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Pancreatic lipase inhibitors from natural sources: unexplored potential

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The prevalence of obesity is increasing at an alarming rate, but, unfortunately, only a few medications are currently on the market. Obesity is primarily regarded as a disorder of lipid metabolism and the enzymes involved in this process could be selectively targeted to develop antiobesity drugs. Recently, newer approaches for the treatment of obesity have involved inhibition of dietary triglyceride absorption via inhibition of pancreatic lipase (PL) as this is the major source of excess calories. Natural products provide a vast pool of PL inhibitors that can possibly be developed into clinical products. This article reviews various extracts and secondary metabolites from plants and microbial origin with PL inhibitory activity that can be focused for drug development programs.

Introduction

Although widely regarded as a problem confined to the developed world, the obesity epidemic is, in reality, sweeping inevitably through the developing nations as well [1]. Obesity is becoming one of the greatest threats to global health in this millennium, with more than 1 billion overweight adults and of those, at least 300 million are clinically obese [2,3]. The regulation of energy homeostasis for metabolic diseases is one of the most rapidly advancing topics in biomedical research today. Breakthroughs in understanding of the molecular mechanisms regulating body weight have also provided potential opportunities for therapeutic intervention and brought renewed hope and vitality for the development of antiobesity drugs [4–6]. Despite the plethora of research data available on obesity, it still remains, largely, an unsolved medical problem [7–9]. The market for antiobesity drugs is potentially huge, as it accounts for 2–6% of total health care costs in several developed countries. With its growing worldwide prevalence, the obesity market has been predicted to reach US$ 3.7 billion by 2008. The mushrooming market for these drugs and the vast sum of money at stake guarantee that research in this therapeutic area will not slow down within the foreseeable future [10]. Table 1 summarises those antiobesity drugs that are currently approved and investigational drugs that are in various clinical trial phases [2,7,13] (http://www.clinicaltrials.gov).

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The surge in the number of reviews on the subject of obesity clearly indicates the amount of research devoted to this field. Several excellent reviews have appeared covering the detailed mechanisms associated with energy homeostasis, newly identified targets and current and investigational agents [11–22].

At present, the potential of natural products for the treatment of obesity is still largely unexplored and might be an excellent alternative strategy for the development of safe and effective antiobesity drugs [23]. Over the counter remedies for obesity, based on nutritional supplements, are extremely popular; however, although such treatments are widely used, none has yet been convincingly demonstrated to be safe and effective.

Obesity and lipid metabolism

Lipid metabolism is elegantly balanced to maintain homeostasis [9,17,18]. When the balance is lost, obesity or hyperlipidemia develops, leading to a variety of serious diseases, including atherosclerosis, hypertension, diabetes and functional depression of certain organs. Therefore, the control of lipid metabolism by drugs could be used to prevent or treat these diseases. A growing number of enzymes involved in lipid metabolic pathways are being identified and characterized; as such they represent a rich pool of potential therapeutic targets for obesity and other metabolic disorders [11]. One of the most important strategies in the treatment of obesity includes development of inhibitors of nutrient digestion and absorption, in an attempt to reduce energy intake through

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TABLE 1

Current and investigational antiobesity drugs

Drug	Target/mechanism	Company name	Status	Refs
Current antiobesity drugs on the market				
Orlistat	Pancreatic lipase	Roche	FDA approved	[7,13][a]
Sibutramine	Serotonin and noradrenaline reuptake inhibitor	Abbott laboratories	FDA approved	[7,13][a]
Rimonabant	CB1 cannabinoid receptor antagonist	Sanofi-Aventis	Approved in Europe	[7,13][a]
Selected antiobesity drugs in clinical trials				
ATL-962 (cetilistat)	Pancreatic lipase	Alizyme	Phase IIb	[2,7,13][a]
GT389-255	Lipase inhibitor	Peptimmune	Phase I	[2]
APD356	Selective 5HT2C agonist	Arena Pharmaceuticals	Phase II completed	[13][a]
SLV319	CB1 receptor Antagonist	Solvay Pharmaceuticals	Phase IIb	[2]
CP945 598	CB1 receptor Antagonist	Pfizer	Phase II	[7]
SR58611A	β 3-adrenergic receptor agonist	Sanofi-Synthelabo	Phase IIa	[2]
L796568	β 3-adrenergic receptor agonist	Merck	Phase II	[2]
Metreleptin	Modified leptin	Amgen	Phase II	[2]
Leptin	Leptin receptor	Amgen	Phase II	A
GI181771	CCK-A agonist	GlaxoSmithLline	Phase II	A
Oleoyl estrone		Manhattan pharmaceuticals	Phase IIa	[13]
PYY(3–36)	Synthetic form of the appetite suppressing hormone PYY(3–36)	Nastech pharmaceutical	Phase II	[2,7,13]
TM30338	Neuropeptide Y2 and Y4 agonists	7TMPharma	Phase I/II	[7,13]
Pramlintide	Delays gastric emptying	Amylin	Phase II	[7,13]
1426	Peripheral mechanism	Sanofi-Aventis	Phase IIa	A
CYT-009-GhrQb	Ghrelin-targeted vaccine	Cytos Biotechnology	Phase I/II	A
AOD9604	Human growth harmone	Metabolic pharmaceuticals	Phase II b completed	[7,13][a]
P57	Apetite suppressant	Phytopharm	Phase II	[2]

[a] Data source: http://www.clinicaltrials.gov.

gastrointestinal mechanisms, without altering any central mechanisms [4,11,22]. Since dietary lipids represent the major source of unwanted calories, specifically inhibiting triglyceride (TG) digestion forms a new approach for the reduction of fat absorption [24,25].

Pancreatic lipase

Lipases are enzymes that digest fats, including triacylglycerol and phospholipids. The human lipases include the pre-duodenal (lingual and gastric) and the extra-duodenal (pancreatic, hepatic, lipoprotein and the endothelial) lipases [24].

PL (triacylgycerol acyl hydrolase), the principal lipolytic enzyme synthesized and secreted by the pancreas, plays a key role in the efficient digestion of triglycerides. It removes fatty acids from the α and α′ position of dietary triglycerides, yielding β-monoglycerides and long chain saturated and polyunsaturated fatty acids as the lipolytic products [11,24,25]. PL is responsible for the hydrolysis of 50–70% of total dietary fats. Figure 1 depicts the physiological role of PL. The three-dimensional structure of human PL was determined by X-ray crystallography. The primary structure of the PL was established by analysis of cDNA clones isolated from a human pancreas cDNA library and found to be a single chain glycoprotein of 449 amino acids. The encoded protein shows 86% and 68% homology with porcine and canine PL, respectively [26]. The polypeptide chain is divided into two folding units, the larger N-terminal domain, comprising amino acid residues 1–336 and a C terminal domain containing amino acid residues 337–449 [27] typical of β-sandwich type. The N-terminal domain is the catalytic domain and the C-terminal domain binds the colipase, a cofactor required for activity [26,27]. In the structure of human PL His 263, Asp-176 and Ser-152 form a triad, analogous to the serine proteases, representing the lipolytic site. Enzymatic activity has shown to be diminished after chemical modification of Ser 152, located in the larger N-terminal domain at the C-terminal edge of a doubly-wound parallel β-sheet and is a part of Asp-His-Ser triad, thus indicating that Ser 152 is essential for the catalytic activity [26].

PL requires another pancreatic exocrine protein, colipase, for full activity under physiological conditions**.** Colipase is secreted by the exocrine pancreas as a precursor molecule, procolipase, which is processed to mature colipase by cleavage of the procolipase propeptide (APGPR). Procolipase binds exclusively to the C-terminal domain of the PL molecule, without inducing any conformational change [27].

Lingual lipase, secreted by serous gland, digests approximately one third of ingested fat. Gastric lipase, secreted in response to mechanical stimulation, ingestion of food or sympathetic activation, accounts for the hydrolysis of 10–40% of dietary fat. These two enzymes, thus, potentially limit the nutritional impact of the inhibition of lipid absorption that could result from the reduction in the activity of PL alone [25].

PL inhibition is one of the most widely studied mechanisms for the determination of the potential efficacy of natural products as antiobesity agents. Orlistat, one of the two clinically approved drugs for obesity treatment, has been shown to act through inhibition of PL. Although it is one of the best-selling drugs worldwide, it has certain unpleasant gastrointestinal side effects like oily stools, oily spotting, flatulence among others. The success of orlistat has prompted research for the identification of newer PL inhibitors that lack some of these unpleasant side effects.

Pancreatic lipase Inhibitors from plants

Phytochemicals identified from traditional medicinal plants present an exciting opportunity for the development of newer

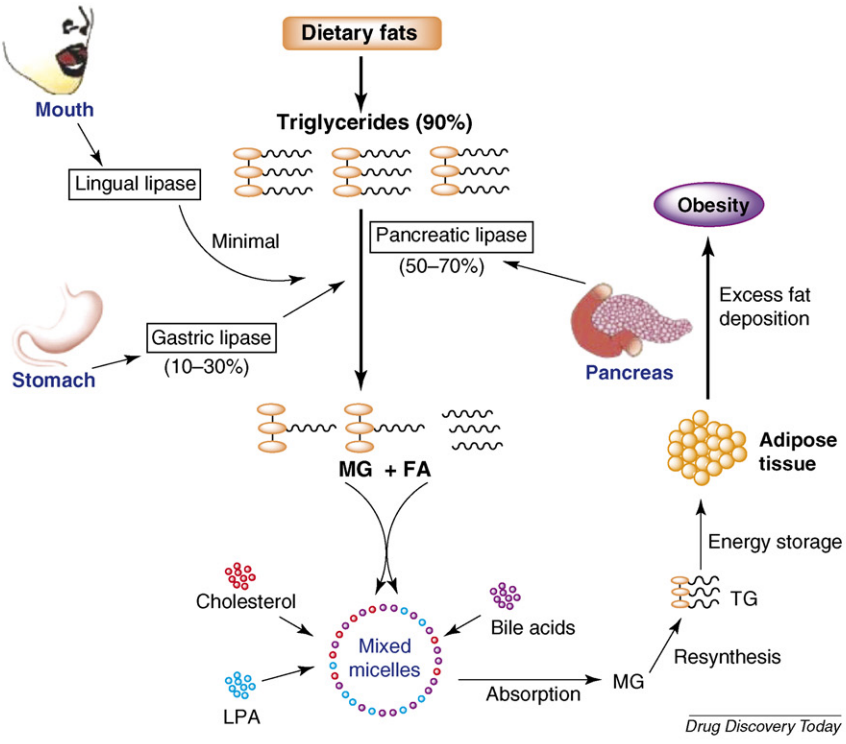

FIGURE 1

Physiological role of pancreatic lipase in lipid absorption.

Dietary fats are mainly (90%) comprised mixed triglycerides (TGs) and are required to be hydrolyzed for their absorption. Of the various lipases, PL is the principle lipolytic enzyme accounting for the hydrolysis of 50–70% of dietary fats to their respective fatty acids (FA) and monoglycerides (MGs). The MGs and free FAs, released by lipid hydrolysis, form mixed micelles with bile salts, cholesterol and lysophosphatidic acid (LPA) and are absorbed into enterocytes where resynthesis of TGs takes place. TGs are stored in adipocytes as their main energy source.

therapeutics. As part of the continuing search for biologically active antiobesity agents from natural herbal resources, various plants have been screened for their antilipase activity. The review classifies these inhibitors into following chemical classes.

Saponins

Saponins are primary constituents of the roots and rhizomes of various plants. They are comprised sugars attached to a steroid or triterpene and are responsible for a diversity of biological effects. These types of plant secondary metabolites are found to inhibit PL and, thus, may represent potentially effective treatments for obesity and related disorders.

Platycodin saponins

In China and Korea, the fresh roots of *Platycodin grandiflorum* are consumed as pickles for preventing obesity. The saponin-rich fraction of *Platycodin grandiflorum* radix has been screened for its antiobesity effect and these effects correlate with inhibition of PL [28–32]. Among the various triterpenoidal saponins isolated, platycodin D **(1)** showed the strongest PL inhibitory activity in a competitive manner, with a K_i of 0.18 ± 0.03 mM [30].

Scabiosaponins

Scabiosa tschiliensis has long been used as herbal medicine for the treatment of headache, fever, cough and jaundice in Mongolia. Certain triterpenoid saponins, called scabiosaponins, isolated from the whole plant include scabiosaponin E **(2)**, scabiosaponin F **(3)**, scabiosaponin G **(4)**, scabiosaponin I **(5)**, hookeroside A **(6)**, hookeroside B **(7)** and prosapogenin 1b **(8)** and all exhibited strong inhibition of PL *in vitro*. Of these, **(8)** showed the strongest *in vitro* inhibitory activity at a concentration of 0.12 mg/ml which was similar to that produced by orlistat at a dose of 0.005 mg/ml [33].

Sessiloside and chiisanoside

Bioactive-guided fractionation of a saponin-rich fraction of the leaves of *Accanthopanax sessiliflorus* led to the isolation of the active lupane-type saponins, sessiloside **(9)** and chiisanoside **(10),** both of which showed strong inhibition of PL *in vitro*. Further, **(9)** and **(10)** inhibited lipase activity in a dose-dependent manner, and their IC_{50} values were 0.36 and 0.75 mg/ml, respectively [34].

Chikusetsusaponins

The rhizomes of *Panax japonicus* are used as a folk medicine for the treatment of lifestyle-related diseases, such as arteriosclerosis, hyperlipidemia, hypertension and non-insulin dependent diabetes mellitus as a substitute for ginseng roots in China and Japan. Total chikusetsusaponins isolated from *P. japonicus* have been shown to prevent high fat diet-induced increase in body weight and fat storage in adipose tissue by preventing intestinal absorption of

dietary fat via inhibition of PL activity. Chikusetsusaponin III **(11)**, chikusetsusaponin IV **(12)** and 28-deglucosyl-chikusetsusaponins IV **(13)** and 28-deglucosyl-chikusetsusaponins V **(14)** were isolated from the total saponin fraction and **(11)**, **(13)** and **(14)** were found to be active at concentrations of 125–500 μg/ml [35].

Dioscin and derivatives

Dioscin **(15)** isolated from methanol extract of *Dioscorea nipponica* powder was shown to inhibit PL with an IC_{50} of 20 μg/ml. Its aglycone, diosgenin **(16)**, was also found to be active, with an IC_{50} value of 28 μg/ml. Both **(15)** and **(16)** suppressed the time-dependant increase of plasma triglyceride concentration in mice injected with corn oil.

Other oleanan type of saponins isolated from the same plant viz. prosapogenin A (IC_{50} 1.8 μg/ml), prosapogenin C (IC_{50} 42.2 μg/ml), and gracillin **(17)** (IC_{50} 28.9 μg/ml) also showed a strong inhibition of PL *in vitro* [36].

Escins

A mixture of triterpene oligoglycosides (escins) from Japanese horsechestnut (*Aesculus turbinate*) and European horsechestnut seeds (*Aesculus hippocastanum*) have nutraceutical properties associated, potentially, with antidiabetic or anti-obesity effects. Detailed structure activity relationship (SAR) studies of escins and their derivatives deacetylescins and desacylescins, with respect to their PL inhibitory activity, demonstrated that the potency of these compounds was in the order of escins > desacylescins > deacetylescins. Escins Ib **(18)** (IC_{50} 24 μg/ml) and IIb **(19)** (IC_{50} 14 μg/ml) with angeloyl moieties were found to be more potent than escins Ia **(20)** (IC_{50} 48 μg/ml) and IIa **(21)** (IC_{50} 61 μg/ml) with tigloyl moieties. Escins also have inhibitory effect on the elevation of blood glucose in the order of escins > deacetylescins > desacylescins [37].

Teasaponins

Three kinds of tea, oolong, green and black, have been widely used for their purported health properties from ancient times all over the world, especially to prevent obesity and lipid metabolism. Of the three teas, oolong tea is traditionally reported to have anti-obesity and hypolipidemic actions. Teasaponins (a mixture of theasaponins E_1 and E_2) dose-dependently inhibited PL activity. The inhibition was found to be competitive and the K_m and V_{max} values of the lipase activity for lecithin-emulsified triolein were 1.42 mg/ml and 476.2 nkat/l respectively. The K_i value of teasaponin was determined to be 0.25 mg/ml [38,39].

Cyclocariosides

Cyclocariosides are dammarane type of triterpene saponins isolated from the leaves of *Cyclocarea paliurus*. The leaves of *C. paliurus* have been a food source for maritime people for a long time, and are known to have beneficial effects on health and used as a traditional remedy for prevention of hyperglycemia and diabetes mellitus. Three cyclocariosides viz. cyclocarioside A **(22)**, cyclocarioside II **(23)** and cyclocarioside III **(24)** have been isolated and demonstrated to exhibit an insulin-like activity in adipocytes, *in vitro* and *in vivo*. *C. paliurus* extract was shown to inhibit PL activity in a dose-dependent manner at an IC_{50} value of 9.1 mg/ml. The cyclocariosides are considered to be mainly responsible for these activities of the extract [40] (Figure 2).

Polyphenolics

It is well-known that polyphenols from plants have an affinity for proteins, primarily through hydrophobic, as well as hydrogen, bondings. Thus, hot water extracts of various plant materials could exhibit inhibitory activity for enzymes, because of aggregation of enzyme proteins [34,41]. Many polyphenolics such as flavones, flavonols, tannins and chalcones are active against PL. Luteolin **(25)**, a commonly occurring flavonoid, has been shown to be a weak inhibitor of PL [42]. 3-Methylether-ganglin **(26)** and Mangiferin **(27)** flavonoids obtained from rhizomes of *Alpinia officinarum* and from fruits of *Mangifera indica,* respectively, showed moderate inhibition of PL [43,44]. Hesperidin **(28)** isolated from the peels of *Citrus unshiu* inhibited PL with IC_{50} value of 32 μg/ml. Other flavonoids from the peel of, such as neohesperidin from same peel weakly inhibited the lipase, while narirutin and naringin did not show any activity [45].

Oolong tea polyphenols

Of the polyphenols identified from oolong tea, (−)-epigallocatechin 3,5-di-O-gallate **(29)** (IC_{50} 0.098 μM), prodelphinidin B-2 3,3′-di-O-gallate **(30)** (IC_{50} 0.107 μM), assamicain A **(31)** (IC_{50} 0.120 μM), oolonghomobisflavan A **(32)** (IC_{50} 0.048 μM), oolonghomobisflavan B **(33)** (IC_{50} 0.108 μM), theasinensin D **(34)** (IC_{50} 0.098 μM), oolongtheanin 3′-O-gallate **(35)** (IC_{50} 0.068 μM), theaflavin **(36)** (IC_{50} 0.106 μM), and theaflavin 3,3′-O-gallate **(37)** (IC_{50} 0.092 μM) showed the most potent PL inhibitory activities. Furthermore, detailed SAR studies suggested that functional galloyl moieties and the polymerization of flavan-3-ol were required for PL inhibition [46].

Polyphenol rich extracts

Grape seed extract (GSE)

Grape seed extract (GSE) is rich in bioactive phytochemicals and has inhibitory activity on PL and lipoprotein lipase, suggesting that it may be useful as a treatment to limit dietary fat absorption and the accumulation of fat in adipose tissue. Further, GSE was shown to decrease isoproterenol-stimulated lipolysis in 3T3-L1 adipocytes. The effect of GSE on lipases might be caused by a synergistic action of several compounds within the extract, viz. flavonoids, procyanidins and their antioxidative metabolites, rather than by a single compound. The results from several studies have indicated a lack of toxicity which supports the use of proanthocyanidin-rich extracts from grape seeds in various foods [47].

Nelumbo nucifera extract (NNE)

Blend tea or extract of leaf of *N. nucifera* has recently been used to treat obesity in China. Extracts of *N. nucifera* leaves (NNE) inhibited PL with an IC_{50} value of 0.46 mg/ml. The inhibitory activity was attributed to the phenolic constituents of the leaves. NNE is also thought to increase thermogenesis by increasing UCP3 expression [48].

Salacia reticulata hot water extract (SRHW)

The roots and stems of the plant *S. reticulata* have been used as a supplementary food in Japan to prevent obesity and diabetes. The

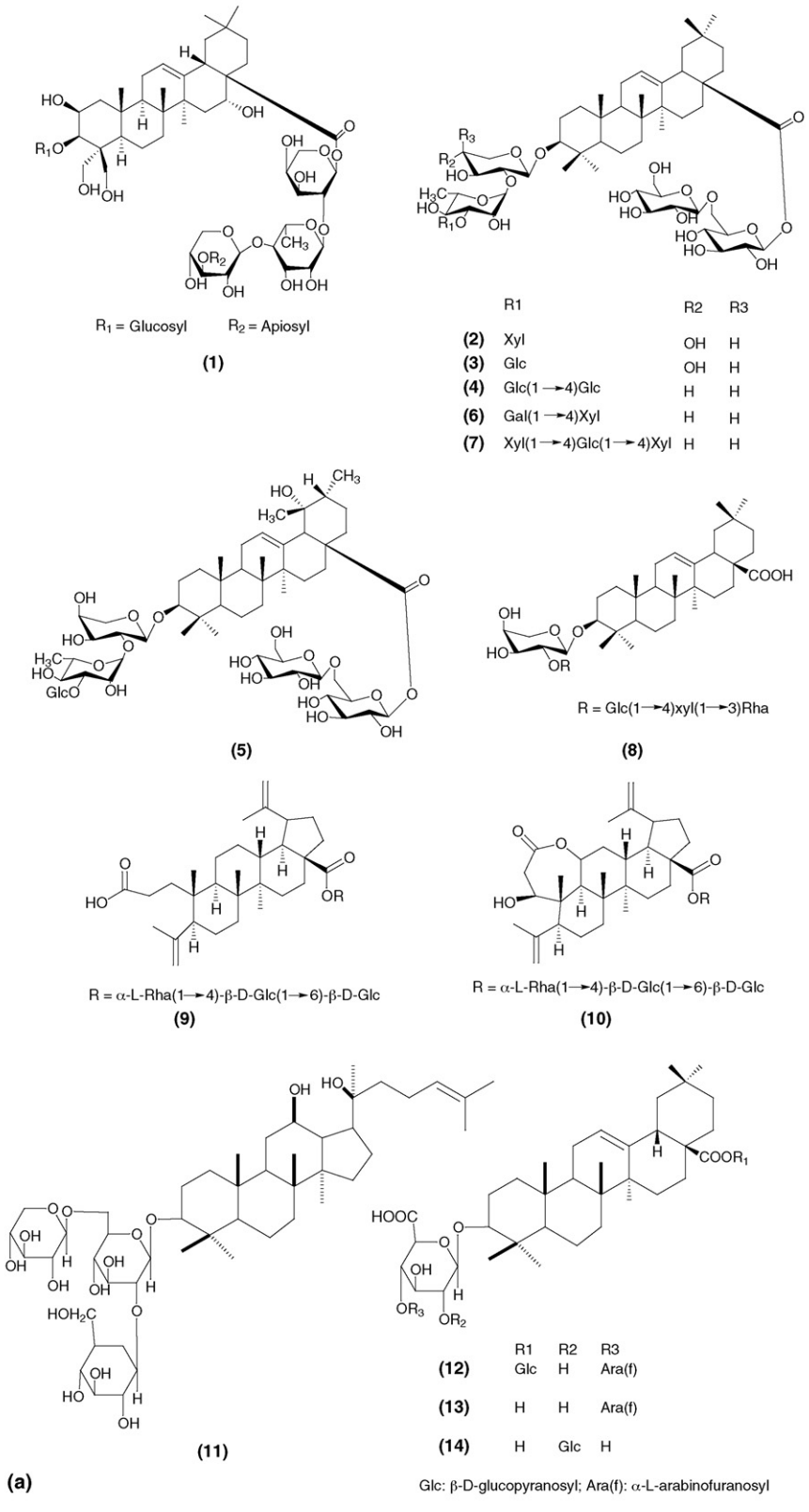

FIGURE 2

Structure of Saponins with pancreatic lipase inhibitory activity.

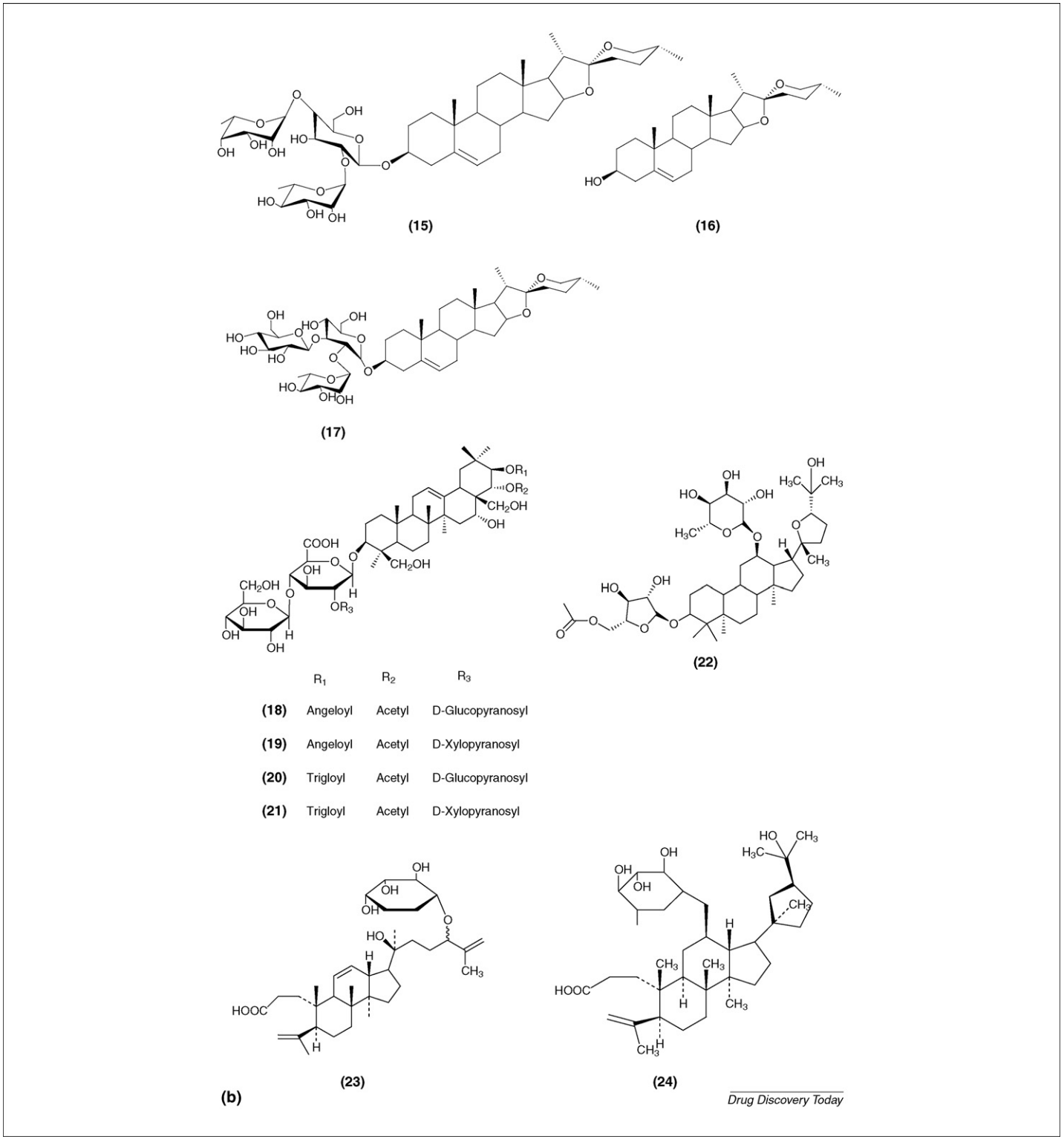

Figure 2. (*Continued*).

hot water extract of *S. reticulata* roots (SRHW) has been reported to inhibit PL in a concentration-dependent manner with an IC_{50} of 264 μg/ml. It was also shown to suppress body weight in *in vivo* rat antiobesity models. SRHW contained a high concentration of polyphenols (24%), including mangiferin, catechins and condensed tannins and were considered to be responsible for the inhibitory effect [41].

Peanut shell extract (PSE)

Arachis hypogaea or peanut shell extract has been reported to possess PL inhibitory activity. The extract also was shown to prevent body weight gain induced by high fat diet to male wistar rats. Peanut shell contained several bioactive molecules, such as luteolin, certain fatty acids, caffeic, ferulic and benzoic acids, all of which were reported to inhibit lipases. Coumarin derivatives and

flavonoid glycosides were also present and were assumed to be the major active constituents [49].

Mangifera indica leaf and stem bark extracts (ML and MSB)

M. indica, widely distributed in many tropical and sub-tropical regions is one of the most popular edible fruits in the world. Mango leaf and stem bark extracts possessed a variety of polyphenols, including phenolic acids, phenolic esters, flavan-3-ols and mangiferin and these extracts were found to be strong inhibitor of PL. These extracts also showed antiobesity effects in high fat diet-induced obesity models [44].

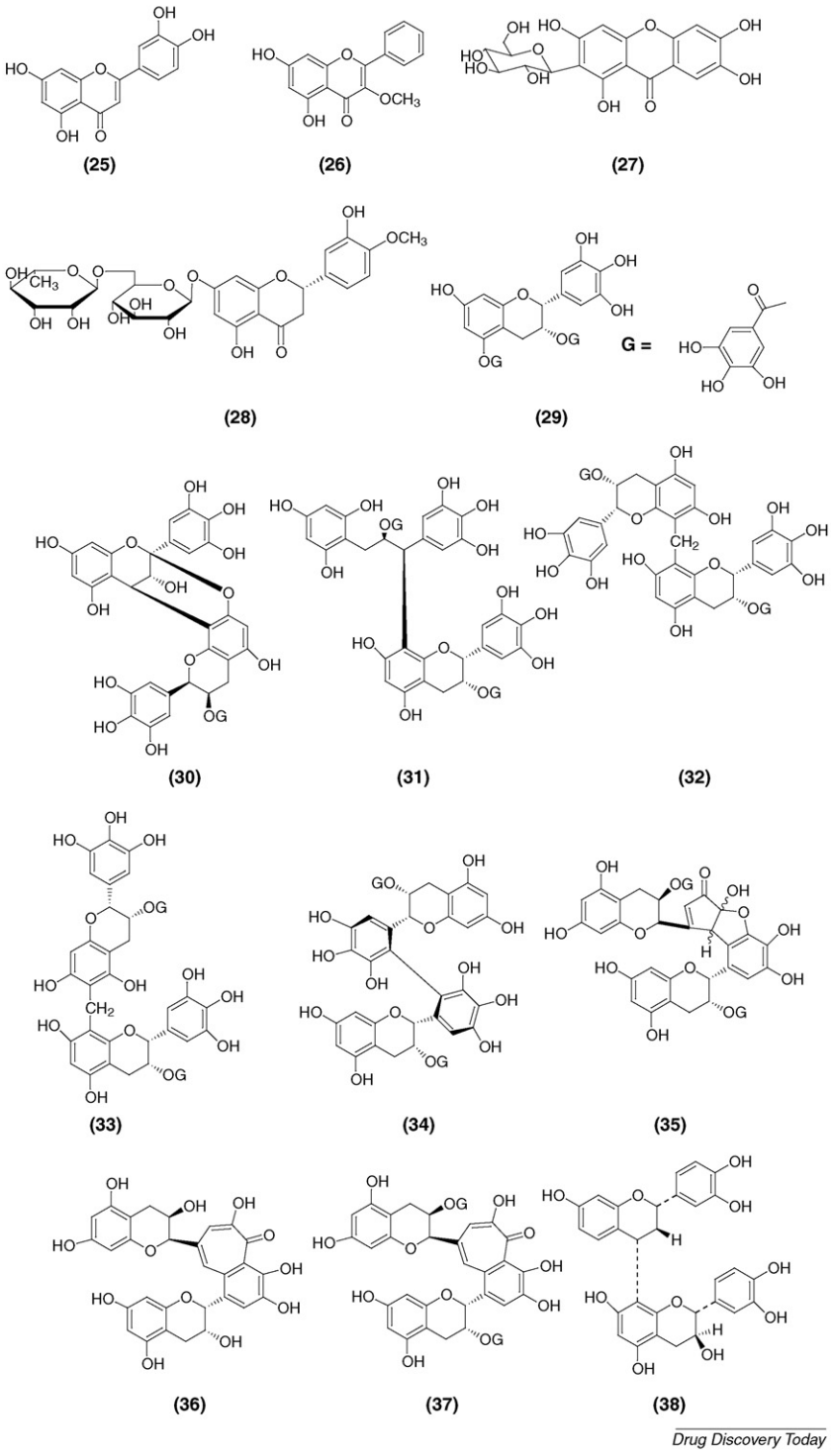

FIGURE 3

Structures of polyphenolic pancreatic lipase Inhibitors.

CT-II extract

CT-II, a proanthocyanidin rich fraction of the aqueous ethanol extract of *Cassia nomame* fruits, showed inhibitory effect on PL activity *in vitro* and also showed anti-obesity effects in rats fed with high-fat diet *in vivo*. CT-II inhibited porcine PL with an IC_{50} value of less than 0.1 mg/ml [42]**.** Further investigation of lipase-inhibiting substances in fruits revealed several constituents related to condensed tannins, among which (2S)-3′,4′,7-trihydroxyflavan-(4 $\alpha \rightarrow 8$)-catechin **(38)** showed the most potent inhibitory effect (IC_{50}, 5.5 μM) *in vitro* [50] (Figure 3).

Terpenes

Carnosic acid

Carnosic acid **(39)**, an abietan type of diterpene isolated from the methanolic extract of *Salvia officinalis* leaves that competitively inhibited PL in a concentration-dependant manner with an IC_{50} value of 12 μg/ml (36 μM) and a K_i of 5.4 μg/ml (16.1 μM). Further, carnosic acid was shown to suppress serum triglyceride elevation in olive oil-loaded mice and epididymal fat weight increase in high fat diet-fed mice. Bioactive-guided fractionation of *S. offcinalis* also led to the isolation of carnosol **(40)**, roylenoic acid **(41)** and 7-methoxyrosmanol **(42)** and a triterpene oleanolic acid **(43)**. All these compounds inhibited PL *in vitro* with an IC_{50} value of 4.4 μg/ml, 35 μg/ml 32 μg/ml and 83 μg/ml, respectively [51].

Crocin and crocetin

Crocin **(44)** a glycosylated carotenoid, major active constituents of *Gardenia jasminoids,* exhibited potent hypotriglyceridemic and hypocholesterolemic activities. Crocin competitively and reversibly inhibited PL at an IC_{50} of 28.63 μmol [52] and its metabolite crocetin **(45)** also potently inhibited PL. Crocin and crocetin also showed potent hypolipidemic activity in Triton WR-133 or corn-oil induced hyperlipidemic mice [53] (Figure 4).

Pancreatic lipase inhibitors from microbial sources

Many metabolic products from microorganisms have potent PL inhibitory activity. In the continued search of effective antiobesity agent several bacterial, fungal and marine species have been screened to find new compounds with PL inhibitory activity.

Lipstatin

Lipstatin **(46)**, a very potent inhibitor of PL was first isolated from *Streptomyces toxytricini*. The lipstatin molecule has an unusual β-lactone structure incorporated into a hydrocarbon backbone. Lipstatin irreversibly inhibited PL with an IC_{50} value of 0.14 μm and also dose-dependently inhibited the absorption of dietary triolein in mice. Lipase inhibitory activity was lost on opening of β-lactone ring. Crystalline tetrahydrolipstatin, the catalytic hydrogenation product of lipstatin, commonly known as orlistat is currently on the market as an antiobesity agent [54,55].

Panclicins

Panclicins are another class of potent PL inhibitors produced by *Streptomyces* sp. *NR 0619*. Panclicins too contain β-lactone structures with two alkyl chains, one of which has *N*-formylalanyloxy or *N*-formylglycyloxy substituent. Panclicins A **(47)** and B **(48)** are alanine type while panclicins C **(49)**, D **(50)** and E **(51)** are glycine type of compounds. All panclicins, dose-dependently inhibited porcine PL with IC_{50} values of 2.9, 2.6, 0.62, 0.66, and 0.89 μM, respectively. The inhibitory activity was attributed to the amino acid moiety, alanine-containing compounds being two to three-fold weaker than glycine-containing compounds [56,57].

Valilactone

Valilactone **(52)**, first isolated from shaken culture and jar fermentation of the strain MG147-CF2 from *Streptomyces albolongus,* potently inhibited hog PL with an IC_{50} of 0.14 ng/ml. It also

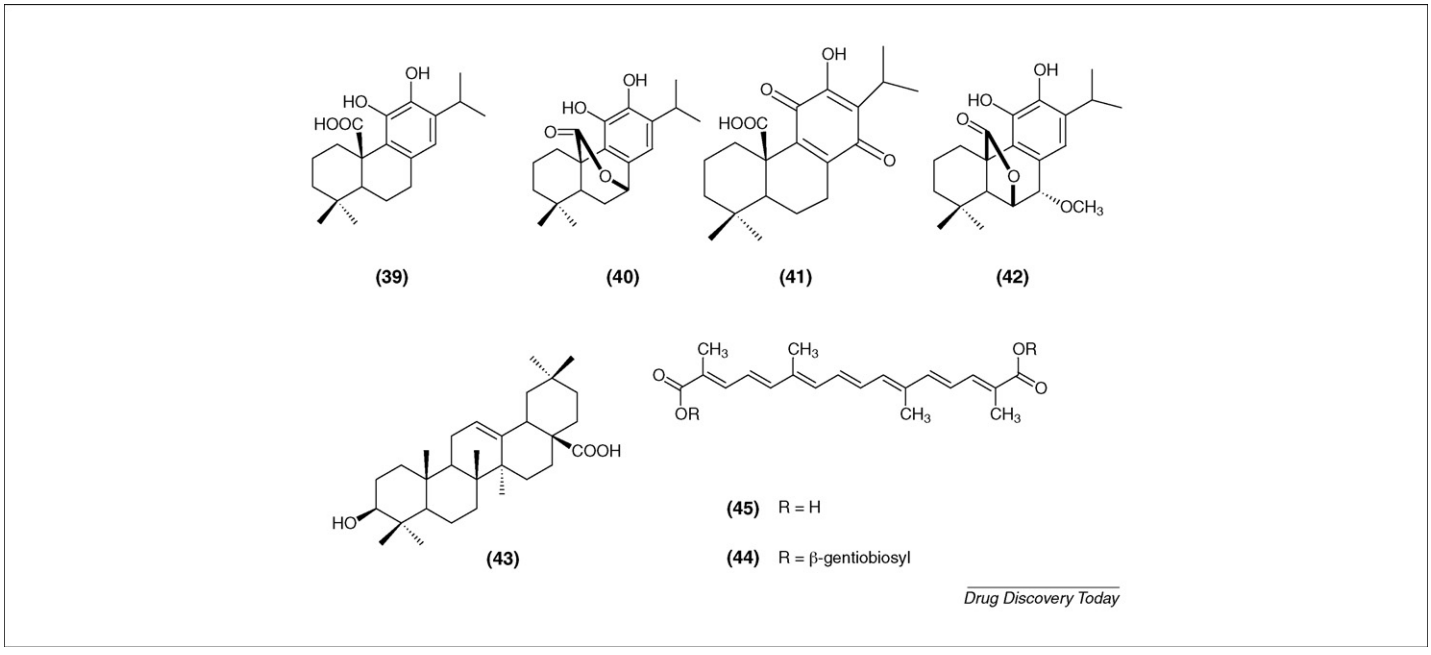

FIGURE 4

Structures of terpenoidal pancreatic lipase Inhibitors.

possessed esterase inhibitory activity and inhibited esterase from hog liver with an IC_{50} value of 0.029 μg/ml [58].

Ebelactones

Ebelactones are another type of microbial metabolite identified as inhibitors of PL and liver esterase. Two ebelactones, Ebelactone A **(53)** and B **(54)**, were isolated from the fermentation broth of actinomycetes strain G7-Gl, closely related to *Streptomyces aburaviensis*. Both **(53)** and **(54)** showed PL inhibitory activity with IC_{50} values of against hog PL are 3 ng/ml and 0.8 ng/ml, respectively. They also inhibited esterase from hog liver with an IC_{50} value of 0.056 μg/ml and 0.35 ng/ml, respectively [59].

Esterastin

Esterastin **(55)** was isolated from the fermentation broth of actinomycetes *Streptomyces lavendulae* strain MD4-C1. Esterastin competitively inhibited the hog pancreas lipase with IC_{50} value of 0.2 ng/ml [60].

Caulerpenyne

Caulerpenyne **(56)**, purified from an extract of *Caulerpa taxifolia* competitively inhibited lipase activity with IC_{50} values of 2 mM and 13 μM, using emulsified triolein and dispersed 4-methylumbelliferyl oleate as substrates, respectively. The inhibitory activity of caulerpenyne was dependent on the lipase concentration but independent of substrate concentration suggesting direct interaction with the lipase protein, rather than interacting with the substrate. Oral administration of corn oil with caulerpenyne to rats demonstrated a reduced and delayed peak plasma triacylglycerol concentration, suggesting its potential as a lipid absorption inhibitor [61].

Vibralactone

Vibralactone **(57)**, an unusual fused β-lactone-type metabolite of microfungi *Boreostereum virans,* covalently but reversibly modifies the active site serine of the enzyme via acylation by the β-lactone. The IC50 of the vibralactone was determined to be 0.4 μg/ml [62].

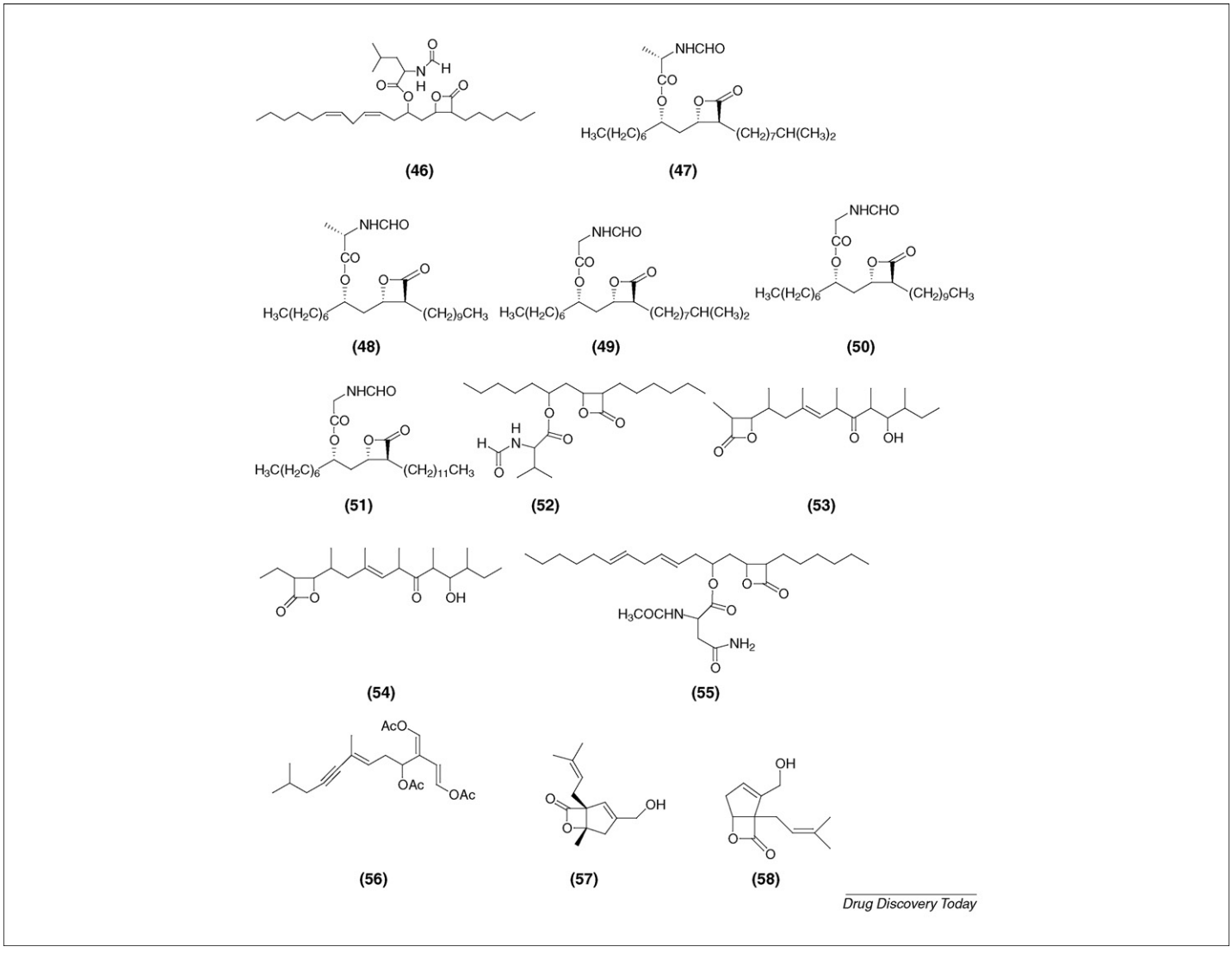

FIGURE 5

Pancreatic lipase inhibitors from microbial source.

Percyquinin

Percyquinin **(58)**, another β-lactone metabolite, obtained from the cultures of *Basidiomycete stereum complicatum,* ST 001837, inhibited PL with an IC_{50} of 2 μm [63].

In one study on β-lactone class of compounds, the stereochemistry (2S, 3S) of the β-lactone ring was found to impart specificity for the PL, while (2R, 3R) stereochemistry was responsible for inhibition of HMG-CoA synthase [64] (Figure 5).

Conclusion

Natural products identified from traditional medicinal plants and microbial sources have always presented an exciting opportunity for the development of new types of therapeutics. About half of all compounds that were successful in clinical trials during the past 20 years have, at least, been derived from natural origin. Despite this scenario, only orlistat, a semi-synthetic derivative of lipstatin (a natural product) is in clinical use and P57, an appetite suppressant, is in clinical trials for obesity. This clearly suggests that the rich potential of nature to combat obesity has not been fully explored yet and many newer leads may be obtained from the natural sources. Recent developments in understanding the pathophysiology of the disease process have opened up new avenues to identify and develop novel therapies to combat obesity, among these various enzymes involved in lipid metabolism provide interesting targets in the development of antiobesity agents. PL, the principle lipolytic enzyme, hydrolyses dietary fats in the first step of lipid metabolism. Orlistat is a potent, specific and irreversible inhibitor of PL. Thus, PL inhibitors may provide an answer to the ever-increasing problem of obesity. Many plants and microbial products have been screened for their PL inhibitory potential but the work has remained more of academic interest and nothing substantial has gone up to the clinical level. Thus, there is an urgent need to update the studies on the known inhibitors as well as to discover newer natural sources in detail to fully realize their potential on PL and focally develop them as new antiobesity therapeutics.

References

1 Cairns, E. (2005) Obesity: the fat lady sings? *Drug Discov. Today* 10, 305–307
2 Arbeeny, C.M. (2004) Addressing the unmet medical need for safe and effective weight loss therapies. *Obes. Res.* 12, 1191–1196
3 Harrold, J. *et al.* (2003) Neuroendocrine targets for the treatment of obesity: physiological roles and unrealized opportunities. *Curr. Med. Chem. Central Nerv. Syst. Agents* 3, 141–155
4 Foster-Schubert, K.E. and Cummings, D.E. (2006) Emerging therapeutic strategies for obesity. *Endocr. Rev.* 27, 779–793
5 Halford, J. *et al.* (2003) The psychopharmacology of appetite: targets for potential anti-obesity agents. *Curr. Med. Chem. Central Nerv. Syst. Agents* 3, 283–310
6 Bray, G.A. and Tartaglia, L.A. (2000) Medicinal strategies in the treatment of obesity. *Nature* 404, 672–677
7 Cooke, D. and Bloom, S. (2006) The obesity pipeline: current strategies in the development of anti-obesity drugs. *Nat. Rev. Drug Discov.* 5, 919–931
8 Halford, J. (2006) Obesity drugs in clinical development. *Curr. Opin. Investig. Drugs* 7, 312–318
9 Hofbauer, K.G. (2002) Molecular pathways to obesity. *Int. J. Obes.* 26, S18–S27
10 Das, S.K. and Chakrabarti, R. (2006) Antiobesity therapy: emerging drugs and targets. *Curr. Med. Chem.* 13, 1429–1460
11 Shi, Y. and Burn, P. (2004) Lipid metabolic enzymes: Emerging drug targets for the treatment of obesity. *Nat. Rev. Drug Discov.* 3, 695–710
12 Mancini, M.C. and Halpern, A. (2006) Investigational therapies in the treatment of obesity. *Expert Opin. Investig. Drugs* 15, 897–915
13 Melnikova, I. and Wages, D. (2006) Antiobesity therapies. *Nat. Rev. Drug Discov.* 5, 369–370
14 Marcini, M.C. and Halpern, A. (2006) Pharmacological treatment of obesity. *Arq. Bras. Endocrinol. Metab.* 50, 377–389
15 Szewczyk, J.R. and Sternbach, D.D. (2005) Combating obesity by targeting nuclear receptors. *Curr. Med. Chem. – Immun., Endoc. & Metab. Agents* 5, 73–84
16 Nisoli, E. and Carruba, M.O. (2004) Emerging aspects of pharmacotherapy for obesity and metabolic syndrome. *Pharmacol. Res.* 50, 453–469
17 Srivastava, R.K. and Srivastava, N. (2004) Search for obesity drugs: Targeting central and peripheral pathways. *Curr. Med. Chem. – Immun., Endoc. & Metab. Agents* 4, 75–90
18 Weigle, D.S. (2003) Pharmacological therapy of obesity: Past, present, and future. *J. Clin. Endocrinol. Metab.* 88, 2462–2469
19 Halpern, A. and Mancini, M.C. (2003) Treatment of obesity: an update on anti-obesity medications. *Obes. Rev.* 4, 25–42
20 Je'quier, E. (2002) Pathways to obesity. *In.t J. Obes.* 26, S12–S17
21 Hauner, H. (2001) Current pharmacological approaches to the treatment of obesity. *Int. J. Obes.* 25, S102–S106
22 Strader, C.D. *et al.* (1998) Novel molecular targets for the treatment of obesity. *Drug Discov. Today* 3, 250–256
23 Bhutani, K.K. *et al.* (2007) Potential antiobesity and lipid lowering natural products: a review. *Nat. Product Commun.* 2, 331–348
24 Mukherjee, M. (2003) Human digestive and metabolic lipases—a brief review. *J. Mol. Catal., B Enzym.* 22, 369–376
25 Thomson, A.B.R. *et al.* (1997) Inhibition of lipid absorption as an approach to the treatment of obesity. In *Methods in Enzymology* (Rubin, B. and Dennis, E.A., eds), pp. 3–41, Academic Press
26 Winkler, F.K. (1990) Structure of human pancreatic lipase. *Nature* 343, 771–774
27 Tilbeurgh, H.V. (1992) Structure of the pancreatic lipase-procolipase complex. *Nature* 359, 159–162
28 Han, L.K. *et al.* (2000) *Platycodi* Radix affects lipid metabolism in mice with high fat diet-induced obesity. *J. Nutr.* 130, 2760–2764
29 Han, L.K. *et al.* (2002) Saponins from *Platycodi* Radix ameliorate high fat diet-induced obesity in mice. *J. Nutr.* 132, 2241–2245
30 Zao, H.L. and Kim, Y.S. (2004) Determination of the kinetic properties of platycodin D for the inhibition of pancreatic lipase using a 1,2-diglyceride-based colorimetric assay. *Arch. Pharm. Res.* 27, 968–972
31 Xu, B.J. *et al.* (2005) *In vitro* inhibitory effect of triterpenoidal saponins from *Platycodi* Radix on pancreatic lipase. *Arch. Pharm. Res.* 28, 180–185
32 Zhao, H.L. *et al.* (2005) Antiobese and hypolipidemic effects of platycodin saponins in diet-induced obese rats: evidences for lipase inhibition and calorie intake restriction. *Int. J. Obes.* 29, 983–990
33 Zheng, Q. and Koike, K. *et al.* (2004) New biologically active triterpenoid saponins from *Scabiosa tschiliensis*. *J. Nat. Prod.* 67, 604–613
34 Yoshizumi, K. *et al.* (2006) Lupane type saponins from leaves of *Acanthopanax sessiliflorus* and their inhibitory activity on pancreatic lipase. *J. Agric. Food Chem.* 54, 335–341
35 Han, L.K. *et al.* (2005) Anti-obesity effects of chikusetsusaponins isolated from *Panax japonicus* rhizomes. *BMC Complement. Altern. Med.* 5, 9–18
36 Kwon, C.S. *et al.* (2003) Anti-obesity effects of *Dioscorea nipponica* Makino with lipase inhibitory activity in rodents. *Biosci. Biotechnol. Biochem.* 67, 1451–1456
37 Kimura, H. *et al.* (2006) Identification of novel saponins from edible seeds of Japanese horse chestnut (*Aesculus turbinata* Blume) after treatment with wooden ashes and their nutraceutical activity. *J. Pharm. Biomed. Anal.* 41, 1657–1665
38 Han, L.K. *et al.* (1999) Anti-obesity action of oolong tea. *Int. J. Obes.* 23, 98–105
39 Han, L.K. *et al.* (2001) Anti-obesity effects in rodents of dietary teasaponin, a lipase inhibitor. *Int. J. Obes.* 25, 1459–1464
40 Kurihara, H. (2003) Hypolipemic effect of *Cyclocarya paliurus* (Batal) Iljinskaja in lipid-loaded mice. *Biol. Pharm. Bull.* 26, 383–385
41 Masayuki, Y. *et al.* (2002) *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lypophilic activities have mild antiobesity effects in rats. *J. Nutr.* 132, 1819–1834
42 Yamamota, M. *et al.* (2000) Anti-obesity effects of lipase inhibitor CT-II, an extract from edible herbs, Nomame Herba, on rats fed a high-fat diet. *Int. J. Obes.* 24, 758–764
43 Shin, J.E. *et al.* (2002) 3-Methylethergalangin isolated from *Alpinia officinarum* inhibits pancreatic lipase. *Biol. Pharm. Bull.* 25, 1442–1445
44 Moreno, D. *et al.* (2006) Inhibition of lipid metabolic enzymes using *Mangifera indica* extracts. *J. Food Agric. Environ.* 4, 21–26

45 Kawaguchi, K. *et al.* (1997) Hesperidin as an inhibitor of lipases from porcine pancreas and Pseudomonas. *Biosci. Biotechnol. Biochem.* 61, 102–104
46 Nakai, M. *et al.* (2005) Inhibitory effects of oolong tea polyphenols on pancreatic lipase *in vitro*. *J. Agric. Food Chem.* 53, 4593–4598
47 Moreno, D.A. *et al.* (2003) Inhibitory effects of grape seed extract on lipases. *Nutrition* 19, 876–879
48 Ono, Y. *et al.* (2006) Anti-obesity effect of *Nelumbo nucifera* leaves extract in mice and rats. *J. Ethnopharmacol.* 106, 238–244
49 Moreno, D.A. *et al.* (2006) Effects of *Arachis hypogaea* nutshell extract on lipid metabolic enzymes and obesity parameters. *Life Sci.* 78, 2797–2803
50 Hatano, T. *et al.* (1997) Flavan dimers with lipase inhibitory activity from *Cassia nomame*. *Phytochemistry* 46, 893–900
51 Ninomiya, K. *et al.* (2004) Carnosic acid, a new class of lipid absorption inhibitor from sage. *Bioorg. Med. Chem. Lett.* 14, 1943–1946
52 Lee, I.A. *et al.* (2005) Antihyperlipidemic effect of crocin isolated from the fructus of *Gardenia jasminoides* and its metabolite crocetin. *Biol. Pharm. Bull.* 28, 2106–2110
53 Sheng, *et al.* (2006) Mechanism of hypolipidemic effect of crocin in rats: Crocin inhibits pancreatic lipase. *Eur. J. Pharmacol.* 543, 116–122
54 Weibel, E.K. *et al.* (1987) Lipstatin, an inhibitor of pancreatic lipase, produced by *Streptomyces toxytricini* I. Producing organism, fermentation, isolation and biological activity. *J. Antibiot.* XL, 1081–1085
55 Hochuli, E. *et al.* (1987) Lipstatin, an inhibitor of pancreatic lipase, produced by *Streptomyces toxytricini* II. Chemistry and structure elucidation. *J. Antibiot.* XL, 1086–1091
56 Mutoh, M. *et al.* (1994) Panclicins, novel pancreatic lipase inhibitors I. Taxonomy, fermentation, isolation and biological activity. *J. Antibiot.* 47, 1369–1375
57 Yoshinari, K. *et al.* (1994) Panclicins, novel pancreatic lipase inhibitors II. Structural elucidation. *J. Antibiot.* 47, 1376–1384
58 Kltahara, M. *et al.* (1987) Valilactone, an inhibitor of esterase, produced by actinomycetes. *J. Antibiot.* XL, 1647–1650
59 Umezawa, H. *et al.* (1980) Ebelactone, an inhibitor of esterase, produced by actinomycetes. *J. Antibiot.* XXXIII, 1594–1596
60 Umezawa, H. *et al.* (1978) Esterastin, an inhibitors of esterase produced by actinomycetes. *J. Antibiot.* XXXI, 639–641
61 Tomoda, H. *et al.* (2002) Microbial metabolites with inhibitory activity against lipid metabolism. *Proc. Japan Acad.* 78, 217–240
62 Dong-Ze, L. *et al.* (2006) Vibralactone: a lipase inhibitor with an unusual fused-lactone produced by cultures of the *Basidiomycete Boreostereum vibrans*. *Org. Lett.* 8, 5749–5752
63 Cordula, H. *et al.* Aventis Pharma. Percyquinnin, a process for its production and its use as a pharmaceutical, 6596518.
64 Bitoua, N. *et al.* (1999) Screening of lipase inhibitors from marine algae. *Lipids* 34, 441–445