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Navigating the Global Obesity a Global Catastrophe: The Role of Pancreatic Lipase Inhibition and Endophytic Fungi in Developing Innovative Therapeutics for Metabolic Health

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Abstract

The global obesity epidemic is highlighting its extensive health implications and economic costs. It notes that over 1. 4 billion adults were classified as overweight by the World Health Organization in 2014 to till now, with rates tripling since 1975. Obesity is linked to numerous chronic diseases, including Type 2 Diabetes and cardiovascular issues, and disproportionately affects women and socioeconomically disadvantaged groups. The text emphasizes the role of pancreatic lipase in fat metabolism and its significance as a drug target for obesity treatment. It reviews existing medications like Orlistat that inhibit this enzyme, thereby reducing fat absorption. Furthermore, it explores the potential of medicinal plants and their endophytic fungi derivatives in developing alternative treatments for obesity, underscoring their ability to produce bioactive compounds with therapeutic effects. The document also outlines various challenges in researching endophytic fungi and their lipase inhibitory activities, suggesting that these microorganisms could be valuable resources for new obesity treatments. It concludes by discussing the need for further studies to explore the diversity and capabilities of endophytic fungi in producing lipase inhibitors

Keywords: Medicinal plants; Obesity; Pancreatic lipase; Lipase inhibitors; Endophytic fungi; Chronic diseases; Bioactive compounds; Drug development.

INTRODUCTION

The worldwide obesity epidemic constitutes one such challenge for public health, with increasing rates of overweight and obesity now reported in different populations (*Anwar et al., 2022*). The World Health Organization (WHO) stated that more than 1. 4 billion adults aged 20 and older were overweight in 2014-as a result of these numbers, nearly 300 million were classified as obese. In fact, from 1975, these have become tripled, and more than 2. 3 billion adults and children live with overweight or obesity today. At this point, no single country, whether developed or developing, it has been spared from the "Globesity" increase

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in obesity rates around the world *(Sowmya et al., 2022)*. Obesity can be found across ages, across levels of socioeconomic status, and across localities. However, it is more frequent among women and the socioeconomically disadvantaged. Obesity poses a health risk for many chronic illnesses, including Type 2 Diabetes and cardiovascular diseases, as well as various cancers, metabolic illnesses, and psychological issues with depression, anxiety, and low self-esteem *(Asif et al., 2023)*. The economic impact of obesity is huge, and in many countries, a significant portion of healthcare costs is attributed to obesity-to between 2 and 6 percent of total spending on health in most developed countries. Such costs include the medical care applied to conditions caused by obesity and lost productivity *(Mahmudova et al., 2021)*. Pancreatic lipase is the most important enzyme during lipid metabolism, especially on digestion and absorption of fats from dietary sources. The enzyme plays a major role during fat absorption because it can degrade complex lipids into an absorbable form by enterocytes. Effective action is observed in the presence of bile salts, because emulsification of dietary fats increases the surface area for lipase action. The action takes place in the form of a substrate-enzyme complex through the enzyme pancreatic lipase catalyzing, in which triglyceride is hydrolyzed at C-1 and C-3 and convert them to free fatty acids along with monoacylglycerols, forming mixed micelles with bile salts-which are needed for absorption by the lining in the intestines (*Li et al., 2023*). So, the action of pancreatic lipase directly controls the absorption of fat. The following enzyme is an important drug target because its inhibition diminishes calorie intake from fat. There are some medications in clinical use that appear useful, like Orlistat, which decreases the fat digestion by 30% after irreversible covalent binding of a functional group to the catalytic site of pancreatic lipase. Continuing research has relied on medicinal plants and their endophytic fungi derivatives where some candidates have shown an inhibitory activity against the pancreatic lipase, creating new sources of alternative treatments for this disease. Such inhibitors may therefore provide drugs that are less harmful than the drugs produced. Implication of inhibiting pancreatic lipase may also carry further preventive applications in the co-morbidities related to obesity that include type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease. These are microorganisms that live inside the tissues of plants during their whole life cycle, thus improving the host's growth and tolerance to stresses *(Kumar et al., 2023)*. They contribute to a plant becoming healthy by promoting nutrient uptake, tolerance to stress, and protection against pathogens. It produces phytohormones that promote growth in the plant and secondary metabolites that act as antibiotics or antifungals for reducing biotic stress. These endophytic fungi in the plants could enhance biomass, root development, and also confer resistance to adverse environmental conditions *(Al-hasbi et al., 2023)*. The diversity of endophytic fungi is quite immense and each species is different from others with capabilities of synthesizing wide ranges of secondary metabolites such as alkaloids, terpenes, polyketides, and Phenolic compounds. Such compounds have been shown to possess antimicrobial, antioxidant, anticancer, and anti-inflammatory properties as shown in the *Fig. 1.* While other endophytes, such as endophytic fungi acting as an inhibitor of pancreatic lipase, have been proven to inhibit the absorption of fats in the gastrointestinal tract and thus proved with potential therapeutic application for obesity control and other metabolic syndromes, compounds produced by endophytes like host plants have immense value as potential drug discoveries. Some endophyte strains have been found to produce such inhibitory compounds that could open new lines of treatment for obesity. Production of bioactive compounds by endophytic fungi holds many advantages over the classical method of using whole plants. Fungal fermentation can prove to be more efficient, sustainable, and even environmental friendly as the production environment can easily be controlled for enhancing yields and potency of bioactive substances *(Khan et al., 2023)*. This approach also saves reliance on plant materials, which may be limited or even endangered by overharvesting or loss of habitat.

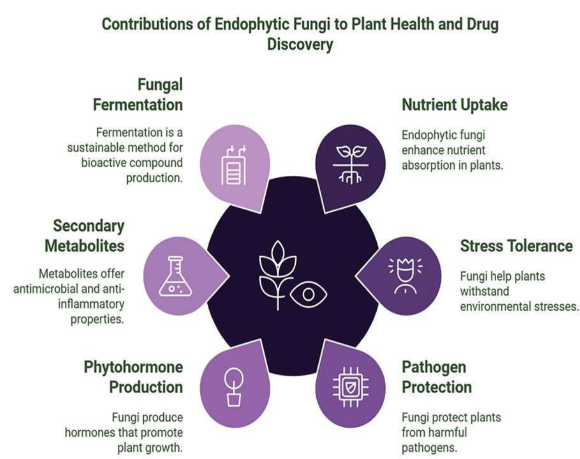

Fig. 1: Showing the contribution of fungi in various pharmaceutical branches

The Associated issues on Obesity

The scientific term of "obesity" is the accumulation of extra body fat to the point where it results in health issues and excessive mortality. Because an increase in body mass is primarily caused by an increase in stored fat, the pragmatic definition of obesity is based on this fact *(Zhang et al., 2024)*. For any particular size of fat mass, it is possible to observe wide range in lean body or non-fat mass; yet again, that appears to be connected and causally related to the fat mass. Obesity causes or worsens many diseases. These include ischemic heart disease, stroke, obstructive sleep apnea, asthma, nonalcoholic steatohepatitis, gastroesophageal reflux disease, degenerative joint disorders, depression, infertility, polycystic ovary syndrome, hypertension, dyslipidemia, ischemic heart disease, and type II diabetes. Perhaps the most evident condition linked to obesity is type II diabetes (*Bhatia et al., 2023)*.

Specific medication treatments for obesity

In the 1990s, serotonin (5-hydroxytryptamine, or 5-HT), catecholamines, and some neuropeptides were among the central and/or peripheral neurochemical pathways that were promising for the pharmacotherapy of obesity *(Ahmed et al., 2023)*. Fen-Phen, or successful combination treatment, addressed serotonergic and catecholaminergic pathways by combining the 5-HT releasers fenfluramine or dexfenfluramine with the noradrenergic releaser phentermine. The combined treatment was chosen because medications work on different monoaminergic systems and may thus work in concert to lower dosage and, as a result, minimize adverse effects *(Malik et al., 2024)*. These expectations were met, and the synergistic dose of the combination medication was lower than that of either medication taken alone. Unfortunately, cardiac vulvulopathy—a major side effect of even lower doses of fenfluramine caused this treatment to be withdrawn from the market. Peripheral β-3 adrenergic receptors were another attractive target. Selective agonists were used to target the receptor to activate brown fat and enhance energy expenditure, though these drugs were ineffective in humans, and the least selective had adverse side effects.

Lipase inhibitors originate from plants

The fruits of *Cassia nomame* (Leguminosae) were used to extract *flavan dimmers* that showed lipase-inhibiting activity. Two of the new compounds were characterized by their structures as (2S)-31, 41, and 7-trihydroxyflavan-(4-8)-catechin *(Birari et al., 2013)*. For comparison of the spectra, four *flavan dimers* that are physically similar to these two compounds were also prepared. 7-trihydroxyflavan-(2S)-catechin possessed the highest inhibitory activity of the ten *flavan dimers* screened for lipase inhibitory activity (2S)-31, 41. Fresh *Platycodin grandiflorum* roots are consumed in China and Korea as pickles to prevent individuals from getting obese. It has been found that the saponin-enriched fraction of *Platycodin grandiflorum radix* possesses anti-obesity effects, which are linked with PL inhibition. The methanolic extract of *Salvia officinalis L.* (sage) showed inhibitory activity (IC50 94 µg/mL) against pancreatic lipase and an inhibitory effect on the increase of blood triglycerides in mice treated with olive oil (500 and 1000 mg/kg). Four abietan-typediterpenes (carnosic acid, carnosol, royleanonic acid, and 7-methoxyrosmanol) and a triterpene (oleanolic acid) were isolated from the active fraction through bioassay-guided separation based on inhibitory activity against pancreatic lipase activity *(Jabeen et al., 2021)*. With IC50 values of 36 µM and 13 µM, respectively, carnosic acid and carnosol considerably inhibited pancreatic lipase activity. At dosages of 5–20 mg/kg, carnosic acid dramatically reduced the increase in triglycerides in mice given olive oil. However, at a dosage of 200 mg/kg, other components, including carnosol, oleanoic acid, and rorleanonic acid, did not exhibit any effects. Additionally, in mice fed a high-fat diet, carnosic acid (20 mg/kg/day) reduced the gain in body weight and the accumulation of epididymal fat weight after 14 days. Bioactive-guided fractionation of a saponin-rich fraction of the leaves of Accanthopanaxsessiliflorus led to the isolation of the active lupane-type saponins, sessiloside and chiisanoside, both of which showed strong inhibition of PL in vitro. Further, it inhibited lipase activity in a dose-dependent manner and their IC50 values were 0. 36 and 0. 75 mg/mlrespectively. Dougall *et al.* investigated the efficacy of polyphenol-rich berry extracts in 2009 to suppress pancreatic lipase activity in vitro *(Iqbal et al., 2021)*.

The extracts of blackcurrant and rowan had no inhibition; blueberries had a weak inhibition, while lingonberries, cloudberries, raspberry, and Arctic bramble were much stronger. The cloudberry extract shows an obvious saturation effect of inhibition, with an apparent EC50 close to 5 µg phenols/ml. Furthermore, the inhibitory parts of the cloudberry were recovered in a tannin-rich fraction obtained by sorption onto Sephadex LH-20. The polyphenol composition of both active and inert fractions was characterized in detail using liquid chromatography-mass spectrometry (LC-MS) and indicated that the active ingredients consisted of ellagitannins *(Hussain et al., 2023)*. It was also found that equally prepared strawberry and raspberry fractions were potent pancreatic lipase inhibitors. Although the strawberry tannin fraction was enriched in a combination of ellagitannin and proanthocyanidin components, the DIMS of the raspberry tannin and cloudberry tannin fractions presented similarities with differences in some of the particular ellagitannin components in abundance. Components of proanthocyandin might have been accountable for the efficient inhibition of lipase presented by the lingonberry extract. It was shown that dioscin, which was isolated from the methanol extract of powdered *Dioscorea nipponica,* inhibited PL with an IC50 of 20 mg/ml. With an IC50 value of 28 mg/ml, this glycone diosgenin was also found to be active. Both of them inhibited the time-dependent increase in plasma triglyceride levels in mice injected with maize oil. Prosapogenin A (IC50 1. 8 mg/ml), prosapogenin C (IC50 42. 2 mg/ml), and gracillin (IC50 28. 9 mg/ml), three additional oleanan saponins that were isolated from the same plant, were also found to cause significant PL suppression in vitro as mention in the *Fig. 5.2*.

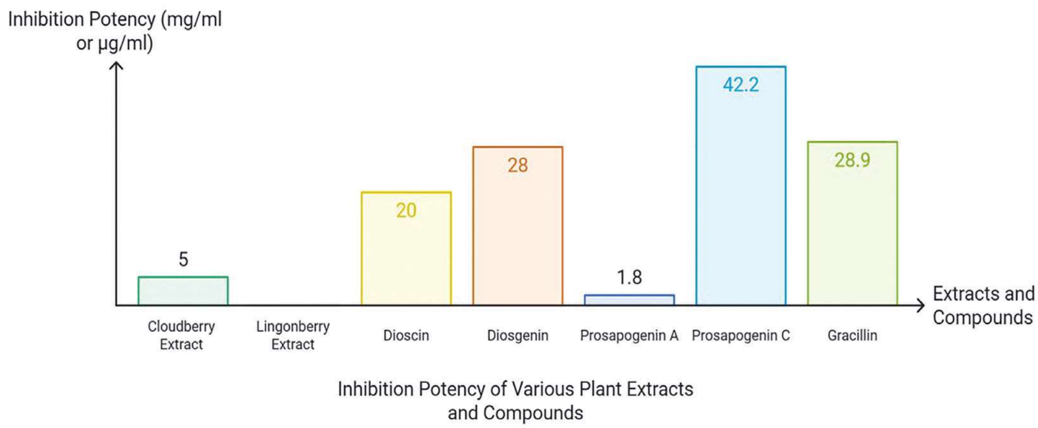

Fig. 2: Analysing the graph of inhibition potency from different plant extracts

The family *Rutaceae*is another famous medicinal plant, commonly referred to as bael or Aegle marmelos *(Gupta et al., 2023).* It is one of the chief plants in the Ayurvedic pharmacopeia of India. The plant has numerous medicinal properties in its leaves, roots, seeds, bark, and Beal extracts contain anti-diabetic activities. *Birari and Bhutani (2007)* worked on the lipolytic effects of n-butanol, ethyl acetate, and DCM extracts of A. marmelos leaves. The amount of glycerol at 12 and 24 hours for 50 µg/ml and 100 µg/ml was utilized to measure the lipolysis. Fourteen constituents were detected using phytochemical analysis of the most active DCM extract. The lipolytic activities of the purified compounds were subsequently evaluated at 50 µM and 100 µM as demonstrated in the *Fig. 3.* The anti-obesity efficacy of the majority of the active ingredients, umbelliferone and esculetin, was further evaluated using an obese rat model produced by a high-fat diet (HFD) in vivo.

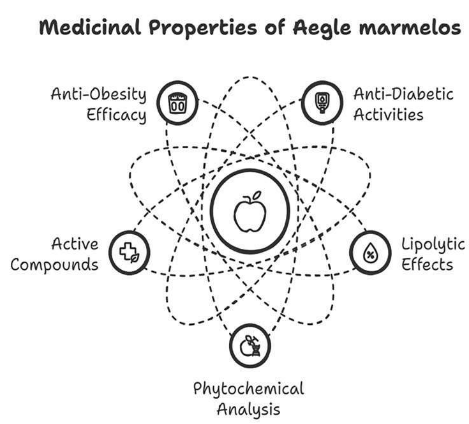

Fig. 3: Showing the unique properties of the medicinal plants

Endophytic fungi the green gold of nature

Endophytic fungus is a source of ample new chemical compounds with biological activity. They are an ecological source, and due to interaction with the host, their secondary metabolites are active *(Sowmya et al., 2024)*. For example, anticancer properties were developed by the endophytic fungus Taxomycesandreanae in taxol. Some endophytic fungi have been reported to produce more than twelve metabolites comparable to those produced by host plants and with therapeutic functions, which include alkaloids, steroids, terpenoids, isocoumarin derivatives, flavonoids, quinines, phenylpropanoids, phenylpropanoids and ligans, peptides, phenol and phenolic acid, aliphatic compounds, and chlorinated metabolites as showed in the *Fig. 4.* There are no reports on the production of lipase inhibitors by endophytic fungus *(Killedar et al., 2024).* Thus, endophytic fungi might be a great biological resource for the production of lipase inhibitors that could act as a form of obesity cure.

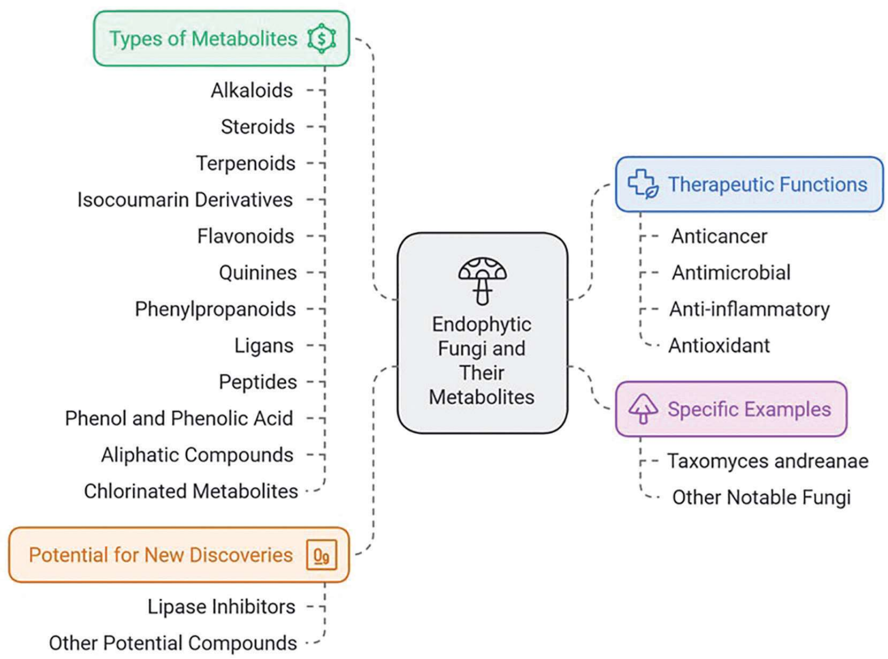

Fig. 4: Showing the bioactive compounds of the medicinal plants extracts and their therapeutic functions

Lipase inhibition quantification assays

- **Rhodamine B Assay:** The zone of lipolysis is observable as an orange fluorescence at 350 nm when viewed with UV light using rhodamine B. Fatty acids and monoglycerides are released upon the breakdown of the introduced olive oil by lipases *(Farhan et al., 2023).* These free fatty acids react with rhodamine to form a fluorescent complex, producing an orange luminous halo that is observable under UV light.
- **Phenol Red Assay:** One type of pH indicator dye called phenol red changes colors at several ranges of pH, from basic to acidic. It turns yellow to orange below pH 7 and turns blood red above pH 7. From pH 8 onward, it ranges from magenta to pink. When the lipases act on the introduced olive oil in the medium, the medium produces fatty acids and monoglycerides *(El-sayed et al., 2022).* This production of fatty acids makes the pH of the media acidic, leading to a yellow-colored halo.

Utilising spectrophotometric assays for quantitative estimation

p-nitrophenol release is measured spectrophotometrically at 410 nm using p-nitrophenolyl esters of different chain lengths as substrates. Since short-chain esters are soluble in water, their hydrolysis gives an indicator of esterase activity rather than the activity of lipase *(Abubakar et al., 2023).* However, the activity of lipase is measured using p-nitrophenyl palmitate. As in the *Fig. 5.5*. Where inability to carry out enzymatic reactions at acidic pH because p-nitrophenol does not absorb at acidic pH is a major limitation of this test. Therefore, this method can only be used to determine enzyme activity at neutral and alkaline pH values *(Sowmya et al.*, *2023)*. This test has been employed to acid enzymes by raising the pH of the reaction mixture after the completion of the reaction. This technique has also been used to screen crude plant extracts.

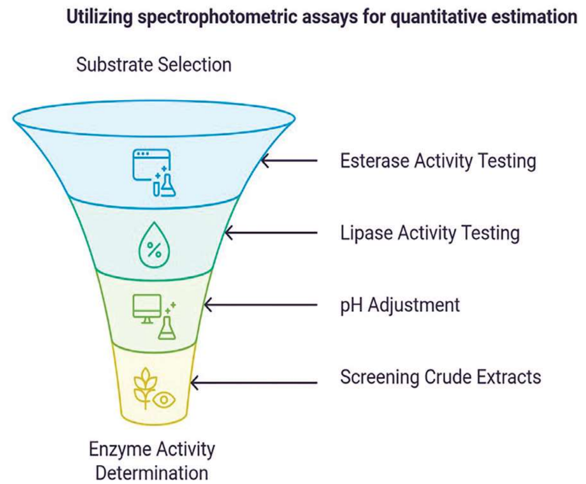

Fig. 5: Utilizing the analytical method to show the different enzyme activity

Challenges and future directions

Many factors are hindering the research on endophytic fungi showing lipase inhibitory activities. The number of species of fungi studied is also insufficiently explored, considering the fact that many medicinal plants possess a significant diversity of endophytes that have not yet been evaluated for their bioactivity against pancreatic lipase. In addition, geographical variations also pose a problem, because a lot of regions are unexplored, which follows as in the *Fig. 6.*

- Lack of sufficient mechanistic understanding is also a concern since the exact mechanisms by which these inhibitors interact with the enzyme are not well understood. Extensive SAR studies are required to define specific structural features of endophytic fungal metabolites that confer lipase inhibitory activity *(Sowmya et al., 2023).*
- In vivo validation is the utmost necessity because most of the work has been focused on in vitro assays, which do not reliably represent the effectiveness and safety of these inhibitors in actual biological systems *(Dangall et al., 2023)*. There has been a scarcity of clinical trials, and the transition from experimental laboratory results to practical clinical implementation is inadequately delineated. Standardization and quality control processes are essential for ensuring reproducibility and comparability in the research studies.
- The established protocols for quality control for evaluating purity and potency of fungal extracts used in scientific investigations are highly deficient. Combination treatments have primarily focused on individual agents, ignoring exploration of potential synergistic interactions between different endophytic fungal metabolites or extracts and other natural products *(Dasguta et al., 2023)*. Understanding the policy environment for the development of natural products from fungi supports their development as medicinal products.

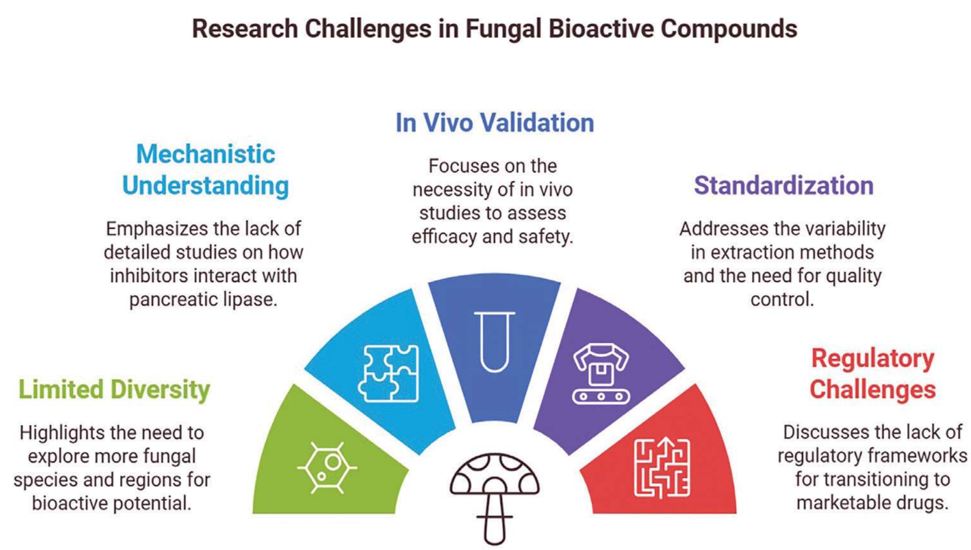

Fig. 6: Showing the Research challenges in finding the various pharmacological compounds

CONCLUSION

The exploration of pancreatic lipase inhibitors derived from endophytic fungi associated with medicinal plants presents a promising avenue for addressing obesity and its related health issues. With the global obesity epidemic on the rise, characterized by alarming rates of overweight and obesity across diverse populations, there is an urgent need for effective therapeutic strategies *(Choudhary et al., 2023)*. Pancreatic lipase plays a critical role in lipid metabolism, facilitating the digestion and absorption of dietary fats. Inhibiting this enzyme can significantly reduce fat absorption, making it a key target for obesity management. Recent research has highlighted the potential of endophytic fungi as sources of bioactive compounds that can inhibit pancreatic lipase, offering a natural alternative to synthetic drugs like Orlistat. These fungi produce a variety of secondary metabolites with demonstrated biological activities, including those that exhibit lipase inhibitory effects. However, several research gaps remain, such as the limited diversity of fungal species studied, insufficient mechanistic understanding, and a lack of in vivo validation. Addressing these gaps through comprehensive screening and characterization efforts could lead to the discovery of novel lipase inhibitors that are both effective and safe for use in obesity treatment. Overall, the integration of endophytic fungi into obesity management strategies represents a promising frontier in pharmacotherapy.

Conflict of Interest: There are no conflicts of interest to declare.

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