics, Inc, NCT00339014, Safety and Efficacy of Different Combinations of Zonisamide-CR Plus Bupropion-SR to Treat Uncomplicated Obesity, *Government Document*, 2008, **https://clinicaltrials.gov/ct2/show/NCT00339014**.
254 E. A. Day, R. J. Ford and G. R. Steinberg, *Trends Endocrinol. Metab.*, 2017, **28**, 545–560.
255 Pubchem, Acadesine, *Online Database*, 2021, **https://pubchem.ncbi.nlm.nih.gov/compound/Acadesine**.
256 S. Krishan, D. R. Richardson and S. Sahni, *J. Clin. Pathol.*, 2014, **67**, 758–763.
257 R. Ceddia, *Mol. Cell. Endocrinol.*, 2013, **366**, 194–203.
258 B. Kola, A. B. Grossman and M. Korbonits, *Obes. Metab.*, 2008, **36**, 198–211.
259 R. Bergeron, R. R. Russell, 3rd, L. H. Young, J. M. Ren, M. Marcucci, A. Lee and G. I. Shulman, *Am. J. Physiol.*, 1999, **276**, E938–E944.
260 B. Viollet, L. Lantier, J. Devin-Leclerc, S. Hébrard, C. Amouyal, R. Mounier, M. Foretz and F. Andreelli, *Front. Biosci.-Landmark*, 2009, **14**, 3380.
261 N. N. Global, R&D pipeline, **https://www.novonordisk.com/science-and-technology/r-d-pipeline.html**.