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Effects of Combined Lemongrass Extract (*Cymbopogon citratus*) and Physical Exercise on Lipid Profile in Male Wistar Rats (*Rattus norvegicus*) with Hyperlipidemia Model: A Literatur Review

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ABSTRACT

Hyperlipidemia remains a significant global health concern as a major risk factor for cardiovascular diseases. This review examines the potential synergistic effects of combining lemongrass (*Cymbopogon citratus*) leaf extract and physical exercise on improving lipid profiles in hyperlipidemia male Wistar rats. Current evidence suggests that lemongrass extract contains bioactive compounds with antihyperlipidemia properties that can regulate lipid metabolism and exhibit antioxidant effects. Similarly, regular physical exercise improves lipid profiles through various physiological mechanisms. When combined, preliminary studies indicate that lemongrass extract and physical exercise may produce enhanced therapeutic effects in managing hyperlipidemia compared to either intervention alone. The synergistic mechanisms appear to involve improved antioxidant defense systems, enhanced lipid metabolism, reduced lipid peroxidation, and improved insulin sensitivity. This review synthesizes current research findings on this promising combinatorial approach and identifies areas requiring further investigation.

Keyword: Hyperlipidemia, Physical Exercise, Lemograss Extract, Profil Lipid

ABSTRAK

Hiperkolesterolemia tetap menjadi masalah kesehatan global yang signifikan karena merupakan faktor risiko utama penyakit kardiovaskular. Ulasan ini menelaah potensi efek sinergis dari kombinasi ekstrak daun serai (Cymbopogon citratus) dan aktivitas fisik dalam memperbaiki profil lipid pada tikus Wistar jantan dengan hiperlipidemia. Bukti terkini menunjukkan bahwa ekstrak serai mengandung senyawa bioaktif dengan sifat antihiperlipidemia yang dapat mengatur metabolisme lipid serta menunjukkan efek antioksidan. Demikian pula, olahraga teratur meningkatkan profil lipid melalui berbagai mekanisme fisiologis. Ketika dikombinasikan, studi awal mengindikasikan bahwa ekstrak serai dan olahraga dapat menghasilkan efek terapeutik yang lebih kuat dalam mengatasi hiperlipidemia dibandingkan dengan intervensi tunggal. Mekanisme sinergis tersebut tampaknya melibatkan peningkatan sistem pertahanan antioksidan, peningkatan metabolisme lipid, penurunan peroksidasi lipid, dan peningkatan sensitivitas insulin. Ulasan ini menyintesis temuan penelitian terkini mengenai pendekatan kombinatorial yang menjanjikan ini serta mengidentifikasi area yang memerlukan penelitian lebih lanjut.

Kata kunci: *Hiperlipidemia, Olahraga, Ekstrak Serai, Profil Lipid*

1. Introduction

Hyperlipidemia, characterized by elevated serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C), is a major risk factor for atherosclerosis and cardiovascular diseases (CVD). Despite advances in pharmaceutical interventions, CVD remains a leading cause of mortality worldwide, necessitating exploration of complementary therapeutic approaches [1]. Natural products and lifestyle modifications represent promising alternatives or adjuncts to conventional treatments, with growing interest in their combined effects.

Lemongrass (*Cymbopogon citratus*) has been traditionally used in many cultures for its medicinal properties, including anti-inflammatory, antioxidant, and lipid-lowering effects. Recent scientific investigations have substantiated some of these traditional claims, identifying bioactive compounds responsible for these therapeutic effects [2]. Concurrently, physical exercise is well-established as a non-pharmacological intervention for improving lipid profiles and overall cardiovascular health through multiple physiological adaptations [3]. This review aims to synthesize current evidence regarding the individual and combined effects of lemongrass extract and physical exercise on lipid profiles in hyperlipidemia Wistar rats, exploring the underlying mechanisms and potential clinical implications of this combinatorial approach [4].

2. Content

A. Hyperlipidemia

Hyperlipidemia represents a group of disorders characterized by abnormal lipid metabolism resulting in elevated serum levels of cholesterol, triglycerides, or both. The condition affects approximately 39% of the global adult population and serves as a critical modifiable risk factor for cardiovascular diseases [5]. In experimental models, particularly Wistar rats, hyperlipidemia can be reliably induced through high-fat diets, genetic manipulation, or chemical induction using agents like poloxamer-407 or streptozotocin, providing valuable platforms for investigating therapeutic interventions [6].

The pathophysiology of hyperlipidemia involves complex interactions between genetic predisposition and environmental factors, including diet, physical activity levels, and existing metabolic conditions. At the cellular level, dysregulation occurs in lipid synthesis, transport, and clearance mechanisms, involving key organs such as the liver, intestines, and adipose tissue. Prolonged hyperlipidemia contributes to atherosclerotic plaque formation through endothelial dysfunction, inflammation, and foam cell development, ultimately increasing cardiovascular risk [7].

B. Hyperlipidemia Metabolism

The metabolism of lipids in hyperlipidemia states involves dysregulation across several pathways governing lipid synthesis, transport, utilization, and excretion. In hyperlipidemia Wistar rat models, hepatic lipid metabolism alterations are particularly prominent, with upregulation of sterol regulatory element-binding proteins (SREBPs) increasing cholesterol and fatty acid synthesis. Concurrently, reduced expression of peroxisome proliferator-activated receptors (PPARs) impairs fatty acid oxidation, exacerbating lipid accumulation [8].

Lipoprotein metabolism becomes significantly altered in hyperlipidemia states. Recent studies demonstrate increased secretion of very low-density lipoproteins (VLDL) from the liver coupled with reduced lipoprotein lipase activity in peripheral tissues of hyperlipidemia rats [9]. Oxidative stress plays a crucial role in hyperlipidemia metabolism, with elevated reactive oxygen species (ROS) production promoting lipid peroxidation, oxidizing LDL particles, and contributing to endothelial dysfunction through reduced nitric oxide bioavailability. Additionally, hyperlipidemia-induced inflammation involves activation of nuclear kappa B (NF-κB) signaling pathways, increasing pro-imflammatory cytokine production and creating a chronic imflammatory state [10].

C. Lemongrass Extract (*Cymbopogon citratus*)

Lemongrass (*Cymbopogon citratus*) leaf extract has gained scientific attention for its diverse pharmacological properties, particularly its potential in managing metabolic disorders including hyperlipidemia. Phytochemical analyses have identified numerous bioactive compounds, with citral (a mixture of geranial and neral) as the predominant component, comprising 65-85% of the essential oil [11]. Additional compounds include flavonoids (luteolin, kaempferol), phenolic acids, alkaloids, tannins, and saponins, which collectively contribute to its therapeutic effects [12].

The antihyperlipidemia properties of lemongrass extract have been demonstrated in several recent experimental studies. Costa et al. (2022) reported that lemongrass extract administration (300 mg/kg/day) to hyperlipidemia rats for 28 days significantly reduced serum total cholesterol by 27%, triglycerides by 31%, and LDL-C by 36%, while increasing HDL-C by 22%. These effects were attributed to several mechanisms of action, including inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis [13]

The antioxidant capacity of lemongrass extract represents another important mechanism underlying its effects on lipid metabolism. Recent investigations have demonstrated that lemongrass extract increases antioxidant enzyme activities while reducing malondialdehyde levels, a marker of lipid peroxidation [14]. Additionally, lemongrass extract exhibits anti-inflammatory effects through suppression of NF-κB activation and subsequent reduction in pro-inflammatory cytokine production, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [15].

D. Physical Exercise

Regular physical exercise constitutes a fundamental non-pharmacological intervention for managing hyperlipidemia through multiple physiological adaptations. Moderate-intensity aerobic exercise (treadmill running at 15-20 m/min for 30-60 minutes daily, 5 days per week) for 8-12 weeks has consistently demonstrated significant improvements in lipid parameters in hyperlipidemia rats [16]. High-intensity interval training (HIIT) protocols have also shown efficacy, with some studies suggesting potentially superior effects on HDL-C levels compared to continuous moderate-intensity training.

The mechanisms underlying exercise-induced improvements in lipid metabolism are multifaceted. Increased skeletal muscle lipoprotein lipase (LPL) activity represents a primary adaptation, enhancing triglyceride clearance from circulation and reducing serum triglyceride levels by 20-30% in hyperlipidemia rat models following regular exercise training. Exercise also stimulates reverse cholesterol transport, the process by which cholesterol is removed from peripheral tissues and transported to the liver for excretion [17].

Exercise-induced mitochondrial adaptations contribute significantly to improved lipid metabolism. Regular physical activity increases mitochondrial content and function in skeletal muscle through activation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), enhancing fatty acid oxidation capacity. Additionally, exercise training improves insulin sensitivity through increased glucose transporter type 4 (GLUT4) translocation and enhanced insulin signaling pathways, indirectly benefiting lipid metabolism by reducing hepatic VLDL production [18].

E. Effects of Lemongrass Extract on Hyperlipidemia

Recent experimental investigations have provided substantial evidence for the therapeutic effects of lemongrass extract in hyperlipidemia conditions. Ramírez-Silva et al. (2021) demonstrated that daily administration of aqueous lemongrass extract (300 mg/kg) to poloxamer-407-induced hyperlipidemia Wistar rats for 30 days resulted in significant reductions in total cholesterol (32%), triglycerides (41%), and LDL-C (39%) compared to untreated hyperlipidemia controls. Histopathological examination revealed reduced hepatic steatosis and preserved hepatocyte architecture in treated animals [19].

The molecular mechanisms underlying these effects have been increasingly elucidated. Lemongrass extract reduces hepatic lipid synthesis by inhibiting sterol regulatory element-binding proteins (SREBP-1c and SREBP-2), transcription factors regulating genes involved in lipogenesis and cholesterol synthesis [20]. A dose-dependent reduction in HMG-CoA reductase expression and activity has been consistently observed in hyperlipidemia rat livers following lemongrass extract treatment. Additionally, lemongrass extract enhances fecal bile acid and cholesterol excretion, suggesting increased reverse cholesterol transport and cholesterol conversion to bile acids [21].

The antioxidant properties of lemongrass extract contribute significantly to its anti-hyperlipidemia effects. In hyperlipidemia conditions characterized by increased oxidative stress, lemongrass extract treatment significantly increases endogenous antioxidant enzyme activities while reducing lipid peroxidation products. These antioxidant effects protect LDL particles from oxidation, a critical step in atherogenesis, and preserve endothelial function through enhanced nitric oxide bioavailability [22].

F. Effects of Physical Exercise on Hyperlipidemia

Physical exercise exerts profound effects on lipid metabolism in hyperlipidemia states through multiple adaptive mechanisms. Zhao et al. (2022) comparing different exercise modalities found that moderate-intensity continuous training for 12 weeks reduced total cholesterol by 25%, triglycerides by 29%,

and LDL-C by 32%, while increasing HDL-C by 19% in high-fat diet-induced hyperlipidemia rats. Interestingly, high-intensity interval training produced comparable improvements in lipid parameters with shorter total exercise duration [23].

The exercise-induced improvement in lipoprotein metabolism involves several key adaptations. Enhanced skeletal muscle lipoprotein lipase activity represents a primary mechanism, facilitating increased triglyceride-rich lipoprotein clearance. Exercise training also increases hepatic LDL receptor expression, enhancing LDL-C removal from circulation. Additionally, regular physical activity stimulates lecithin-cholesterol acyltransferase (LCAT) activity, promoting HDL maturation and reverse cholesterol transport [24].

Exercise-induced improvements in insulin sensitivity significantly impact lipid metabolism in hyperlipidemia states. Regular physical activity enhances insulin signaling pathways, reducing insulin resistance that typically accompanies hyperlipidemia [25]. This improved insulin sensitivity decreases hepatic VLDL production and secretion. Furthermore, exercise training reduces adipose tissue inflammation, creating a more favorable metabolic environment for lipid homeostasis [26].

G. Effects of Combined Lemongrass Extract and Physical Exercise on Hyperlipidemia

The combination of lemongrass extract and physical exercise represents a promising integrative approach for managing hyperlipidemia, potentially offering synergistic benefits. Kumar et al. (2021) investigated this combinatorial approach in high-fat diet-induced hyperlipidemia Wistar rats, comparing four intervention groups: control, lemongrass extract (200 mg/kg/day), exercise (moderate-intensity treadmill running, 5 days/week), and combined therapy for 10 weeks [27]. The combined intervention demonstrated superior lipid-lowering effects, reducing total cholesterol by 42% (versus 28% and 25% for extract and exercise alone, respectively), triglycerides by 47% (versus 33% and 30%), and LDL-C by 51% (versus 35% and 31%), while increasing HDL-C by 38% (versus 22% and 20%).

The synergistic effects observed with combined therapy appear to result from complementary mechanisms of action. The combination enhances hepatic lipid metabolism more effectively than either intervention alone, with García-Pérez et al. (2022) reporting significantly greater reductions in hepatic steatosis and triglyceride content. Mechanistically, the combination more potently suppresses hepatic SREBP-1c expression while upregulating PPAR-α expression, creating a metabolic environment that simultaneously reduces lipogenesis and enhances fatty acid oxidation [28].

Oxidative stress reduction represents another area where synergistic effects are evident. The combination therapy increases hepatic antioxidant enzyme activities more substantially than either intervention alone, while more effectively reducing markers of oxidative damage [29]. This enhanced antioxidant capacity may result from lemongrass extract providing exogenous antioxidants while exercise upregulates endogenous antioxidant defense systems through hormetic adaptations. Additionally, the combined approach more effectively improves endothelial function, attributed to enhanced nitric oxide bioavailability and reduced inflammatory markers [30].

The combination also shows superior effects on glucose metabolism and insulin sensitivity compared to monotherapy, with greater reductions in fasting insulin levels and HOMA-IR scores in the combined intervention group [31]. Moreover, the combination therapy more effectively modulates gut microbiota composition, increasing beneficial bacteria while reducing pathogenic strains, potentially contributing to improved lipid metabolism through altered bile acid metabolism and reduced endotoxemia [32].

3. Conclusion

This comprehensive literature review illuminates the complex molecular mechanisms underlying the therapeutic effects of lemongrass (*Cymbopogon citratus*) extract on hyperlipidemia and inflammation. The evidence compiled from recent research demonstrates that lemongrass extract exerts its beneficial effects through multiple interconnected pathways that synergistically modulate lipid metabolism and inflammatory processes [33].

The bioactive compounds in lemongrass extract, particularly flavonoids, and phenolic compounds, target key molecular pathways including PPAR signaling, HMGCR inhibition, AMPK activation, and NF-κB suppression. These mechanisms collectively contribute to improved lipid profiles, reduced inflammatory responses, and enhanced metabolic function [34]. The intercorrelation between these pathways creates a therapeutic network that addresses both the metabolic and inflammatory aspects of hyperlipidemia, offering advantages over conventional therapies that typically target isolated pathways.

Clinical evidence increasingly supports the efficacy and safety of lemongrass extract for managing hyperlipidemia and inflammation, with standardized preparations showing significant improvements in lipid profiles and inflammatory markers in controlled trials [35]. These findings position lemongrass extract as a promising natural therapeutic option, particularly for individuals with mild to moderate hyperlipidemia, those with concurrent inflammatory conditions, or as an adjunct to conventional treatments.

Future research directions should focus on further elucidating the specific bioactive compounds responsible for each therapeutic effect, optimizing extraction and standardization methods, and conducting larger-scale clinical trials with diverse patient populations. Additionally, investigating potential synergistic effects with conventional antihyperlipidemic medications could unveil new integrative treatment approaches. In conclusion, the scientific evidence reviewed herein provides a strong foundation for the continued exploration and development of lemongrass extract as a natural intervention for hyperlipidemia and inflammation. The multifaced mechanisms of action and favorable safety profile make it a valuable addition to the therapeutic against thes prevalent and interconnected health conditions.

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