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Fat-Rich Food Review on Obesity Control through Induction Enzyme Inhibitors

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Background: Obesity is an imbalance between height and weight due to excessive body fat tissue. The purpose of writing this review is to find out the effect of enzyme inhibitor induction on fat-rich foods as control of obesity. **Method:** Writing and assessing source problems related to using literature study methods. **Results:** One way of controlling obesity is by regulating dietary patterns and consumption of lipase inhibitors. Inhibition of lipase is one of the most widely developed effective ways in diet medicine. Inhibitory compounds cause pancreatic lipase to lose its ability in decomposition that enters the blood. The potency of plant-origin lipase inhibitor compounds can be increased in both number and performance. Increasing the production of secondary metabolite group inhibitors is by fermentation of microorganisms. **Conclusion:** Inhibition of triglyceride hydrolysis through inhibition of lipase enzymes can decrease and prevent obesity. Secondary metabolite induction can be fermented with microorganisms. The production of secondary metabolite compounds in medicinal plants can be increased in the presence of fermentation. Flavonoids can decrease the accumulation of lipids in the heart, reduce glucose absorption, inhibit the breakdown of polysaccharides into monosaccharides.

Review Makanan Kaya Lemak Pada Kontrol Obesitas melalui Penghambatan Induksi Enzim

Kata kunci:
Lipase;
Obesitas;
Penghambatan;

A B S T R A K

Background: Obesitas merupakan ketidakseimbangan antara tinggi dan berat badan akibat jumlah jaringan lemak tubuh yang berlebihan. Tujuan penulisan review ini yaitu mengetahui pengaruh induksi inhibitor enzim pada pangan kaya lemak sebagai pengendali obesitas. **Metode:** Penulisan dan pengkajian masalah sumber terkait dengan menggunakan metode studi literatur. **Hasil:** Salah satu cara pengendalian obesitas adalah dengan pengaturan pola diet dan konsumsi inhibitor lipase. Penghambatan kerja lipase merupakan salah satu cara yang efektif yang paling banyak dikembangkan dalam obat diet. Senyawa inhibitor menyebabkan lipase pankreas kehilangan kemampuannya dalam dekomposisi yang masuk ke darah. Potensi senyawa inhibitor lipase asal tanaman dapat ditingkatkan baik jumlah maupun performa. Mekanisme peningkatan produksi inhibitor golongan metabolit sekunder adalah dengan fermentasi mikroorganisme. **Kesimpulan:** Penghambatan hidrolisis trigliserida melalui inhibisi enzim lipase dapat menurunkan dan mencegah obesitas. Induksi metabolit sekunder dapat dilakukan fermentasi dengan mikroorganisme. Produksi senyawa metabolit sekunder pada tanaman obat dapat ditingkatkan dengan adanya fermentasi. Flavonoid dapat menurunkan akumulasi lipid di hati, mengurangi penyerapan glukosa, menghambat penguraian polisakarida menjadi monosakarida.

Introduction

Obesity is a condition of imbalance between height and weight due to excessive body fat tissue (Listiyana, Mardiana, & Prameswari, 2013). Obesity poses the biggest threat to world health today, with more than 1.5 billion overweight adults (Drew, Dixon, & Dixon, 2007). Increasing obesity rates, the World Health Organization (WHO) considers it an epidemic of the XXI century and promotes

strategies for preventing and controlling obesity (Lobstein, 2009).

The development of obesity is characterized by an imbalance between energy intake and energy expenditure (Voshol et al., 2009; Abete et al., 2010). Influencing factors are genetic, environmental, and physiological factors. Research on individual twins confirms the presence of genetic factors that play a role in the onset of obesity. In contrast, the rapid increase in the prevalence of obesity in the last 30 years shows the contribution of environmental factors (Comuzzie et al., 2012). This abnormal condition results in health problems in various diseases, such as type 2 diabetes mellitus, hyperlipidemia, atherosclerosis, cancer, and metabolic syndrome (Kim et al., 2019).

The step most people take in overcoming obesity is by setting a balanced diet. The emphasis on eating control, emotions, and hunger should be done by obese people, while limiting eating is not easy (Ballinger & Peikin, 2002). Weight loss and adipocytes should also be based on changes in lifestyle habits (Rubio et al., 2007). A therapeutic approach in lowering obesity is to slow the absorbance of fatty acids by inning pancreatic lipase enzymes in the digestive tract (Ballinger & Peikin, 2002). increase daily metabolism with physical activity and increase energy expenditure (Schrauwen & Westerterp, 2000). However, the therapeutic approach to date is less effective because of its excruciating nature and not for the long term. Therefore, it is necessary to do comprehensive boxing to inhibit lipase work using lipase enzyme inhibitors.

Method

The method used in this narrative review is to look for both Indonesian and international journals. The research procedure carried out in the preparation of this narrative review is to look for various literature studies electronically by accessing national and international article searches and books through databases such as Google Scholar, ScienceDirect, and others using keywords related to the discussion of lipase, obesity, inhibition and bioactive compounds. The title and abstract of the article read are then selected and classified based on the needs of the review writing and the year of publicity. Reference sources were obtained, summarized in word to than imported and stored into Zotero according to certain sub-sub-sub-headings and reanalyzed by looking at the completeness of the selected source or article. Articles relevant to the topic are grouped using narrative methods.

Results and Discussion

Fat Metabolism and Chronic Obesity

Fats consist of triglycerides, phospholipids, or similar compounds, as well as sterols. One of the formations of energy is fat, whose metabolism consists of anabolism and catabolism. Triglycerides are fats that supply energy almost entirely with fatty acids used by cells to form energy (Kovar & Havel, 2002). The triglyceride content of food that enters the body will be broken down by lipoprotein lipase enzymes in the endothelial capillaries in the blood to form fatty acids and glycerol. At this stage, fat again undergoes preparation in fat cells. The enzyme lipase decomposes the triglyceride fat tissue, and triglyceride reserves are catalyzed into fatty acids, and glycerol is then transported to active tissue. After oxidation, glycerol is converted into glycerol triphosphate for the breakdown of glucose on the glycolysis and energy production pathways. Fatty acids produce acetyl CoA from the beta-oxidation process that goes into the Krebs cycle and makes energy (Welty et al., 1999; Siregar & Makmur, 2020).

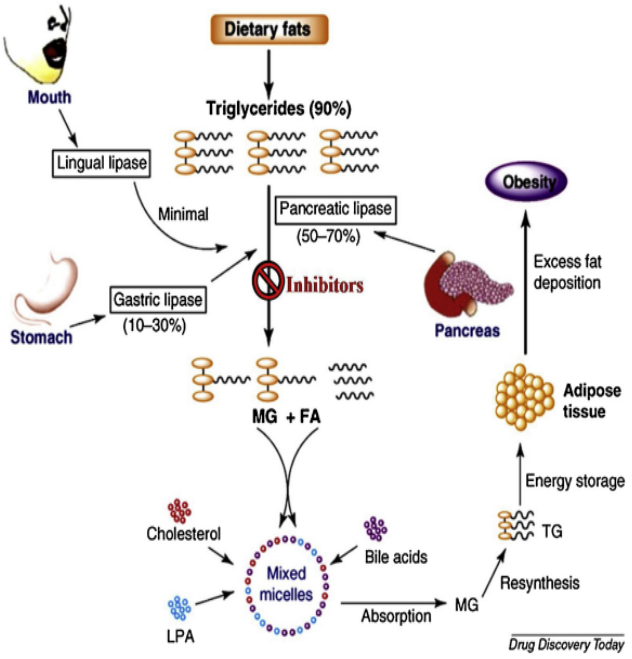

Figure 1. Lipid Metabolic Pathways in the Body (Birari & Bhutani, 2007).

Excessive consumption of foods high in carbohydrates and fats can cause excess fat in his body. The excess that occurs is caused by the body's inability to store fat reserves so that it is buried in fat tissue located under the skin and around the abdomen (Triyanti & Ardila, 2020). Research shows that consumption of omega-six fatty acids can cause weight gain through the mechanism of adipogenesis if consumption is done in excess. The side effect is that it can block the work of omega-three fatty acids (Rachmawati et al., 2018). The accumulation of triglycerides will result in proliferation and differentiation signals in adipose tissue because cAMP protein kinase has been activated by arachidonic acid through the P12 receptor causing the browning process in adipose tissue that failed to form. Therefore, an unbalanced ratio of omega six or omega-three will support PUFA omega six, which is included in the

prevalence of degenerative diseases, namely obesity (Simopoulos, 2013, 2016).

Obesity is defined as a condition characterized by excessive fat accumulation in adipose tissue (Rismawati et al., 2012). Accumulation of excess fat will affect the onset of health problems (Rathnayake et al., 2013; Vásquez et al., 2017). Risk factors in people with obesity are physical changes and can cause abnormalities in physiological, psychological, and social metabolism (Teixeira et al., 2011). Other risk factors can also cause complications such as type 2 millitus diabetes, high blood pressure, cancer, and liver disease (Polyzos, et al., 2019). The results link obesity to excess accumulation of adipocytes in lung and respiratory diseases. The buildup of fatty tissue in the abdominal wall and around the abdominal organs inhibits the movement of the diaphragm, decreases lung expansion during inspiration, and decreases lung capacity (Shore, 2007).

Bioactive Compounds Potentially as Lipase Inhibitors

The process of inhibition of fat metabolism is an interesting method to study about reducing the absorption of fat in the body (Bray & Ryan, 2007). Orlistat is an anti-obesity drug that the FDA has approved that is effective and proven in inhibiting pancreatic lipase enzymes (Filippatos et al., 2008; McClendon et al., 2009). Orlistat is a derivative of hydrogenated lipstatin and pancreatic lipase inhibitor isolated from *Streptomyces toxytricini* bacteria (Ballinger & Peikin, 2002). Based on literature studies, the effective concentration of orlistat used as a lipase inhibitor is 100 ppm, where the inhibitory ability is 10.6% (Iswantini et al., 2010).

In general, the mechanism of action of lipase inhibitors is to covalently bind to the active part of pancreatic lipase and form a stable complex. The complex induces changes in lipase so that it becomes inactive. This inactivated lipase cannot hydrolyze fats into fatty acids and monoglycerides, so it is eventually wasted through faeces (Al-Suwailem et al., 2006).

Human pancreatic lipase consists of 449 amino acids. When the lipase enzyme exhibits the hydrophobic part of the active site, it can increase the binding capacity of the substrate and lipase. At the same time, the substrate can easily enter the hydrophobic channel and bind to the active site. Pancreatic lipase activity is affected by *Colipase*, the exocrine protein of the pancreas. *Colipase* is formed by the division of pro-colloidal lipase-producing (*Procolipase*) restricted by the pancreas. *Procolipase* can specifically bind to the terminal C lipase area of the pancreas and not cause any changes to its conformation (Mancini & Halpern, 2006).

The results showed that inhibitory compounds could bind to the amino acid residue of the hydrophobic cavity at the catalytic site of lipase, resulting in a decrease in enzymes. Some compounds that can inhibit lipase activity obtained from microorganisms and plants are presented in Table 1.

Table 1. Compounds Potentially Inhibit Lipase Activity Based on Research Results

Compound Name	Reference
Stilbene, phenolic acid, flavonoids, anthrax in fungi *P. multiflorum*	Kim et al., (2019)
Panclicins A and B produced by *Streptomyces* sp. NR 0619	Moreno et al., (2003); Ono et al., (2006)
Hydroxyciic acid in *Garcinia cambogja*	Iswantini et al., (2010)
Flavonoids, saponins, steroids, and tannins in tamarind leaves	Pradono et al., (2012)
Alkaloids, saponins, flavonoids, triterpenoids, quoins, and steroids in gelugur acid fruit, galangal rhizome, and Kencur	Iswantini et al., (2010)

Extracts from medicinal plants, vegetables, fruits, and microorganisms such as fungi have been widely studied related to the inhibition of lipase activities. *P. multiflorum* inhibits lipase enzymes and treats hyperlipidemia in test animals (Wang et al., 2020). Components of *P. multiflorum* compounds are stilbene, phenolic acids, flavonoids, and anthrax KIM 08 Phenolic compounds such as gallic acid and catechins, have in vivo antioxidant activity that plays a role in inhibiting the work of enzymes (Yim et al., 1998; Luximon-Ramma et al., 2002). In addition, anthrax has anti-inflammatory, hemostatic, laxative, and anti-bacterial activities (Yim et al., 1998).

In addition, there are also Panclicins, compounds that are known to inhibit pancreatic lipase activity. This compound is produced by *Streptomyces sp.* NR 0619, namely *Panclicins A* and *B,* are alanine compounds (Moreno et al., 2003; Ono et al., 2006). *Panclicins C, D,* and *E* are glycine compounds (Hatano et al., 1997; Moreno et al., 2006). Alanine compounds have a weaker inhibition power of two to three times that of glycine-containing compounds (Mutoh et al., 1994; Yoshinari et al., 1994). Research from medicinal plants in Indonesia revealed that methanol extract of Dutch teak leaves, a single and combined extract of bangle *in vitro*, was also able to inject lipase isolated from *Rhizopus arrhizus* (Rahardjo et al., 2006).

Some studies show that there are plants that could potentially be used as lipase inhibitors in addition to microbes. Some of these plant extracts include *Cassia mimosoides* herb extract, soybean seeds, grape seeds, ginger rhizomes, *Kochia scoparia* fruit, *Juglans mandshurica* fruit, *Platycodon grandiflorus* root, and *Actinidia arguta* plant root is also known to be able to inhibit pancreatic lipase *in vitro* (Iswantini et al., 2010). *In vivo*, dutch teak leaf ethanol extract is able to inhibit the activity of serum lipase *Rattus novergicus* (Rahardjo et al., 2006). the plant

that can be anti-obesity is *Garcinia cambogja* because it contains much hydroxycirate acid (Iswantini et al., 2010). Galangal and kencur are potentially anti-obesity because their ethanol extracts can effectively lower cholesterol, triglycerides, and total phospholipids in tissues and serums. Tamarind leaves are also known to have the ability to inhibition of pancreatic lipase in vitro. The content of tamarind leaves is bioactive compounds such as flavonoids, saponins, steroids, and tannins (Pradono et al., 2012). The results showed that tamarind leaf water extract has an inhibition power at a concentration of 300 ppm, 39.4%. In addition, it is also known that the key rhizome pepet (*Kaempferiae rotundae*) is a medicinal plant that can lose weight through the suppression mechanism of pancreatic lipase activity. The bioactive compounds that can inhibit pancreatic lipase activity are flavonoids, tannins, and saponins with an inhibition power of 65.1% at a concentration of 200 ppm (Pradono et al., 2012).

Gelugur acid fruit, galangal rhizome, and kencur extracted with 70% ethanol solvent also have an inhibition power of 86.3% at a concentration of 150 ppm, galangal rhizomes of 56.2% at a concentration of 200 ppm and kencur extract of 37.6% at a concentration of 300 ppm. Its bioactive compounds include alkaloids, saponins, flavonoids, triterpenoids, calcons, and steroids (Iswantini et al., 2010). Dayak onions, also known as the onions, have almost all phytochemical content, including alkaloids, flavonoids, phenolics, tannins, saponins, and calcons.

Secondary Metabolite Induction of Lipase Inhibitors by Fermentation

Secondary metabolite induction can be done in various ways, one of which is by fermenting microorganisms. Many studies have proven that the production of secondary metabolite compounds in medicinal plants can be increased in the presence of fermentation. Microorganisms that work in the fermentation process will produce various enzymatic reactions that play an important role in breaking down plant tissues and modifying the active makeup of active plant ingredients. This is evidenced in some jeringau plants and sleigh rhizomes.

Jeringau (*Acorus calamus*) is a rhizome plant that is widely used as a traditional medicine for infectious diseases caused by bacteria or fungi (Wijaya & Surdijati, 2020). Its ability as an antimicrobial is due to the presence of phenolic compounds, flavonoids, alkaloids, terpenes, and tannins in the jeringau (Barua et al., 2014). The content of secondary metabolites of plants is stored in vacuoles, which are the inside of plant cells protected by cell walls (Dhaniaputri, 2015). To obtain secondary metabolite compounds in the jeringau need to be extraction, and destruction of the cell wall, for example, by fermentation.

This is done because plants have a strong cell wall. In the presence of cell destruction by these microorganisms, secondary metabolites are expected to be released maximally (Wijaya & Surdijati, 2020). The fermentation process in plants can cause phenol levels to increase (Sulasiyah et al., 2018). In the study, it was produced that the phenol levels of fresh rhizome extract are different from those fermented. Fermented jeringau rhizome extract has a higher phenolic content than fresh jeringau rhizome extract. The increase in phenolic levels after this fermentation reached 129.82%. This increase in phenolic groups occurs in the fermentation process due to the breakdown of the cell wall and microorganisms that metabolize through enzymatic reactions (Ayuratri & Kusnadi, 2018).

Another plant that experiences increased phenolic levels after fermentation is the rhizome of sleighs (*Curcuma heyneana*). Rhizomes are widely used to maintain skin health by the community. Rhizomes that have been extracted contain phenol compounds, curcumin, and flavonoids. The existence of a fermentation process carried out on the rhizomes of sleighs causes the levels of phenolic compounds to increase. This is known when determining phenolic levels. Fresh sleigh extract has a phenolic level of 9,476 ± 2,042 mgGAE / gram, while fermented sleigh extract produces phenolic compounds of 61,333 ± 1,643 mgGAE / gram. This increase in phenolic levels occurs due to an enzymatic reaction on the substrate, thus releasing high phenolic compounds as the final product (Murelina & Wijayanti, 2018).

Some secondary metabolite compounds lipase inhibitors that can be increased production through fermentation are flavonoid compounds. Flavonoid compounds are antioxidants that can work as pancreatic lipase inhibitors and decrease appetite. Flavonoids are phenolic compounds that have an essential role in preventing various diseases through antioxidant activity. Through its antioxidant potential, this compound can prevent and reduce the accumulation of fat in the body to treat the problem of obesity and its risk factors (Anwar et al., 2017). Inhibition of triglyceride hydrolysis through inhibition of lipase enzymes can reduce and prevent obesity (Han et al., 2005). Flavonoids can also decrease the accumulation of lipids in the heart by inhibiting glucose absorption and suppressing the breakdown of polysaccharides into monosaccharides (Al Shukor et al., 2016). This causes fat absorption to decrease so that you lose weight.

In addition, polyphenol compounds are also known to potentially prevent obesity and inhibit enzymes associated with fat metabolisms, such as pancreatic lipase, lipoprotein lipase and glycofosate dehydrogenase (Yoshikawa et al., 2002). Phenol extract can also lower glucose, triglyceride, and LDL cholesterol levels and increase energy expenditure and oxidation of weight loss (García et al., 2009; Terra et al., 2009).

Conclusion

Excessive consumption of foods high in carbohydrates and fats can cause excess fat in his body. The excess that occurs is caused by the inability of the body to store fat reserves so that it is buried in fat tissue located under the skin and around the stomach. Pancreatic lipase inhibitors have an important role in human fat metabolism. Inhibition of triglyceride hydrolysis through inhibition of lipase enzymes can decrease and prevent obesity. Secondary metabolite induction can be fermented with microorganisms. Many studies have proven that the production of secondary metabolite compounds in medicinal plants can be increased in the presence of fermentation. Flavonoids can decrease the accumulation of lipids in the heart, reduce glucose absorption, inhibit the breakdown of polysaccharides into monosaccharides. In addition, compounds such as alkaloids, tannins, saponins, triterpenoids, quinones, steroids, stilbene, phenolic acids, anthrax, panclicins, and hydroxylic acid also play an essential role as compounds that can inhibit lipase activity in the body.

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Declaration statement

The authors reported no potential conflict of interest.

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