Natural Polyphenol-Rich Inhibitors of Pancreatic Lipase for Obesity Management – A Systematic Review

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Abstract

Background: Obesity, a critical public health challenge, is associated with an increased risk of chronic diseases such as cardiovascular disease, diabetes, and cancer. Body mass index (BMI) categorizes obesity levels, with trends indicating a growing prevalence worldwide. Dietary choices and sedentary lifestyles contribute significantly to this condition, yet treatments remain limited by side effects. Pancreatic lipase, the primary enzyme in dietary fat digestion, presents a promising target for obesity management. Inhibitors of pancreatic lipase reduce fat absorption, lowering caloric intake and aiding in weight management. Synthetic inhibitors like orlistat are effective but lead to adverse gastrointestinal and systemic effects, creating a demand for safer alternatives. Methods: A thorough literature review was conducted using PubMed, Elsevier, ScienceDirect, and Google Scholar databases, employing search terms such as "herbal drugs," "polyphenols," "pancreatic lipase inhibitors," "antilipase," "natural products," and "antiobesity herbal drugs." Discussion and Conclusion: Polyphenol-rich plants such as Camellia sinensis (tea), Coffea (coffee), Punica granatum (pomegranate), Vitis vinifera (grape), and Curcuma longa (turmeric) exhibit natural pancreatic lipase inhibitory properties, offering therapeutic potential for obesity management. This review explores the bioactive compounds in these plants, emphasizing their efficacy and minimal side effects compared to synthetic drugs, and underscores the importance of further research in developing natural, polyphenol-based treatments for obesity.

Keywords: Polyphenols, Pancreatic lipase inhibitors, Obesity, Fat absorption, Plant-based therapy

Significance | This review discusses the plant-derived pancreatic lipase inhibitors as potential for natural, effective obesity management, reducing fat absorption and promoting metabolic health.

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Introduction

Obesity is defined by the World Health Organisation (WHO) as an abnormal or excessive deposition of fat in adipose tissue to the level that health may be negatively impacted. (Bays and Dujovne, 2002). Obesity and overweight are measured by Body Mass Index (BMI). People with a BMI lesser than 18.5 kg/m^2 are known as underweight (Cheah, 1996). A BMI of more than 25 to 29.9 specifies overweight, a BMI of 30 or more than 30 is known as obesity. In severe cases, additional classifications are made based on BMI categories that define the levels of obesity: 30 to 34.9 is considered obese Grade I; 35 to 39.9 is considered obese Grade II; and 40 or higher is considered obese Grade III (Tan, 2004; Ryan et al., 2013; Haase et al., 2020). If present trends persist, estimates suggest that by 2030, 38% of adult people worldwide will be overweight, and an additional 20% will be obese (Gill, 2006; Kelly et al., 2008; Hruby A, Hu, 2015).

Obesity has emerged as a constantly spreading public health issue around the world, alongside diabetes, hypertension, and cancer. It is commonly known that obesity raises the risk of several acute and long-term illnesses, such as dyslipidemia, cardiovascular disease,

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and type 2 diabetes. Epidemiological studies establish a strong correlation between obesity and a higher risk of developing several types of cancer. In particular, being overweight is linked to an increased risk of developing certain cancers, such as postmenopausal breast cancer, endometrial cancer, esophageal cancer, pancreatic cancer, colorectal cancer, and kidney cancer. This link emphasizes how crucial it is to control obesity to lower the risk of cancer possibly (Vincent et al., 2019; Koene et al., 2016; Masoudkabir et al., 2023). Contributing factors include poor diet, physical inactivity, genetic predisposition, and environmental influences. The chance of developing these disorders can be considerably decreased by eating a balanced diet, getting regular exercise, and seeking medical attention when needed (Haase et al., 2020; Smith et al., 2020; Safaei et al., 2021).

2. Role of Pancreatic Lipase in Fat Digestion

Excess calories are produced by consuming oil and fats in daily diet. Dietary lipids are a significant source of excess calories, making lipid metabolism crucial in regulating energy balance and maintaining overall energy homeostasis (Martin et al., 2015; Dechakhamphu and Wongchum, 2015). Adverse diseases such as atherosclerosis, hypertension, diabetes, and organ failure can arise from obesity or hyperlipidaemia, which disrupt this balance. Potential treatment options for these medical conditions encompass a therapeutic approach to identify, characterize, and target the enzymes involved in lipid metabolism (Sukhdev and Singh, 2013). Dietary triglycerides are broken down by PL into free fatty acids and absorbable monoglycerides. To hinder the effective breakdown of triglycerides, pancreatic lipase inhibitors attach to this enzyme, obstructing its active site or changing its structure. As a result, the triglycerides remain in their original, larger form, which the intestines cannot easily absorb. These unabsorbed fats are then excreted from the body, leading to reduced fat absorption and, consequently, a decrease in caloric intake from fats. This mechanism is beneficial in managing obesity, as it helps lower the overall fat and calorie absorption from the diet.

3. Mechanism of Action of Pancreatic Lipase Inhibitors

Triglycerides must be hydrolyzed into free fatty acids and monoglycerides for the intestinal lumen to be able to absorb dietary fat. Both of these are generated by pancreatic acinar cells due to the digesting enzyme pancreatic lipase. For maintaining overall health, Dietary lipids must be actively digested and absorbed, as these processes provide essential fatty acids and energy required for various physiological functions (Singh, 2022). Pancreatic lipase, the key enzyme involved in lipid digestion, hydrolyzes dietary triglycerides by removing fatty acids from the α and α' positions. This results in the formation of β-monoglyceride and long-chain fatty acids, both saturated and polyunsaturated. Inhibiting this enzyme could be a promising method for combating obesity. (Du et al., 2018; Thomas et al., 2012; Lunagariya et al., 2014).

4. The Need for Natural Pancreatic Lipase Inhibitors

Orlistat is a natural lipase inhibitor originally derived from the bacterium *Streptomyces toxytricini*. It is a synthetic derivative of lipstatin. It works by reducing the absorption of dietary fat in the digestive system (Weibel et al., 1987). The drug works in the gastrointestinal lumen by forming a covalent bond with the active serine sites of pancreatic and gastric lipases. By effectively blocking these enzymes, orlistat stops ingested fat from being broken down into absorbable monoglycerides and free fatty acids (Heck et al., 2000). Orlistat is associated with adverse effects such as low bioavailability and Oily spotting, liquid stools, incontinence or urgency of faeces, flatulence, and cramps in the abdomen are examples of gastrointestinal problems (Dragano et al., 2020). According to various reports, orlistat may cause serious liver side effects such as subacute liver failure, cholelithiasis, and cholestatic hepatitis (Filippatos et al., 2008). Vitamins A, E, D, and K that are fat-soluble may be less readily absorbed when using orlistat. To mitigate this, it is recommended to consume a daily multivitamin supplement to guarantee sufficient consumption of these vital minerals (McDuffie et al., 2002; Scheen et al., 2006; Padwal and Majumdar, 2007).

Many herbal drugs exhibit anti-pancreatic lipase activity, which can have beneficial effects on the human body, particularly in the context of managing overweight and obesity. Blocking pancreatic lipase can significantly limit fat absorption and decrease overall calorie intake, providing an effective approach to managing weight and reducing obesity by preventing the breakdown and assimilation of dietary fats in the digestive system (Zhou et al., 2021). The mechanism of pancreatic lipase inhibition is mostly used to identify new drugs and drug molecules for obesity management (Lunagariya et al., 2014). By inhibiting this enzyme, herbal drugs can reduce the amount of fat absorbed by the intestines, leading to lower calorie intake and supporting weight management (Zhou et al., 2021; Su et al., 2020). In efforts to discover natural products that can help combat obesity, researchers have increasingly focused on identifying new inhibitors of pancreatic lipase with less unwanted side effects (Liu et al., 2020; Rajan et al., 2020; Kim et al., 2016; Seyedan et al., 2015). This review explores the potential of polyphenol-rich plants that have been studied for their PL inhibitory activity. It explores how these plant polyphenols might help to overall controlling weight and metabolic health by decreasing fat digestion and possibly providing therapeutic benefits (Table 1; Figure 1).

5. Dietary Polyphenols as Pancreatic Lipase Inhibitor

Polyphenols are a very well-distributed group of naturally occurring compounds that can be obtained from plant foods like vegetables, fruits, spices, berries, tea, coffee, chocolates, and wines. Polyphenols include phenolic acids, flavonoids, tannic acid, Stilbenes, and Lignans. The pancreatic lipase inhibitory activity of plants containing polyphenols has been extensively studied to determine the potential alternative of orlistat and their efficacy as anti-obesity agents (Seyedan et al., 2015). Various bioactive constituents including polyphenols have demonstrated pancreatic lipase inhibitory activity, including polyphenols from the leaves of *Camellia sinensis* (Tea) and the seeds of grapes (*Vitis vinifera*); flavonoids from various species of citrus fruits; saponins from fenugreek (*Trigonella foenum-graecum*) and ginseng (*Panax ginseng*); and alkaloids like berberine from *Berberis aristata*. In this review, I am focusing on polyphenols containing plants with pancreatic lipase inhibitory activities used in managing overweight and obesity.

5.1. Tea (Camellia sinensis)

Tea, or Camellia sinensis, is an extremely common drink from the Theaceae family that is enjoyed throughout the world. The major catechins included epicatechin, epigallocatechin, epigallocatechin gallate, and epicatechin gallate (Koo and Noh, 2007). Other polyphenols included in tea include kaempferol-3-O-glucoside (kaempferol-3-G), gallic acid, chlorogenic acid, ellagic acid, galloylquinic acid, and a variety of flavonoids (Tang et al., 2019). In a study, Theophylline extracted from Fu Brick Tea showed a significant pancreatic lipase inhibitory activity (IC_{50} of 1.02~0.03 μg/mL) and had a high impact on the metabolism of preadipocytes and reduced body fat in mice. It effectively reduced the degree of fatty liver, prevented liver fibrosis and fat accumulation, and improved the damage to mitochondrial membrane structure (Liu et al., 2022). According to Juhel et al., a green tea extract (60 mg/g) considerably reduced the activities of pancreatic and gastric lipase by stopping fat from emulsifying in the presence of bile acids (Juhel et al., 2000). The mixture of catechins (enriched in epigallocatechin gallate (EGCG) and epigallocatechin (ECG)) demonstrated *in-vitro* antilipase actions directly related to doses. It also decreased the postprandial rise in serum triglyceride levels (Ikeda et al., 2005; (Koo and Noh, 2007; Jian et al., 2022).

Theaflavin-3,3′-digallate, theaflavin-3′-gallate, theaflavin-3-gallate, and theaflavin from black tea (*Camellia sinensis*) have been shown to inhibit PL with IC50 values of 1.9, 4.2, 3.0, and greater than 10 μmol/L, respectively (Glisan et al., 2017). Qingzhuan tea, a significant Chinese dark tea primarily produced in Hubei province, has traditionally been consumed in regions with high-fat and high-calorie diets, including Mongolia, Xinjiang, Qinghai, and Gansu provinces in China (Liu et al., 2017). Research has demonstrated that this tea has more than ten polyphenols, amino acids, and caffeine. It significantly inhibited pancreatic lipase and decreased the fatty acids and triglycerides absorption in the intestines (Feng et al., 2020; Yuda et al, 2012). *In-vitro*, studies have demonstrated the efficacious antilipase activity by strictinin, a bioactive substance belonging to the ellagitannin family of hydrolyzable tannins. Strictinin-rich both the extracts of white tea showed the inhibition of PL at the IC_{50} value of 22 μg per mL while the IC_{50} value of green tea extracts was 35 μg/mL, respectively (Gondoin et al., 2010). Similarly, strictinin extracted from Pu'er Tea (*Camellia sinensis*) showed anti-obesity activities by Inhibiting PL in mice (Chen et al., 2018). Pan et al. (2016) reported that pancreatic lipase activity was reduced in vitro by black tea extract and polyphenols, with IC50 values equal to 15.5 mg/mL and 36.4 mg/mL, respectively (Pan et al., 2016).

5.2. Coffee

Coffee is a beverage made from roasted and ground seeds of the *Coffea* plant (Rubiaceae) and is among the most widely consumed drinks daily, alongside tea. It produces a stimulating effect on the human body because of the presence of caffeine. Apart from caffeine, it also contains many bioactive compounds that have various beneficial effects on the human body. These compounds include flavonoids such as catechins, epicatechin, epicatechin Gallate, anthocyanins, various acids like chlorogenic, caffeic, ferulic, gallic, and protocatechuic acids, as well as rutin (Tylewicz et al., 2018). The ethyl acetate fraction of coffee leaves (enriched in 3,5-dicaffeoylquinic acid, epicatechin, and isoquercetin, 146.50, 87.51, and 48.29 mg/g, respectively) demonstrated pancreatic lipase inhibitory action, with an inhibitor constant (Ki) of 0.185 mg/mL and an IC_{50} of 0.469 mg/mL. The results of the study indicated that by inhibiting lipase, catechin derivatives present in coffee leaves play a vital role in controlling obesity (Cao et al., 2024). A study revealed that coffee's total phenolic content varied from 168.21 to 397.38 mg chlorogenic acid equivalent per milliliter. Caffeic acid was the primary bioactive phenolic compound, with 5-caffeoylquinic acid also present. The IC_{50} values for pancreatic lipase inhibition ranged from 222 to 3035.8 μg/mL. The research concluded that coffee beverages, particularly those that are decaffeinated or contain added milk, have a more pronounced inhibitory effect on pancreatic lipase (Soares et al., 2022).

Methylxanthines such as caffeine, theobromine, and theophylline, widely consumed in tea and coffee, inhibit human pancreatic lipase's hydrolysis of triglycerides tributyrin and tripalmitate in a dose-dependent manner. Caffeine achieved maximum inhibition of 25.74% for tripalmitate and 79.54% for tributyrin, while 29.89% and 62.79% with theophylline; and 21.08% and 67.74% with theobromine. (Wikiera et al., 2012).

Inhibiting gastrointestinal lipolysis was shown to be most successful with gomchui (*Ligularia fischeri*) tea, whereas green tea was least effective, according to a study on the pancreatic lipase inhibitory qualities of this polyphenol-rich tea (Cha et al., 2012). A

decaffeinated extract of green coffee beans exhibited PL inhibitory activity at the level of IC_{50} of 1.98 mg/mL. Different chlorogenic acids (caffeoylquinic, dicaffeoylquinic, and feruloylquinic acids along with their three isomers each) present in decaffeinated green coffee bean extract contributed 91.8% of this inhibitory effect (Narita et al., 2012).

5.3. Pomegranate

The pomegranate, or *Punica granatum* L., a deciduous shrub that bears fruit and belongs to the Lytheraceae family, is a versatile food and medicinal plant that has been shown to have numerous health advantages. Every component of the fruit, including the peel, juice, roots, bark, seeds, flowers, and leaves, has a variety of bioactive molecules that have impacts on the heart, blood sugar, and obesity along with anti-inflammatory and antioxidant properties (Laurindo et al., 2024). Various phytoconstituents like alkaloids, anthocyanidins, proanthocyanidins, tannins, flavonoids, phenolics, ellagitannin, punicalagin, ellagic acid, vitamins and minerals, steroids, volatile oils and terpenoids, lignan and ascorbic acid (Vitamin C) have been isolated from *PG* (Maphetu et al., 2022; Rahmani et al., 2017). The ethanolic extract of PG fruit peel was identified as the most effective lipase inhibitor, exhibiting an IC_{50} value of 603.50 µg/mL (Mayasankaravalli et al., 2020). PG peel extracts from the Tunisian cultivar, both methanolic and ethanolic, showed an inhibitory effect on PL. This action is due to large concentrations of flavonoids and phenolic chemicals, specifically gallic acid, ellagic acid, mannogalloylhexoside, and chlorogenic acid (Hadrich, et al., 2014). The PG leaf extract and its isolated compounds (ellagic acid and tannic acid) showed anti-obesity activities by inhibiting pancreatic lipase and suppressing energy intake in HFD-induced obese mice (Lei et al., 2007). The potential of 13 freeze-dried extracts with high concentrations of anthocyanins from Mediterranean sources, including blood orange, pomegranate, blackberry, mulberry, citrus leaves, different vegetables, legume seeds, black rice, and its hull, was assessed for their PL inhibitory activity. The highest concentration of anthocyanin and potent inhibition of PL was found in blood orange and pomegranate (Fabroni et al., 2016).

5.4. Vitis vinifera (Grape Seed)

Vitis vinifera (VV) is a popular grape species in the Vitaceae family that belongs to the genus Vitis. There are seedless and non-seedless cultivars of *VV*, as well as red, black, and white types (Parihar and Sharma, 2022). Proanthocyanidins, procyanidins, aromatic acids, flavonoids, polyphenols, anthocyanins, phenolic compounds, and stilbenoids, such as the stilbene derivative resveratrol, are the primary phytochemical components of VV. Grapevines contain a variety of nutritional components, including minerals, vitamins, lipids, proteins, and carbs. (Insanu et al., 2021; Nassiri-Asl, M., & Hosseinzadeh, 2009; 2016). *VV* leaf extract significantly inhibited pancreatic lipase activity by decreasing obesity-related parameters such as body weight and fat accumulation reduction and decrease in cholesterol, LDL, and TGs levels compared to mice fed with the high-fat diet. It was suggested that antiobesity activity may be mediated by the NPY and FGF15-mediated pathway to control energy metabolism and body weight gain (Meng et al., 2021). Ten plants and orlistat were compared for their anti-lipase activity using a UV-visible spectrophotometer and porcine pancreatic lipase inhibitory test. *VV* ((IC_{50} 14.13 mcg/ml) and *Rhus coriaria* (IC_{50}19.95 mcg/mL) showed the strongest anti-lipase potential in comparison to other remaining plants. PL inhibitory activity of *VV* was found to be comparable with orlistat (IC_{50} 12.38 mcg/mL) (Jaradat et al., 2017). Ethanolic *VV* extract which is rich in bioactive phytochemicals inhibits pancreatic and lipoprotein lipase, potentially reducing fat absorption and adipose. Additionally, it reduces 3T3-L1 cells' intracellular lipolytic activity, which may lower circulatory free fatty acid levels that have been associated with insulin resistance in obese people (Moreno et al., 2003). Seven stilbenoids, namely wilsonol C, heyneanol A, ampelopsin A, pallidol A, cis-piceid, trans-piceid, and trans-resveratrol were separated from the water-methanolic extract of *VV* roots and assessed for antilipase activity. Among seven compounds, wilsonol C showed a strong PL inhibition having an IC_{50} value of 6.7 ± 0.7 µM (Kim et al., 2014). Further studies on various components of VV can be found in the literature. These investigations provide detailed insights into different aspects of VV, contributing to a comprehensive understanding of its multifaceted nature. (Magaña-Rodríguez et al., 2023; Dwibedi et al., 2022).

5.5. Curcuma longa (Turmeric)

Curcuma longa Linn. (CL), commonly known as turmeric, comes in the ginger family, Zingiberaceae. It is widely used for various biological activities related to the protection of the liver, heart, immunity, brain, and skin. It showed antimicrobial, antiallergic, antioxidant, anti-inflammatory, antidermatophytic, and antidepressant activities (Fuloria et al., 2022). Commercial Curcumin, a main bioactive polyphenolic compound, is a combination of curcuminoids that contains roughly 77% curcumin, 18% demethoxycurcumin, and 3% bisdemethoxycurcumin (Tung et al., 2019). Turmeric is an essential spice in Indian and Asian cuisines, known for its rich flavor and bright yellow color, which enhances curries and other dishes. India, the largest producer of turmeric, dominates global production with extensive farming, contributing significantly to its availability and quality worldwide (Kotha and Luthria, 2019). Curcuminoids and hexane extract of *CL* showed the inhibitory activities of lipase enzymes and it was also suggested *CL* and curcuminoids may be used to prevent obesity and obesity-associated comorbidities (Jaradat et al., 2021; Khatlawala and Roghelia, 2023). Computer-aided drug design virtual assays were used to evaluate curcumin derivatives for pharmacokinetics and pancreatic lipase inhibition. Among 19 synthesized curcumin

derivatives, two derivatives namely, 1,7-bis-(4-hydroxyphenyl)-heptane-3,5-dione and 1,7-bis-(4-hydroxy-3-methoxyphenyl)-heptane-3,5-dione exhibited superior lipase inhibitory activity than curcumin (IC_{50} = 42.83 μM; 98.62 μM, respectively) (Jing et al., 2024). PL inhibitory activity was tested in the hydroalcoholic and aqueous extracts of 63 Chinese dietary herbs in which 4 herbs namely, lotus (*Nelumbo nucifera)*, *Curcuma longa*, black pepper (*Piper longum)*, and mulberry (*Morus alba*) showed prominent antilipase activity at IC_{50} of 28.00, 5.24, 14.76, and 4.78 mg/L, respectively (Sun et al., 2012). γ-Ray irradiation of curcumin, a yellow dietary diarylheptanoid produced two new γ-lactones, curculactones A and B, four known compounds. Phenylpropanoids, erythro-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol and, threo-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol showed significantly improved pancreatic lipase inhibition compared to curcumin (Kim et al., 2011). A recent study screened potent PL inhibitors from 20 herbal foods, results showed that turmeric had the strongest PL-inhibitory activity due to the presence of curcumin, demethoxycurcumin, and bisdemethoxycurcumin (IC_{50} = 0.52 ± 0.04, 1.12 ± 0.05, and 3.30 ± 0.08 mg/mL, respectively (He et al., 2024).

5.6. Citrus Fruits

The Rutaceae family, which includes citrus fruits, is renowned for having a wide range of nutritional value. In addition to imparting flavour (enhancers), they are rich in non-nutrient components that are critical nutrients. Rich in flavonoids, limonoids, coumarins, terpenoids, and carotenoids, citrus fruits are significant health-promoting fruits. (Kaur & Kaur, 2015), linked to a variety of disease-preventive qualities, including heart-protective, lipid-lowering, and anticancer benefits (Matheyambath et al., 2016). Lemon (*Citrus limon*), orange (*Citrus sinensis*), grapefruit (*Citrus paradisi*), shaddock (*Citrus maxima*), tangerine (*Citrus reticulata*), citron (*Citrus medica*), mandarins (e.g. *Citrus reticulata*, *Citrus delicia*, *Citrus clementina*, *Citrus unshiu*, and *Citrus nobilis*), limes (e.g. *Citrus latifolia*, *Citrus aurantifolia* and *Citrus limettioides*) and bitter oranges (*Citrus aurantium*) are commonly known popular citrus varieties (Aydeniz-Guneser and Guneser, 2020; Pereira Gonzatto and Scherer Santos, 2023). *C. unshiu* leaves (MeOH extract) showed anti-lipase activity with an IC_{50} value equal to 44 μg/mL. In contrast, further fractionation of methanolic extract showed presence of bioactive compounds namely, nobiletin (IC50 108 μM), rutin (IC50 258 μM), and hesperidin showed pancreatic lipase inhibitory activity (Itoh et al., 2019). The peel extract of *Citrus unshiu* showed potent inhibition of PL in high-fat diet-fed mice, with an IC50 of 507.01 μg/mL. This suggests PCM is a promising anti-obesity treatment by reducing fat absorption through pancreatic lipase inhibition (Kim et al., 2016).

Among the five flavonoids namely hesperidin, neohesperidin, naringin, narirutin, and eriocitrin present in citrus peel extracts, hesperidin was found to be the most active PL inhibitor (Huang et al., 2020). The PL inhibitory activity of tangeretin and nobiletin and their acidic derivatives, 5-demethyl tangeretin and 5-demethyl nobiletin was evaluated using spectroscopical analysis and molecular dyanamics studies. Nobiletin exhibited the strongest inhibition (IC50 = 3.60 μM) compared to the other three polymethoxylated flavones. Nobiletin holds promise as a lipase inhibitor due to its distinctive flavone skeleton structure, which may contribute to its effectiveness in reducing lipase activity. (Huang et al., 2020a). Ultrasonic homogenization with antisolvent precipitation yielded ultrafine nobiletin particles (521.02 nm) from DMSO and deionized water. These particles inhibited pig pancreatic lipase more effectively than raw samples, with unchanged chemical characteristics but decreased crystallinity, improving the potential therapeutic applications of nobiletin (Zhang et al., 2024).

The fruit of *Citrus medica* L. var. *sarcodactylis* Swingle used traditionally and as food, yielded six new (3'→7″)-biflavonoids and twelve known biflavonoids. The first three (3'→7″)-biflavonoids showed moderate PL inhibition with IC50 =f 68.56 ± 1.40%; 56.18 ± 1.57%, 53.51 ± 1.59%, respectively. Polysaccharides containing pectin isolated from four citrus membranes, with high molecular weight fractions (>300,000) effectively inhibited pancreatic lipase, due to the presence of galacturonic acid, outperforming commercial pectin. The data showed support that citrus pectin might be useful for overweight and obesity (Edashige et al., 2008; Tsujita et al., 2003). The extracts from the pericardium of *Citri Reticulatae* were evaluated for antilipase activity utilizing a quantitative single-marker (QAMS) technique. Significant lipase inhibition was shown by six flavonoids: narirutin, hesperidin, didymin, nobiletin, 3,5,6,7,8,3',4'-heptamethoxyflavone, and tangeretin. Nobiletin was found as the most potent lipase inhibitor (Zeng et al., 2018). Naringin and cigranoside C from grapefruit (*Citrus paradisi* Mcfad) and cigranoside C, D, E, and F isolated from pomelo (*Citrus grandis* L. Osbeck) cultivars showed significant PL inhibitory activity with IC50 = 11.4-72.6 mg fruit/mL (Deng et al., 2022). Other investigations have found that certain citrus species and their bioactive components may inhibit pancreatic lipase activity. This inhibition shows that citrus fruits may aid in fat digestion and absorption, thereby improving weight control and metabolic health (Cardullo et al., 2024; Kawaguchi et al., 1997; Iwata et al., 2012; Gironés-Vilaplana et al., 2014).

5.7. Rosa × damascena

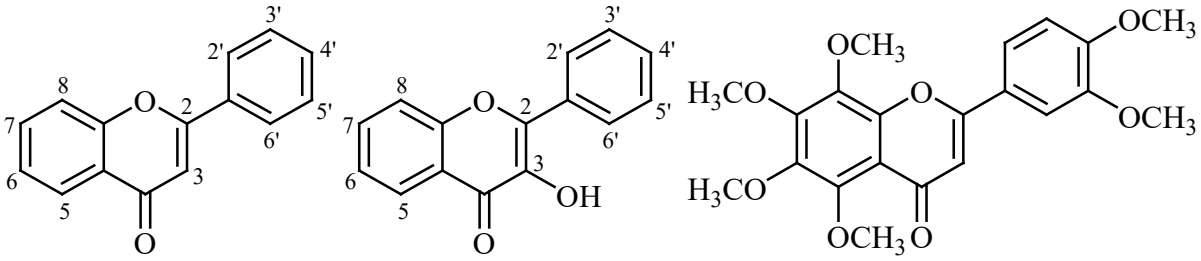
Rosa × damascena Mill. (RD) (a hybrid of *Rosa gallica* L. and *Rosa moschata* Herm.), belongs to the Rosaceae family (Nasery et al., 2016), *Rosa damascena*, popularly known as the Damask rose or "Gol-e-Mohammadi" in Persian, is a flower. This name refers to its introduction to Europe from Damascus, where it was first cultivated and named (Gudin, 2000). Bulgaria, Turkey, Iran, and India are the

Table 1. Pancreatic lipase inhibitory activities of Polyphenol containing Herbal drugs

S. No.	Plant	Extracts/chemical constituents	IC_{50} Value	References
1.	*Juniperus communis* L. (Juniper), Cupressaceae, Bark,	Aqueous-ethanol extracts	20.4 and 21.9 µg/mL	Kim and Kang, 2005
2.	*Illicium religiosum* (Japanese star anise) Schisandraceae, (wood)	Aqueous-ethanol extracts	21.9 µg/mL	Kim and Kang (2005)
3.	*Thea sinensis* L. (Black Tea), Theaceae	Extract and polymerized polyphenol-rich fraction	36.4 and 5.5 µg/mL, respectively	Uchiyama et al., 2011
4.	*Camellia sinensis,* Black tea, Theaceae	Theaflavin-3,3'-digallate, theaflavin-3'-gallate, theaflavin-3-gallate, and theaflavin	1.9, 4.2, 3.0, and >10µmol/L, respectively	Glisan et al., 2017
5.	*Nelumbo nucifera* Gaertn. (Lotus), Nelumbonaceae, Leaves	Leaf extract	0.46 mg/mL	Ono et al., 2006
6.		Leaf flavonoids	0.38 ± 0.022 mg/mL,	Liu et al., 2013
7.		aqueous ethanol or water	28.00 +/- 5.51 mg/L	Sun et al., 2012
8.	*Quercus infectoria* Oliv. (Aleppo oak), Fagaceae, Galls	Methanol extract, turbidimetric assay	Anti-lipase activity of more than 50%	Gholamhoseinian et al., 2010
9.	*Eucalyptus galbie* L'Her., Myrtaceae, Leaf			
10.	*Rosa damanscena* Mill. (Damask Rose), Rosaceae, Floret			
11.	*Levisticum officinale* W.D.J. Koch, Lovage Apiaceae, roots			
12.	*Salvia officinalis* L. (Sage), Lamiaceae, Leaves	Methanolic extract Carnosic acid, Carnosol	94 µg/mL 12 µg/mL 4.4 µg/mL	Ninomiya et al. (2004)
13.	*Ficus carica* L. (Fig), Moraceae, Fruits	The ethanolic extract, which is rich in polyphenols and flavonoids, has concentrations of 104.67±5.51 µg/mL and 81.67±4.00 µg/mL, respectively.	230.475±9.65 µg/mL	Mopuri et al., 2018
14.	*Ficus carica* cultivar Dottato fruits from Italy	dichloromethane fractions of ethanolic extract containing furanocoumarins (rutarenin and pimpinellin)	0.004 mg/mL	Marrelli et al., 2012
15.	*Morus alba,* (White Mulberry), Moraceae, Leaves	Phenolic compounds (morachalcone A)	6.2 µM	Jeong et al., 2015
16.	*Morus alba,* (White Mulberry), Moraceae, Root bark	The compounds include Morusalfurans A through G, a series of seven distinct substances, along with three flavonoids known as morusalnols A, B, and C. Additionally, there is a geranylated stilbene called morusibene A.	0.09 to 0.92µM	Ha et al., 2016
17.	*Crocus sativa* L. (Saffron), Iridaceae, Leaves	Crocin	At 40 µmol/kg, orlistat decreases fat absorption by approximately 30%, and at 102 µmol/kg, it decreases fat absorption by 12%.	Mashmoul et al., 2013
18.	*Nigella sativa, Momordica charantia, Anethum graveolens*	mixture of three compounds in the ratio of 215:50:35 µg/mL. AutoDock Vina,	74.26 ± 4.27 µg/mL	Chavan et al., 2024
19.	*Trigonella foenum graceum* L. (Fenugreek), Fabaceae, Seeds	Vicenin-1, Isoschaftoside, and Schaftoside	IC50 =207 µg/mL, IC50 = 330 µg/mL, and IC50 = 130 µg/mL, respectively	Fernando et al., 2019
20.	*Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae)	Methanolic extracts	Inhibited 74.7% and 53.8% at IC50 = 200 mg/mL,	Zheng et al., 2010

Table 1: continuous

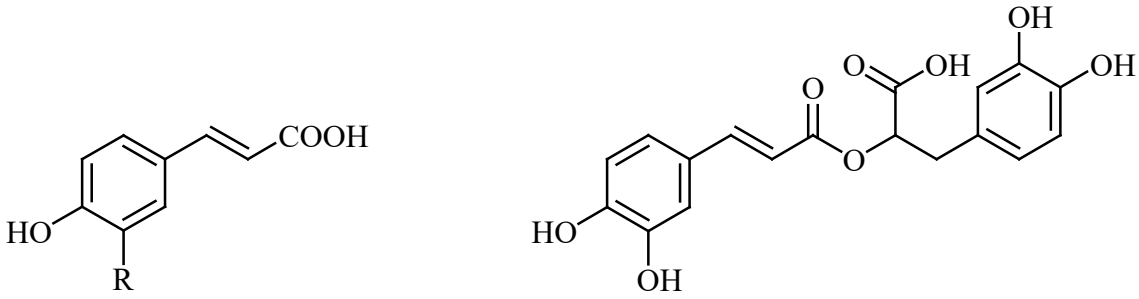
21.	*Trigonella foenum graceum* L. (Fenugreek), Fabaceae, Seeds	Vicenin-1, Isoschaftoside, and Schaftoside	IC50 =207 µg/mL, IC50 = 330 µg/mL, and IC50 = 130 µg/mL, respectively	Fernando et al., 2019
22.	*Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae)	Methanolic extracts	Inhibited 74.7% and 53.8% at IC50 = 200 mg/mL,	Zheng et al., 2010
23.	*Carthamus tinctorius* L.(Safflower), Asteraceae, Flower		12.3 ± 3.5 %	
24.	*Rheum palmatum* L. (Rhubarb), Polygonaceae, Rhizome		53.8 ± 9.0 %	
25.	*Taraxacum officinale,* (Dandelion)	95% ethanol extract	Inhibit 86.3% at a concentration of 250 microg/ml; 78.2 microg/ml	Zhang et al., 2008
26.	*Alpinia galanga* Willd (Zingiberaceae) Rhizome	Galangin	48.20 mg/mL	Kumar and Alagawadi, 2013
27.	*Ligustrum robustum* (Rxob.) Blume	Acteoside lipedoside A, oleuropein and ligurobustoside C	2.469 ± 0.005 mg/mL	Gao et al., 2022
28.	*Sempervivum davisii* Muirhead (Crassulaceae), aerial parts	Polyphenolic compounds, kaempferol glycosides, and quercetin hexoside	11.6-2.96 mg/mL	Uzun et al., 2017
29.	*Opuntia ficus-indica,* Cactaceae	Aqueous extract rich in polyphenolic compounds	IC50 = 588.5 µg/mL	Padilla-Camberos et al., 2015
30.	*Camellia sinensis,* Purple Tea	Due to its high anthocyanin polyphenol content, the beverage from this variety is purple, which is characteristic of purple tea.	67.4 µg/mL	da Silva et al., 2023
31.	*Pistacia vera,* (Anacardiaceae)	Pistachio green hull extract, abundant in phenolic compounds, contains galloyl-O-hexoside, galloyl-shikimic acid, galloylquinic acid, and gallic acid in its tannin fraction.	2.26 mg/ml	Noorolahi et al., 2020
32.	*Forsythia suspensa* (golden-bell), Leaves, Oleaceae	subfractions of *Forsythia suspensa* leaves	Three flavonoids were isolated, showing the following IC50 values: rutin = 149 ± 6.0 µmol/L, hesperidin = 52.4 µmol/L, and kaempferol-3-O-rutinoside = 2.9 ± 0.5 µmol/L. Additionally, two polyphenols were tested with IC50 values of 3150 ± 120 µmol/L for chlorogenic acid and 1394 ± 52 µmol/L for caffeic acid.	Chen et al., 2017
33.	*Araucaria angustifolia* (seed coat)	Tannin-rich extract	Inhibition constants, Ki_1 and Ki_2, 32.7 ± 146.1 µg/mL and 321.2 ± 93.0 µg/mL, equal to IC_{50} value	Oliveira et al., 2015
34.	*Ascophyllum nodosum,* edible seaweed	Polyphenol and phlorotannin-rich extract	200 and 60 µg gallic acid equivalents (GAE), respectively	Austin et al., 2018
35.	*Gustavia gracillima* Miers, Lecythidaceae	Methanol extracts rich in ellagic acid derivatives	362.17 µg/m	Andrade et al., 2020
36.	*Vigna unguiculata* (Fabaceae)	Ethanolic extract Cyanidin Cyanidin-3-glucoside	15.2 µg/mL 28.29 µM 188.28 µM	Vijayaraj et al., 2019
37.	*Ginkgo biloba,* (Ginkgoaceae), Leaf	Extract: biflavones, isoginkgetin, bilobetin, ginkgetin and sciadopitysin	IC50 range from 2.90 µM to 12.78 µM	Liu et al., 2018
38.	*Eucommia ulmoides* tea	The extract includes geniposidic acid, quercetin-3-O-sambuboside,	Significantly reduce the activity of pancreatic lipase	Huang et al., 2023



Apigenin (4',5,6=OH); Luteolin (3',4',5,7=OH)

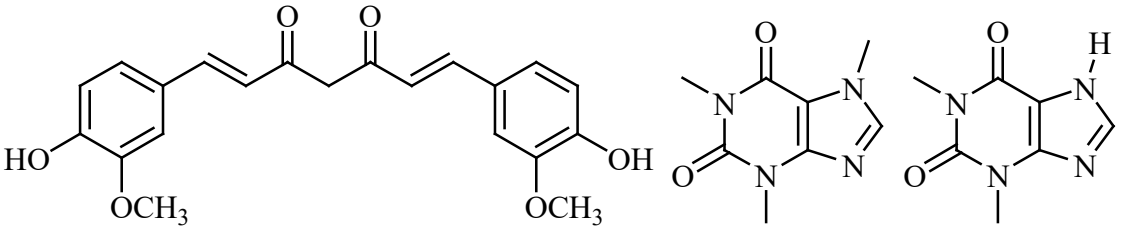
Quercetin (3',4',5,7=OH); Kaempferol (4',5,7=OH);

Nobiletin



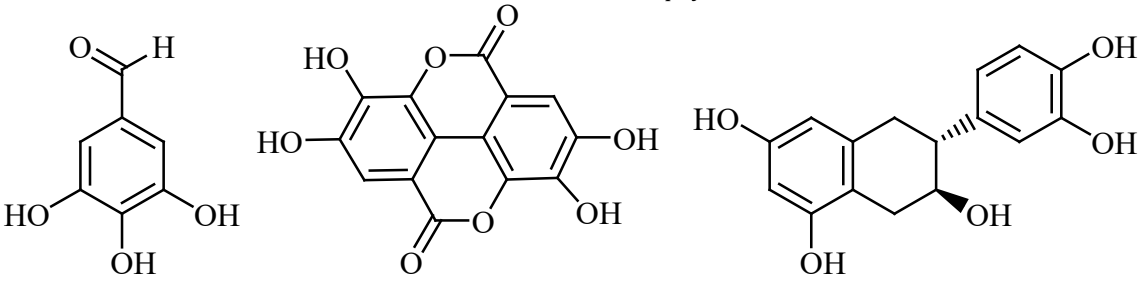
p-Coumaric acid (R=H);
Caffeic acid (R=OH);
Ferulic acid (R= OCH_3)

Rosmarinic acid



Curcumin

Caffeine Theophylline



Gallic Acid Ellagic acid Catechin

Figure 1. Structure of Polyphenolic compounds

main exporters and cultivators of rose oil. Several classes of bioactive constituents are obtained from RD such as phenolics, flavonoids, carotenoids, essential oils, and, anthocyanins. *Rosa damascena* has long been used to treat a wide range of conditions, such as bleeding during the menstrual cycle, inflammatory diseases, GIT disorders, depression, constipation, and chest pain. Because of its medicinal qualities, it is regarded as a flexible treatment in conventional medicine because of its calming, anti-inflammatory, and elevating effects (Alizadeh and Fattahi, 2021). The ethanolic extract of *RD* showed antiobesity activities showed *in-vitro* anti-lipase effect (Gholamhoseinian et al., 2010). Polyherbal formulations containing *RD* as an ingredient were reported to show anti-obesity activity by weight loss in healthy obese patients (Toromanyan et al., 2007). *In vitro* studies revealed that hydroalcoholic extract, aqueous extract, essential oil, and hydrosol of *Rosa damascena* petals all exhibited activity against lipase. Among these, the hydroalcoholic extract demonstrated the strongest PL inhibitory activity 62%, equivalent to 0.11 μg/mL of orlistat (Alnukari, 2020).

5.8. Berries

The genus Vaccinium (Ericaceae) is a globally distributed and diverse group, encompassing approximately 4,250 species (Martău et al., 2023). Berry fruits such as blueberries (*Vaccinium corymbosum* L.), huckleberries (*Vaccinium membranaceum*), cranberries (*Vaccinium macrocarpon*), lingonberries (*Vaccinium vitis-idaea*), and bilberries (*Vaccinium myrtillus*) are very well known for their medicinal and nutritional importance (Padmanabhan et al., 2016). The bioactive compounds found in this genus are anthocyanins, flavonoids, phenolic acids and iridoids. Cyanidin, malvidin, and delphinidin are the common anthocyanins while common flavonoids are quercetin, isoquercetin, and astragalin (Martău et al., 2023). Polyphenol-rich hexane extracts from various berries were evaluated for PL inhibitory activity. Blueberry extracts showed only minor PL inhibition while cloudberries (*Rubus chamaemorus*), arctic bramble (*Rubus stellatus* × *R. arcticus*), lingonberries (*Vaccinium vitis-idaea*), strawberries (*Fragaria ananassa* var. Elsanta) and raspberries (*Rubus idaeus* var. Glen Ample) extracts demonstrated significantly greater effectiveness (McDougall et al., 2009). A study analyzed chokeberry fruits (Aronia melanocarpa) at four stages of development for their pancreatic lipase inhibitory properties. Unripe green fruits had the highest levels of phenolics, including proanthocyanidins (6.83% DW), phenolic acids (6.57% DW), and other beneficial compounds, as well as protein and fiber. Conversely, ripe black fruits contained the most carotenoids, anthocyanins, and sugars. The unripe fruits exhibited superior anti-lipase and antioxidant activities, suggesting their potential in nutraceuticals and functional foods. Additionally, black chokeberry polyphenols, particularly highly polymerized procyanidins, were more effective in inhibiting pancreatic lipase in vitro, whereas fractions with low-molecular-weight phenolic compounds, such as phenolic acids, flavonols, and anthocyanins, were 11–64 times less effective (Sosnowska et al., 2022).

The anthocyanin-rich honeysuckle berry (*Lonicera caerulea* L.) was found to be a good PL inhibitor, therefore, it is good for the management of obesity. With IC50 values of 0.47 mg/mL, honeysuckle berries showed pancreatic lipase inhibitory effect. Additionally, the fecal triglyceride levels of the mice fed HB had higher levels than those of the control group due to their high-fat diet (Kim et al., 2022).

5.9. Origanum vulgare (Oregano)

Origanum vulgare, a well-known member of the Lamiaceae family, is commonly referred to as wild marjoram or Spanish thyme. It is the main cultivar sold as oregano in the United States and Europe, and it is highly valued for its strong, fragrant flavour. It is widely used as a natural preservative, in traditional medicine, and cookery. (Singletary, 2010). Traditionally *OV* is for the treatment of diaphoretic, carminative, antispasmodic, antiseptic, and tonic in many countries (Chun et al., 2005). Turkey is the world's biggest exporter of oregano herb and oil (Baser 2008). Oregano contains important phenolic acids such as caffeic, p-coumaric, ferulic, and neochlorogenic acids, as well as flavonoids such as quercetin, luteolin, apigenin, kaempferol, and isorhamnetin. Oregano essential oil contains thymol (40.9-63.4%), p-cymene (5.1-25.9%), and γ-terpinene (1.4-20.1%), as well as minor chemicals including terpinen-4-ol, α-pinene, 1-octen-3-ol, α-terpinene, carvacrol, β-caryophyllene, and β-myrcene (Verma et al., 2012). While the pancreatic lipase inhibitory activity of oregano extract, which was high in rosmarinic acid (76.01 mg/100 g DW) and protocatechuic acid, was lower than that of the positive control, Orlistat (Parra et al., 2022), its essential oil, which had a phenolic content of 12.47 mg gallic acid/mL, showed notable anti-lipase activity with an IC50 of 5.09 μg/mL and significant DPPH scavenging activity with an IC50 of 0.357 μg/mL (Quiroga et al., 2013).

Conclusion

The prevalence of overweight and obesity is increasing throughout the world. Several chronic illnesses, including depression, type 2 diabetes, cardiovascular disease, multiple malignancies, sleep difficulties, mental health issues, and liver disorders are all associated with an increased risk of obesity (Jin et al., 2023). Orlistat effectively inhibits pancreatic lipase but is associated with side effects, limiting its use to short-term applications. These issues highlight the need for alternative solutions. Compared to chemically synthesized lipase inhibitors, these natural alternatives are more widely available, less expensive, and safer overall. Polyphenolic chemicals, which include tannins, flavonoids, stilbenes, and other phenolic molecules, effectively manage obesity-related disorders by blocking pancreatic lipase. These compounds

are commonly found in everyday foods like tea, coffee, berries, spices, and fruits. As research progresses, these plant-derived inhibitors are expected to play a critical part in the clinical treatment of obesity. The continued exploration and development of these natural inhibitors represent a significant direction for future research in the field of obesity management.

Author contributions

K.J.N. was responsible for the conceptualization, design, and drafting of the manuscript. The author reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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