Effects of High Intensity Interval Training and Asparagus Root Extract Supplementation on Biomarkers of Cardiovascular Health and Disease and Cardiorespiratory Fitness in Overweight and Obese Subjects

TADSAWIYA PADKAO

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR DOCTOR DEGREE OF PHILOSOPHY
IN BIOMEDICAL SCIENCE
FACULTY OF ALLIED HEALTH SCIENCES
BURAPHA UNIVERSITY
2025

ผลของการออกกำลังกายแบบหนักสลับเบาและการบริโภคสารสกัดจากโคนหน่อไม้ฝรั่งต่อตัวชี้วัดทางชีวภาพของสุขภาพและโรคทางระบบหัวใจและหลอดเลือด และสมรรถภาพของหัวใจและปอดในอาสาสมัครที่มีน้ำหนักเกินและอ้วน

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The Dissertation of Tadsawiya Padkao has been approved by the examining committee to be partial fulfillment of the requirements for the Doctor Degree of Philosophy in Biomedical Science of Burapha University

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TADSAWIYA PADKAO : EFFECTS OF HIGH INTENSITY INTERVAL TRAINING AND ASPARAGUS ROOT EXTRACT SUPPLEMENTATION ON BIOMARKERS OF CARDIOVASCULAR HEALTH AND DISEASE AND CARDIORESPIRATORY FITNESS IN OVERWEIGHT AND OBESE SUBJECTS. ADVISORY COMMITTEE: PIYAPONG PRASERTSRI, 2025.

Introduction: High-intensity interval training (HIIT) is widely used in athletics, but its effects on obesity remain unclear. Similarly, the impact of asparagus root crude extract supplementation, which contains ecdysteroids known for their effectiveness in anti-atherosclerosis and promoting muscular growth, on obesity is inadequately understood. Notably, no study has explored the combination of HIIT and asparagus root extract supplementation in the context of obesity. Thus, the objectives of this study was to compare changes in lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness after HIIT combined with asparagus stem extract supplementation in overweight and obese participants, in comparison to control group.

Methods: The randomized controlled trial involved 72 individuals with overweight and obesity (aged 18-30 years and with a body mass index (BMI) > 23 kg/m^2). Participants were randomly assigned to one of four groups: Control (CON), HIIT (HIIT), Asparagus (ASP), and Combined (COM). Over a 12-week period, HIIT with Tabata protocol sessions included body weight progressive interval training consisting of 8 bouts with 20 seconds of high-intensity training (80-90% of maximum rating of perceived exertion), interspersed with 8 periods of 10 seconds of active rest at low-intensity (40-50% of maximum rating of perceived exertion), performed three days per week. Additionally, participants consumed 1.71±0.24 mg/kg/day of 20E of asparagus root crude extract daily in capsule form over the same 12-week period. Various parameters such as white blood cell count, inflammatory biomarkers, oxidative stress biomarkers, lipid profiles, fasting glucose levels, body composition,

vital signs, chest expansions, respiratory muscle strength tests, pulmonary function tests, and cardiopulmonary fitness tests were assessed at both pre-test and 72-hour post-test periods.

Results: 1) The 12-week home-based HIIT program was safe and resulted in a reduction in white blood cell counts, specifically Eosinophils (179±81 /mm^3, p<0.05), and lowered cholesterol levels (-13.89±37.25 mg/DL, p<0.05). It increased the levels of high-density lipoprotein (HDL) by 4.56 mg/dL and reduced the Cholesterol/HDL ratio (-0.64 ±0.45 mg/dL, p<0.05) and the LDL/HDL ratio (-0.23±0.45, p<0.05). Additionally, it increased oxygen saturation levels (0.89±1.28%, p<0.05) and enhanced the expiratory muscles pressure (MEP, 7.61±13.71 cmH_2O, p<0.05) and endurance during exercise (72.33±82.15 seconds, p<0.05). However, it did not cause changes in inflammatory processes, body composition, lung volume, or lung function. 2) Consumption of asparagus root extract over the 12-week period exacerbated cholesterol 6.67±19.47 mg/dl (p<0.05), reduced HDL 1.72±7.92 mg/dl (p<0.05), increased cholesterol/HDL 0.22±0.61 mg/dl (p<0.05), increased LDL/HDL 0.33±0.57 mg/dl (p<0.05), exacerbated oxidative stress (malondialdehyde increased 3.30±1.82 µM, p<0.05, resulting in an increase in eosinophil counts (3.95±2.97%, p<0.05). Nevertheless, it does not bring about changes in fat and sugar levels, body composition, proportions, vital signs, the strength of breathing muscles, or physical fitness. 3) Participating in COM group for twelve weeks resulted in a decrease in eosinophil white blood cells, reduced inflammation in the body (IL-6 decreased 1.75±7.36 pg/ml, p<0.05), decreased oxidative stress (protein carbonyl decreased 0.32±0.47 pg/ml, p<0.05), decreased cholesterol/HDL ratio (0.44±0.91, p<0.05), and a reduced LDL/HDL ratio (0.12±0.30, p<0.05). It also led to a reduced waist-hip ratio (0.88±0.05, p<0.05), enhanced MEP (7.11±13.05 cmH_2O, p<0.05), and increased lung function (FEV_1/FVC and $FEV_1/FVC_{\%predicted}$ increased 2.44±7.17% and 2.83±8.05%, p<0.05, respectively) and resulting to increase exercise endurance time 64.83±76.79 seconds (p<0.05) and improve peak oxygen consumption 0.72±2.92 l/min/kg (p<0.05). However, there were no changes lung volume.

Discussion: The results demonstrated that HIIT combined with asparagus

root extract supplementation was safe for use in individuals with healthy obesity. Moreover, it could lead to a decrease in eosinophil count, reduced chronic inflammation and oxidative stress, a decrease in the total cholesterol/HDL ratio, waist-hip ratio, and upper body fat percentage, improved pulmonary function, and cardiopulmonary fitness in people with overweight and obesity. However, be aware of research limitations.

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Tadsawiya Padkao

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CHAPTER 1

INTRODUCTION

1. Rationale and background

Globally, obesity and overweight are major public health concerns in many countries. They cause several serious chronic diseases and twice-fold increase the risk of the current severe illness from coronavirus disease 2019 (COVID-19) (Richter, Alrubayyi, Teijeira Crespo, Oxford-Cardiff, & Hulin-Curtis, 2021). The worldwide prevalence of overweight and obesity nearly tripled since 1975. In 2016, aboult 13% of adults aged 18 years and over (~650 million) were obses and 39% of adult population (~1.9 billion) were obese (WHO, 2016). In Thailand, data from 2017 showed that the prevalence of obesity and overweight was approximately 34.7% among adults aged 18 years and older (30.9% in men and 38.3% in women) (WHO, 2017).

The World Health Organization (WHO) defines obesity and overweight as excessive fat accumulation that may impair health. The causes of obesity are multifactorial, involving genetic, behavioral factors, environmental, and energy-balance dysregulation. (Heymsfield & Wadden, 2017; Jukaku & Williams, 2021). Greater energy intake than energy expenditure causes “positive energy balance” (K. D. Hall, Guo, Dore, & Chow, 2009; Popkin & Hawkes, 2016). According to the conventional WHO classification, overweight is defined as a body mass index (BMI) between 25.0 and 29.9 kg/m², and obesity is defined as a BMI of 30.0 kg/m² or higher. Additionally, an alternative BMI classification has been proposed for the Asian population, in which overweight is defined as a BMI between 23.0 and 24.9 kg/m², and obesity as a BMI greater than 24.9 kg/m² (World Health Organization. Regional Office for the Western, 2000).

Overweight and obesity are major risk factors for chronic non-communicable diseases (NCDs) such as coronary heart disease, high blood pressure, cerebrovascular disease and type 2 diabetes. The NCDs are considered an important public health problems in Thailand (Health, 2021). Previous studies have shown the mechanical association beween overweight and obesity and the development of type 2 diabetes

mallitus. In overweight and obesity, persons insulin level is higher than normal persons but less effectiveness in lowering blood sugar. This condition, known as insulin resistance, is considered a preclinical marker of type 2 diabetes mellitus. (Tchkonia et al., 2013). Moreover, inflammation-related cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been reported to be elevated in individuals who are obese or overweight (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Lafontan, 2005). Oxidative stress is a key contributor to the pathogenesis of hypertension, especially in the context of obesity (Marseglia et al., 2014; Rother, 2007). Prolonged high insulin level stimulates chronic overactivity of the sympathetic nervous system which is present in some patients with obesity. Consequently, tachycardia and vasoconstriction are exhibited and and high blood pressure is subsequently presented in these persons (J. E. Hall et al., 2010; Thorp & Schlaich, 2015). Oxidative stress is a common pathological feature in individuals with overweight or obesity. Increased malondialdehyde (MDA) which the products of the peroxidation of polyunsaturated fatty acids and decreased of antioxidants production are result (Marseglia et al., 2014). Chronic low-grade systemic inflammation is a hallmark of obesity, underscoring the complex interactions between adipocytes and immune cells (Maurizi, Della Guardia, Maurizi, & Poloni, 2018). Obesity is characterized by a significant increase in adipocyte size and is commonly associated with adipose tissue dysfunction. Adipose tissue dysfunction is characterized by decreased release of homeostatic protective factors and increased activation of stress related pathways leading to pathological adipokine release leading to monocyte recruitment and macrophage accumulation and development of low-grade inflammation (Sun, Tordjman, Clément, & Scherer, 2013). Thus, elevated levels of inflammatory cytokines, free fatty acids and lipid intermediates in nonadipose tissues contribute to impair insulin signaling and insulin-resistant state (Tchkonia et al., 2013).

Impaired pulmonary function is frequently observed in individuals who are overweight or obese. Obesity significantly increases mast cells in adipose tissue. Mast cells are key mediators of allergy (Poglio et al., 2010). Additionally, leptin also plays a significant role in regulating resoiratory drive and may contribute to the pathogenesis of airway diseases. (Bassi et al., 2014; Polotsky et al., 2004). Movement

of the lungs and chest wall is altered significantly in obesity, largely due to fat deposits in the mediastinum and the abdominal cavities. These alterations reduce the compliance of the lungs, chest wall and air entire respiratory system (Hedenstierna & Santesson, 1976; Naimark & Cherniack, 1960; Pelosi et al., 1998; Schachter, Salome, Peat, & Woolcock, 2001; J. T. Sharp, Henry, Sweany, Meadows, & Pietras, 1964). These alterations modify the breathing pattern, leading to a significant reduction in both expiratory reserve volume (ERV) and the static resting lung volume, referred to as functional residual capacity (FRC) (Jones & Nzekwu, 2006). Dynamic measures of pulmonary function such as a forced vital capacity (FVC) and a forced expiratory volume in one second (FEV_1) are slightly reduced in obesity, but FEV_1/FVC ratio is usually unaffected (Biring, Lewis, Liu, & Mohsenifar, 1999; Lazarus, Sparrow, & Weiss, 1997; Schachter et al., 2001; Sin, Jones, & Man, 2002; Zerah et al., 1993). Taken together, these findings suggest that obesity does not substantially impair the dynamic lung function related to full lung inflation or deflation, but it significantly reduces resting lung volumes, also known as static lung volumes.

Severe obesity has been reported to reduced cardiorespiratory fitness (CRF) (Amati, Dubé, Shay, & Goodpaster, 2008; Gallagher et al., 2005; Lee, Blair, & Jackson, 1999; Miller et al., 2012). Low CRF is associated with lower energy expenditure (Arciero, Goran, & Poehlman, 1993; Shook et al., 2014), higher BMI (Gallagher et al., 2005; Miller et al., 2012), and increased waist circumference (Dyrstad, Edvardsen, Hansen, & Anderssen, 2019). Since lower CRF can lead to both reduced daily activity levels and decreased potential for energy expenditure during physical activities, it plays a significant role in overall health outcomes. In contrast, improving CRF could potentially induce weight reduction, consequently reduce AT (Blair, Cheng, & Holder, 2001; De Souza, Faintuch, & Sant'Anna, 2010; Katch, Katch, & McArdle, 1991). The most commonly used measure of CRF is maximal oxygen consumption (VO_2max). A higher VO_2max corresponds to greater energy expenditure at any given relative work intensity, reflecting improved CRF.

Number of modalities may be used to treat overweight and obesity with goals at 1) to reduce weight and maintain weight; 2) to eliminate abdominal fat; and 3) to improve CRF. These interventions encompass physical activity or exercise, dietary therapy, behavioral therapy, combined or lifestyle therapy, pharmacotherapy, and

bariatric surgery. The major evidences strongly recommend the combination of an increased physical activity/exercise and a reduced calorie diet. The American College of Sports Medicine (ACSM) recommends an exercises for weight loss is a moderate-to-vigorous intensity exercise which is also known as aerobic exercise.

High-intensity interval training (HIIT) is a form of aerobic exercise that has been gaining popularity. HIIT consists of repeated bouts of high-intensity exercise interspersed with periods of low-intensity activity or rest, with variable recovery durations. The exercise periods vary in duration, ranging from 5 seconds to 8 minutes, and are conducted at intensities between 80% and 95% of an individual's estimated maximal heart rate. The duration of recovery periods also varies, leading to total exercise sessions ranging from 20 to 60 minutes. (Campbell & Rutherford, 2018; Roy, 2013). HIIT provide similar fitness benefits as continuous endurance exercise, but in shorter periods of time. This is because HIIT tends to burn more calories than traditional exercise, especially during exercise recovery i.e., 2 hours (Campbell & Rutherford, 2018; Roy, 2013). Benefits of HIIT include the following: 1) improved aerobic and anaerobic fitness; 2) improved insulin sensitivity, glucose tolerance, and lipid profiles; 3) reduced arterial stiffness and improved blood pressure; 4) increased skeletal muscle fat oxidation; 5) increased postexercise metabolism; 6) enhanced weight loss; 7) reduced abdominal and subcutaneous fat; and 8) increased exercise adherence (ACSM, 2014; Atakan, Li, Koşar Ş, Turnagöl, & Yan, 2021; Campbell & Rutherford, 2018; Roy, 2013). HIIT can be performed in any exercise modality, including cycling on an ergometer (Francois & Little, 2015; Hannan et al., 2018; McEwan, Arthur, Phillips, Gibson, & Easton, 2018), walking on teadmill (Arboleda-Serna, Feito, Patiño-Villada, Vargas-Romero, & Arango-Vélez, 2019; McEwan et al., 2018), functional training (Feito, Heinrich, Butcher, & Poston, 2018), resistance training (Prasertsri & Padkao, 2021) and in form of exercise class (Hannan et al., 2018).

While it's widely known that extended periods of low or moderate-intensity aerobic training (>45 minutes) can aid in burning body fat and enhancing fitness, there are alternative techniques that offer greater effectiveness and efficiency. These methods deliver satisfying results without necessitating prolonged durations. An

alternative technique is Tabata Training. It follows a 2:1 ratio for work and rest time during training exercises (Tabata et al., 1996).

Tabata training is defined as training or exercise performed at an intensity that exhausts subjects during the 7^{th} or 8^{th} sets of exercise bouts, each set consisting of 20 seconed of exercise followed by a 10-second rest period (I. Tabata, 2019). Tabata training was originally developed for bicycling exercises. However, similar protocols have been adapted to other forms of exercise, including running and various bodyweight-bearing exercises such as burpees and squat jumps. Tabata training provides several benefits, including increased fat oxidation, elevated metabolism during and after exercise, efficient time utilization, improvements in anaerobic and aerobic energy systems, and adaptability to a variety of activities. (I. Tabata, 2019; Tabata et al., 1997; Tabata et al., 1996). One of the most importance change after Tabata training is enhance buffer capacity of muscles recruitd that allows more muscle lactate formation which results in propotional glycolytic ATP production (R. L. Sharp, Costill, Fink, & King, 1986). Previous studies have demonstrated that 4 to 12 weeks of various bodyweight-bearing training programs can lead to a 5–18% increase in VO_2max (Viana et al., 2019). Previous studies of Tabata training in obese pre-adolescent boys and inactive adolescents show quite low dropout rates (6.3%-10%) (Chuensiri, Suksom, & Tanaka, 2018; Logan et al., 2016). These rates may indicate that Tabata training was tolerable and positively accepted. A review of previous Tabata protocol studies suggests the need for further basic research on HIIT, specifically involving Tabata training. This research would help elucidate the mechanisms behind the beneficial effects of such training on health-related outcomes, ultimately contributing to an enhanced quality of life (Izumi Tabata, 2019).

To address limitations of traditional exercise protocols and provide an effective and efficient program for young adult obesity, and, likewise, barriers to exercise in adolescents include financial constraints, limited access to activity, insufficient of core physical literacy skills and inadequate familial support (Charlton et al., 2014), thus, one of the exercise strategies employed in our study is HIIT, utilizing body weight as the primary form of resistance. Home-based HIIT can solve these exercise barriers in young adult because our home-based HIIT is not used any

expensive device, done at their house or dormitory, easy to learn and there is a video clip to help make it easier to understand.

"20-hydroxyecdysone or 20E" is a growth steroid hormone which has been found in insects, shrimp, crabs, and invertebrates in *Arthropoda phylum* and other phylum. The hormone is often referred to as molting hormone because it is found in all stages of these insects growth. Previous studies showed that amount of the 20-hydroxyecdysone that found in plants is higher than that found in animals (Laurence Dinan, 2009; L. Dinan, Bourne, Whiting, Dhadialla, & Hutchinson, 2001; L. Dinan, Hormann, & Fujimoto, 1999; L. Dinan, T. Savchenko, & P. Whiting, 2001). Phytochemicals are effective in against bacteria and fungi, regulating physiological processes to maintain homeostasis (adaptogenic), immunoprotective, anti-inflammatory, anti-diabetic, anabolic and hepatoprotective, wound-healing and anti-tumor. Many studied used of 20-hydroxyecdysone compounds in terms of preventing or reducing the risk of diseases and in promoting health in both general people and athletes. 20-hydroxyecdysone have antioxidant effect and is often mixed into various food products (Cahlíková et al., 2011). Among the plants popularly extracted in many countries is spinach (*Amaranthus viridis*). In Thailand, extracts from the leaves and bark of the E-pae tree, *Asparagus Officinalis* (*A. Officinalis*) (L. Dinan, Dioh, Veillet, & Lafont, 2021), have been utilized, but recent research is still in the laboratory stage (Suksamrarn, Kumpun, & Yingyongnarongkul, 2002).

A. Officinalis is widely recognized as a vegetable bearing the nickname "Asparagus". Renowned as the "King of Vegetables," asparagus is esteemed for its abundance of bioactive compounds, including flavonoids, lignans, steroidal saponins, and 20E, among others (Fukushi, Onodera, Yamamori, Shiomi, & Kawabata, 2000). In various regions, asparagus is utilized for its anti-inflammatory properties and has shown promise in inhibiting cancer cell growth (Zhao et al., 2012). However, in the food and agricultural industries, only the top and stem portions of asparagus are typically consumed and processed, leading to environmental pollution due to the discarding of the base and roots. Hence, recycling residues becomes imperative for both agricultural and food industries to systematically reduce waste, which not only holds economic benefits but also contributes to ecological sustainability. Consequently, the extraction of residues into biologically active extracts is favored to

enhance their value (Shi et al., 2005). Therefore, by extracting and transforming leftover asparagus stems from cutting, selling, and processing into dietary supplements containing biologically active compounds, there is a potential to elevate the value of asparagus stems within both the food and pharmaceutical industries.

However, the pharmacological effects of ecdysteroids are currently unclear in human and clinical trials. Most studies investigated its effects in athletes on physical performance, anaerobic effects, and antroprometric outcomes. It is still lack of the knowledge regarding the effects of ecdysteriod on immune function, inflammation, oxidative stress, lipid levels and blood sugar in overweight and obese people who have high risk at NCDs.

Rationale of this study includes: 1) most of previous studies investigated the immediate effect or training effect of HIIT. The periodic effect of HIIT on changes in immune function have not been previously documented. In addition, investigating direct effects of HIIT on respiratory changes are narrowed and 2) the pharmacological effects of ecdysteroids are currently unclear in clinical trials, especially in overweight and obese people.

2. Research question

Did HIIT and asparagus root extract supplementation improve white blood cell count, inflammatory and oxidative stress biomarkers, lipid and sugar levels, and cardiopulmonary fitness in overweight and obese participants?

3. Objectives of the study

3.1 Overview objectives:

3.1.1 To compare changes in lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness after HIIT combined with asparagus stem extract supplementation in overweight and obese participants, in comparison to control group.

3.2 Specific objectives:

3.2.1 To compare changes in lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness before and after HIIT in overweight and obese participants.

3.2.2 To compare changes in lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness before and after asparagus stem extract supplementation in overweight and obese participants.

3.2.3 To compare changes in lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness before and after HIIT combined with asparagus stem extract supplementation in overweight and obese participants.

4. Hypothesis of the study

4.1 Overview hypothesis:

4.1.1 HIIT combined with asparagus stem extract supplementation for 12 weeks would improve lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness more than control in overweight and obese participants.

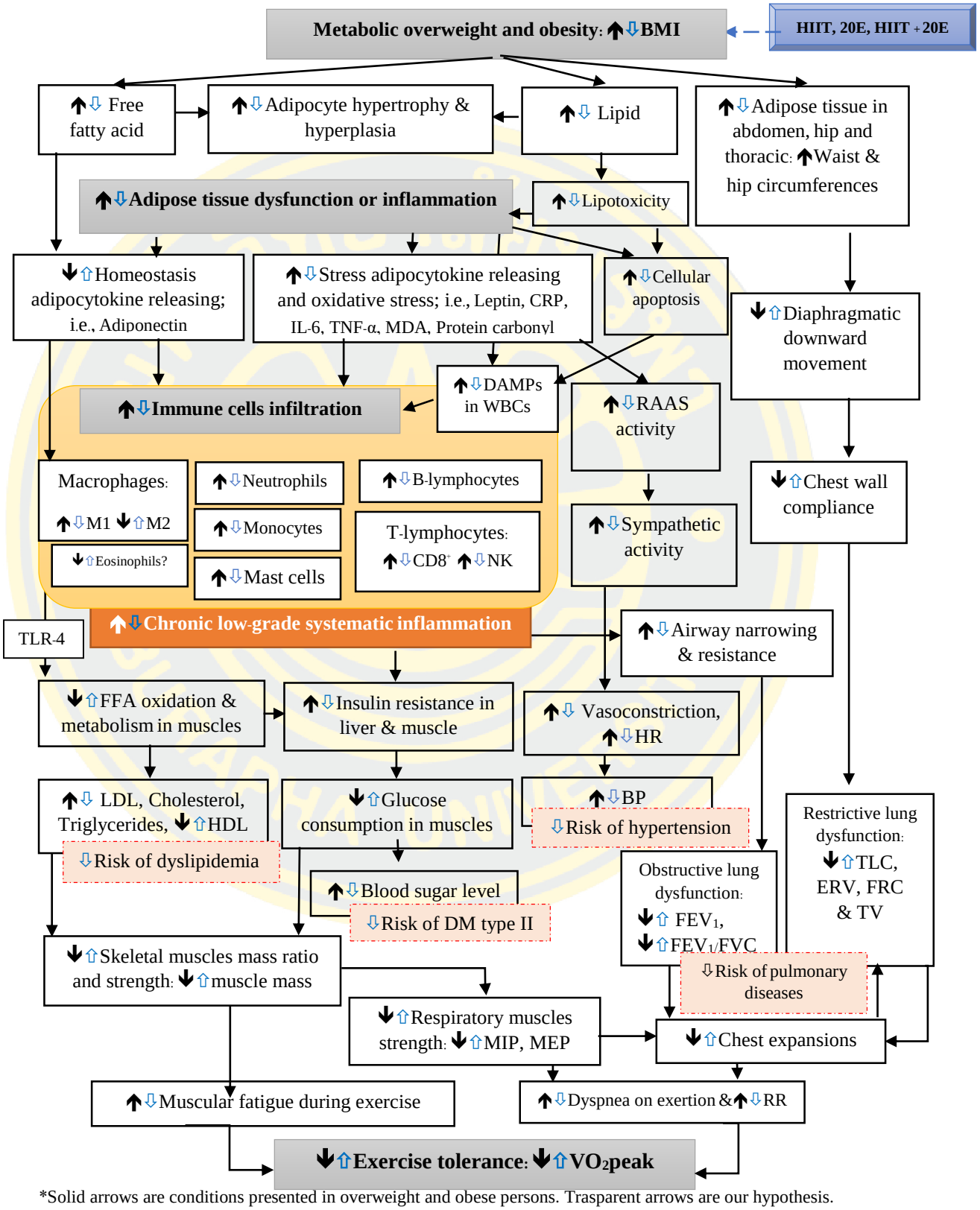
4.2 Specific hypothesis:

4.2.1 HIIT for 12 weeks would improve lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness in overweight and obese participants.

4.2.2 Asparagus stem extract supplementation for 12 weeks would improve lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness in overweight and obese participants.

4.2.3 HIIT combined with asparagus stem extract supplementation for 12 weeks would improve lipid and sugar levels, inflammatory and oxidative stress biomarkers, white blood cell counts and cardiopulmonary fitness in overweight and obese participants.

6. Conceptual framwork



*Solid arrows are conditions presented in overweight and obese persons. Trasparent arrows are our hypothesis.

CHAPTER 2

REVIEW LITERAURES

1. Overweight and Obesity

1.1 Definition and Prevalence

Overweight and obesity are defined by World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health WHO (2021). Globally, obesity and overweight are among the major public health concerns in many countries, with the number of adults who are overweight or obese now exceeding those who are underweight. The worldwide prevalence of overweight and obesity nearly tripled since 1975. In 2016, aboult 13% of adults aged 18 years and over (650 million) were obses and 39% of the world' s adult population (1.9 billion) were obese (WHO, 2016). In Thailand, the overweight and obese's prevalence is about 34.7% of adults aged 18 years and over (30.9% of men and 38.3% of women) in 2017 (WHO, 2017).

1.2 Measurements of Obesity and Its Classifications

There are a lots of measurements to classify overweight and obesity such as the body mass index (BMI), waist circumference, waist-to-hip ratio, bioelectrical impedance, skinfold thickness, dual energy X-ray absorptiometry, magnetic resonance imaging (MRI), and computerized tomography (Katch et al.). The most commonly used and WHO-recommended measure for assessing overweight and obesity is the Body Mass Index (BMI), also known as the Quetelet Index. BMI is a simple, widely accepted indicator that evaluates an individual's weight relative to their height. It is calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2).

According to conventional WHO classification, the BMI is used to classify weight conditions of general population into four groups include: 1) "Underweight" constitutes a BMI of 18.5 kg/m^2 or lesser 2) "Normal" is defined as BMI between 18.5 and 24.9 kg/m^2 3) "Overweight" constitutes a BMI between 25 and 29.9 kg/m^2 and 4) "Obese" constitutes a BMI of 30 kg/m^2 or greater. Obesity is further classified into three categories: Class I (BMI 30.0–34.9 kg/m^2), Class II (BMI

35.0–39.9 kg/m²), and Class III (BMI ≥ 40.0 kg/m²). (Obesity & World Health, 2000). Although the WHO criteria are widely used and internationally accepted, evidence suggests that these standard classifications may not be appropriate for Asian-Pacific populations. This is due to lower BMI cut-off points associated with increased risk factors and morbidities, as well as differences in body fat percentage and body composition compared to European populations. The Asian-Pacific pupolations, such as Chinese and Indian, there are a significantly increased risk of type 2 diabetes, hypertension and other noncommunicable diseases (NCDs) with BMI > 23 kg/m^2 (in Europian > 25 kg/m^2) (World Health Organization. Regional Office for the Western, 2000). Thus, an alternative BMI classification for Asian pupolation is proposed in order to has more appropiate and applicable for the pupolation. The Asian's BMI is classified as normal between 18.5-22.9 kg/m^2, overweight between 23.0-24.9 kg/m^2 and obese >24.9 kg/m^2 (World Health Organization. Regional Office for the Western, 2000) (Table 1).

Table 1 WHO classification of weight status:

Classification	General population BMI (kg/m^2)	Asian population BMI (kg/m^2)	Risk of comorbidities
Underweight	< 18.5	< 18.5	Low
Normal weight	18.5 – 24.9	18.5 – 22.9	Average
Overweight	25.0 – 29.9	23 -24.9	Increased
Obese	>29.9	> 24.9	
Obese class I	30.0 – 34.9	25.0 – 29.9	Moderate
Obese class II	35.0 – 39.9	> 29.9	Severe
Obese class III	> 39.9	-	Very severe

*Comorbidity diseases: type-2 diabetes, hypertension, dyslipidemia and albuminuria Source: (Obesity & World Health, 2000; World Health Organization. Regional Office for the Western, 2000).

1.3 Pathophysiological Mechanism of Obesity and Overweight

Pathophysiological mechanism of Obesity has a multifactorial etiology that includes genetic, environmental and behavioral influences and energy-balance dysregulation (Heymsfield & Wadden, 2017; Jukaku & Williams, 2021). The mechanisms are explained as below.

1.3.1 The Role of Genetic Factors

A lot of studies of twin, family and adoptation related obesity show a rate of heritability of BMI is high, ranging from 40%-70% (M. S. Bray et al., 2016; Williams, Mesidor, Winters, Dubbert, & Wyatt, 2015). Two recent review studies have highlighted monogenic forms of obesity, including deficiencies in the *leptin (LEP)* gene and the *melanocortin-4 receptor (MC4R)* gene. These genes are primarily expressed in the hypothalamus and play key roles in neural circuits that regulate energy homeostasis. The *MC4R* gene heterozygous mutations are currently the most common cause of monogenic obesity (Heymsfield & Wadden, 2017; Loos & Yeo, 2021; Pigeyre, Yazdi, Kaur, & Meyre, 2016). Furthermore, the most prominent signaling polygenic obese gene, which is the single nucleotide polymorphisms associated with BMI and other traits linked with obesity, is the fat-mass-and-obesity-associated-protein also known as alpha-ketoglutarate-dependent dioxygenase (*FTO*) Gene variants; individuals carrying one or two copies of the risk allele experience a weight increase of 1.2 kg or 3 kg, respectively (Loos & Yeo, 2021; Pigeyre et al., 2016). The *FTO* gene is commonly found in high metabolism organs, such as heart, renal, adipose tissue and the hypothalamus, and plays a role in controlling feeding behavior and energy expenditure (Fawcett & Barroso, 2010). The both obese monogenic and polygenic genes have been found to result in hyperplasia and/or is an onset in childhood (Heymsfield & Wadden, 2017; Loos & Yeo, 2021).

1.3.2 The Role of Environment and Behavioral Factors

Over the past several decades, factors contributing to a positive energy balance (where energy intake exceeds energy expenditure) and subsequent weight gain have included increases in per capita food availability and consumption. This trend is particularly notable for high-calorie, palatable foods frequently served in large portions (K. D. Hall et al., 2009; Popkin & Hawkes, 2016), increasing use of medicines associated with weight gain as a side effect (Apovian et al., 2015) (Table 2), decrease time spent in occupational physical activities and the substitution of leisure-time physical activities with sedentary behaviors, such as watching television and using electronic devices (Church et al., 2011; von Loeffelholz & Birkenfeld, 2000) and inadequate sleep (Heymsfield & Wadden, 2017; McAllister et al., 2009). These factors, along with others such as medical advancements, lay the groundwork for the concurrent epidemics of chronic disease and obesity (Omran, 2005).

Table 2 Drugs associated with weight gain and weight loss

Weight gain	Weight changed (kg)	Weight loss	Weight changed (kg)
Amitriptyline	1.8	Metformin	1.1
Mirtazapine	1.5	Acarbose	0.4
Olanzapine	2.4	Miglitol	0.7
Quetiapine	1.1	Pramlintide	2.3
Risperidone	0.8	Liraglutide	1.7
Gabapentin	2.2	Exenatide	1.2
Tolbutamide	2.8	Zonisamide	7.7
Pioglitazone	2.6	Topiramate	3.8
Glimepiride	2.1	Bupropion	1.3
Gliclazide	1.8	Fluoxetine	1.3
Glyburide	2.6		
Glipizide	2.2		
Sitagliptin	0.55		
Nateglinide	0.3		

Source: (Heymsfield & Wadden, 2017)

1.3.3 The Role of Energy-balance Dysregulation

The hypothalamus serves as a central hub for detecting hunger and regulating eating behavior (Brobeck, 1946). The crosstalk between the hypothalamus, other brain regions, and peripheral systems is illustrated in Figure 1. This figure depicts three interconnected major brain areas that form the core processor for controlling ingestive behavior and their relationships with the gastrointestinal tract and peripheral organe, including the microbiome, as well as cells within adipose tissue, the stomach, and pancreas, that are involved in energy storage and utilization. *The cortico-limbic system*, comprising extensive cortical regions, the hippocampus, basal ganglia, and amygdala, is connected to the hypothalamus and brainstem, providing the emotional, cognitive, and executive regulation necessary for ingestive behavior. The *hindbrain* primarily regulates meal size control, housing the necessary components to detect sensory information conveyed by vagal afferents and circulating factors. Additionally, it generates motor output related to food ingestion, digestion, and absorption. The hypothalamus, interconnected with multiple brain regions, plays a central role in regulating eating behavior and exerts significant influence on

peripheral organs via autonomic and endocrine pathways. (Berthoud, Münzberg, & Morrison, 2017; Gadde, Martin, Berthoud, & Heymsfield, 2018).

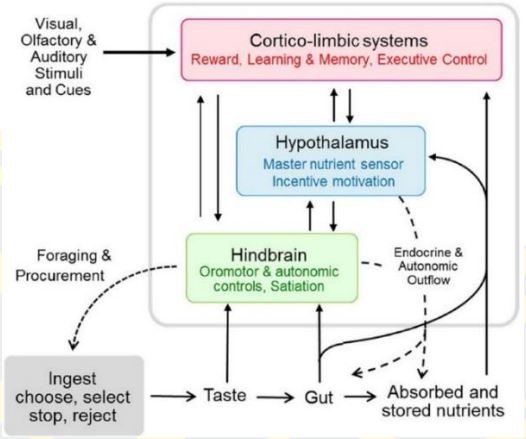


Figure 1 Neural pathways and systems involved in the regulation of ingestive behavior and energy balance.
Source: (Berthoud et al., 2017)

As mentioned above, environment and gene interact in a complex system that controls energy balance and weight (Figure 2). Neurons located in the arcuate nucleus of the hypothalamus, which are either inhibited or activated by circulating neuropeptide hormones such as insulin and leptin (both of which are elevated in obesity) play a critical role in regulating energy homeostasis by modulating food intake and energy expenditure (van der Klaauw & Farooqi, 2015). Reducing food intake or increasing physical activity results in a negative energy balance, triggering a cascade of central and peripheral compensatory adaptive mechanisms aimed at preserving vital functions. (MacLean, Higgins, Giles, Sherk, & Jackman, 2015; Obradovic et al., 2021). These adaptations may be associated with reductions in resting energy expenditure, food preoccupation and other metabolic and psychological processes, depending on the magnitude and duration of energy restriction, as illustrated in Figure 3 (Leibel et al., 2015). An increase in central orexigenic signaling may contribute to a subtle and often overlooked, counterregulatory rise in appetite and food intake, thereby attenuating the expected weight loss associated with interventions such as exercise programs (Thomas et al., 2012). The metabolic and physiological adaptations that occur during weight loss may persist into the weight-reduced state. Although the precise extent and underlying mechanisms of these effects in humans remain unclear, current evidence suggests that

individuals who have lost weight and are no longer classified as obese may not exhibit the same physiological and metabolic profiles as those who have never experienced obesity (Leibel et al., 2015; MacLean et al., 2015). High relapse rates align with this perspective and support the notion of obesity as a chronic condition necessitating ongoing vigilance and sustained weight management efforts. (Heymsfield & Wadden, 2017).

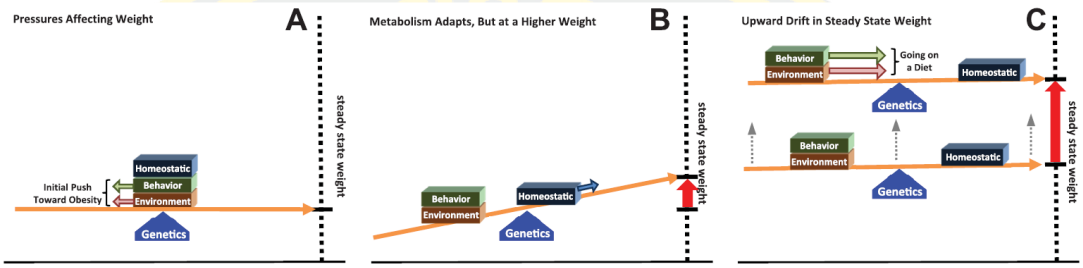


Figure 2 Biology's influence during obesity development.
Homeostatic systems adjust to prevent persistent weight loss or gain in response to changes in environmental and behavioral factors. The interaction between nonhomeostatic pressures and homeostatic adaptations is illustrated in the initial development and progression of obesity (A–C). Source: (Maclean, Bergouignan, Cornier, & Jackman, 2011)

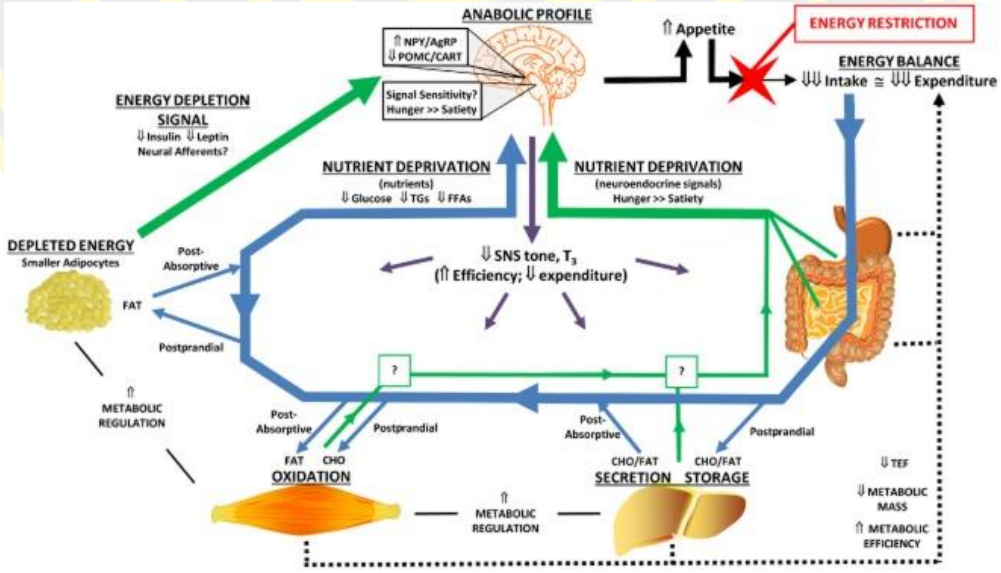


Figure 3 Homeostatic adaptations to weight loss that persist in weight maintenance.
Sorce: (Maclean et al., 2011)

2. Adipose Tissue Dysfunction in Obesity

2.1 Physiological Function of Adipocytes and Adipose Tissue

Adipose tissue (AT) comprises both adipocytes and a vascular-stromal fraction, which contains various cell types including macrophages, fibroblasts, endothelial cells, and preadipocytes (Otto & Lane, 2005). The primary functions of adipose tissue (AT) include insulating and cushioning the body, storing free fatty acids (FFAs) following food intake, and releasing FFAs during periods of fasting to maintain energy homeostasis. During the postprandial phase, FFAs are absorbed from the bloodstream into adipose tissue following the hydrolysis of triglycerides from triglyceride-rich lipoproteins by lipoprotein lipase (LPL). The mobilization of this reserve happens through the hydrolysis of adipocyte triglycerides by hormone-sensitive lipase (HSL). Insulin is the main regulator of adipocyte fat content, since it is both a potent inhibitor of HSL and an important activator of LPL, thereby enhancing FFAs uptake and triglyceride synthesis in adipocytes (Hajer, van Haeften, & Visseren, 2008; Otto & Lane, 2005).

Adipocytes act as endocrine organ or call “adipocytokines”. Adipose tissue produces a wide array of hormones and cytokines that participate in diverse physiological processes, including glucose metabolism (e.g., adiponectin, resistin), lipid metabolism (e.g., cholesteryl ester transfer protein (CETP)), inflammation (e.g., tumor necrosis factor-α (TNF-α) interleukin-6 (IL-6), coagulation (e.g., plasminogen activator inhibitor-1 (PAI-1)), blood pressure regulation (e.g., angiotensinogen, angiotensin II), and the regulation of feeding behavior (e.g., leptin). Consequently, adipose tissue exerts significant influence on the metabolic activity and function of multiple organs and systems, including skeletal muscle, the liver, vasculature, and the central nervous system (Chu et al., 2001; Ran et al., 2006; Yamauchi et al., 2001) (Table 3). Plasma levels of most adipocytokines increase in parallel with the expansion of adipose tissue and adipocyte volume; however, plasma adiponectin levels are typically reduced in individuals with obesity (Hajer et al., 2008; Skurk, Alberti-Huber, Herder, & Hauner, 2007; Wannamethee et al., 2007).

Table 3 Adipocytokines.

Full name	Adipocytokine	Effects on
Angiotensin II	AT II	Blood pressure regulation
Angiotensin converting enzyme	ACE	Blood pressure regulation
Angiotensinogen	AGT	Blood pressure regulation
Plasminogen activator inhibitor-1	PAI-1	Fibrinolysis
Leptin	Leptin	Food intake and adiposity
Tumour necrosis factor-α	TNF-α	Inflammatory process
Interleukin-6	IL-6	Inflammatory process
C-reactive protein	CRP	Inflammatory process
Adipocyte trypsin/complement factor D	Adipsin	Inflammatory process
Visfatin	Visfatin	Insulin resistance
Omentin	Omentin	Insulin resistance
Visceral adipose tissue-derived serpin	Vaspin	Insulin resistance
Adiponectin	Adiponectin	Insulin resistance and inflammatory process
Resistin	Resistin	Insulin resistance and inflammatory process
Cholesteryl ester transfer protein	CETP	Lipid metabolism process
Lipoprotein lipase	LPL	Lipid metabolism process
Hormone sensitive lipase	HSL	Lipid metabolism process
Adipocyte fatty acid-binding protein 4	A-FABP 4 (aP2)	Lipid metabolism process
Perilipin	Perilipin	Lipid metabolism process
Renitol-binding protein[4]	RBP[4]	Lipid metabolism process
Acylation stimulating protein	ASP	Lipid metabolism process
Intercellular adhesion molecule-1	ICAM-1	Macrophage activation
Macrophage chemo attractant protein-1	MCP-1	Macrophage attraction
Apelin	Apelin	Vasodilatation

Source: (Hajer et al., 2008)

2.2 Obesity and AT dysfunction

It has now been firmly established that obesity is associated with the appearance of a chronic, low inflammatory state due to changes in function of adipocytes and macrophages. This indicates that there is a pathological state, i.e. inflammation, ensues from the changes in secretory function as call in term “adipose tissue dysfunction (AT dysfunction)”. Adipose tissue dysfunction is characterized by

the hypersecretion of pro-atherogenic, pro-inflammatory, and pro-diabetic adipocytokines, accompanied by a reduced production of adiponectin (Iacobellis, Ribaudo, Zappaterreno, Iannucci, & Leonetti, 2005).

Macrophages are more prevalent in AT of obese subjects than in AT of lean subjects and the macrophage quantity relates with measures of insulin resistance (Otto & Lane, 2005). AT is divided into two types of macrophages: *M1-macrophages*, predominant in obesity, which secrete TNF-α and IL-6, thereby promoting inflammation; and *M2-macrophages*, which secrete anti-inflammatory cytokines such as IL-10 (Gordon & Taylor, 2005; Lumeng, Bodzin, & Saltiel, 2007). Interestingly, the number of macrophages in AT is reduced after weight loss (Cancello et al., 2005). The interplay between macrophages and adipocytes through paracrine effects is presumed to be central in initiating and sustaining adipocyte dysfunction. Adipocytes enlarge due to hyperalimentation. Enlarged adipocytes release increased amounts of FFAs, which can activate macrophage TLR-4, triggering the nuclear factor kappa B (NF-κB) signaling pathway and subsequently leading to elevated production of TNF-α. (Suganami, Nishida, & Ogawa, 2005). In turn, macrophage-derived TNF-α activates human adipocytes, thereby promoting lipolysis and upregulating the expression of several genes, IL-6, intracellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) (Permana, Menge, & Reaven, 2006). Monocyte migration from the bloodstream into adipose tissue, followed by their differentiation into macrophages, is further facilitated by the actions of MCP-1 and ICAM-1. This local paracrine loop, involving adipocyte-derived FFAs and macrophage-derived TNF-α, establishes a gradually worsening cycle that likely leads to a pro-inflammatory state in both macrophages and adipocytes. It's noteworthy that larger adipocytes tend to produce less adiponectin. Given that adiponectin typically inhibits TLR-activated NF-kB activity, it's assumed that low levels of adiponectin reinforce the aforementioned loop (Figure 4). Interestingly, diet-derived saturated fatty acids activate TLR-4 also directly, while poly-unsaturated fatty acids impede TLR-4.

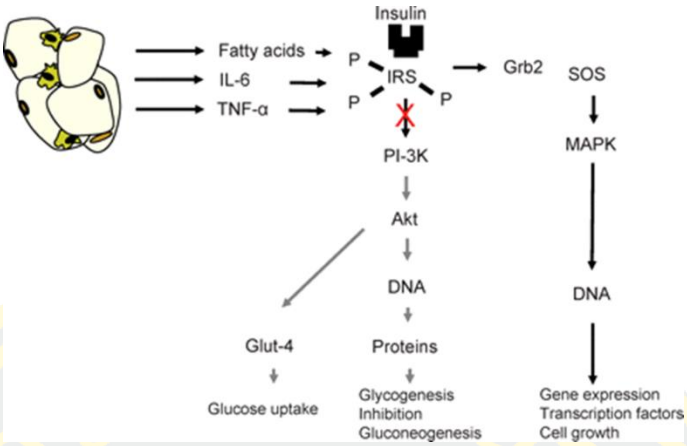


Figure 4 Adipocyte dysfunction leads to insulin resistance.

TNF-α, IL-6, and FFAs induce serine phosphorylation of insulin receptor substrate-1 and insulin receptor substrate-2, diminishing their capacity to be phosphorylated by the insulin receptor in vitro. This may also inhibit insulin receptor autophosphorylation (tyrosine kinase) activity, thereby further impairing the insulin signaling cascade. FFAs likely act through the activation of protein Kinase-C isoforms (PKC) following diacylglycerol formation, while TNF-α acts through the activation of c-Jun N-terminal kinase-1. In muscle tissue, FFAs can generate Acyl-CoA derivatives (e.g., ceramide), which may diminish Akt1 activity and consequently impair insulin action. In the liver, insulin receptor substrate-2 plays a role in inhibiting gluconeogenesis, a process often heightened in an insulin-resistant state, potentially through the activation of both PKC and c-Jun N-terminal kinase-1 by FFAs and TNF-α. (Hajer et al., 2008).

3. Obesity and Inflammation

Inflammation is a regulated process essential for maintaining tissue and organ homeostasis (Romano, 2008). Additionally, inflammation is a protective tissue response to injury that functions to eliminate or neutralize the injurious agents and remove damaged tissue (Feuerstein, Libby, & Mann, 2003). Inflammation can be classified into two types: *acute inflammation*, which is typically short-lived and characterized by edema and leukocyte infiltration and *chronic inflammation*, which persists over a prolonged period and is marked by the presence of lymphocytes and macrophages, along with angiogenesis and connective tissue proliferation. (Seki, Tani, & Arita, 2009).

Obesity, a hallmark of metabolic syndrome or “metabolic inflammation,” is associated with low-grade chronic inflammation in affected individuals (Stępień et al., 2014). This syndrome is characterized by the altered secretion of both pro-inflammatory and anti-inflammatory adipokines, primarily derived from adipose tissue, including leptin, adiponectin and resistin as well as *cytokines* and *chemokines* such as IL-6, TNF-α and MCP-1 (Lafontan, 2005). Key inflammatory markers in obesity include leptin, IL-6, and CRP, while adiponectin serves as a prominent anti-inflammatory biomarker (Ellulu et al., 2017).

3.1 Obesity and IL-6

IL-6 is a cytokine produced by various cell types, including immune cells and adipose tissue, that plays a key role in mediating inflammatory responses (Brichory et al., 2001). The IL-6 receptor is also expressed in various regions of the brain, including the hypothalamus, where it modulates appetite and energy intake. It plays a role in regulating energy homeostasis by suppressing lipoprotein lipase activity (Stenlöf et al., 2003). Previous studies have demonstrated a positive correlation between obesity and elevated plasma IL-6 levels (Straub et al., 2000), with approximately one-third of circulating IL-6 believed to originate from adipose tissue (Fontana, Eagon, Trujillo, Scherer, & Klein, 2007). The excessive release of pro-inflammatory cytokines in obesity is a critical link connecting obesity and systemic inflammation (Hotamisligil, 2006). AT responds to nutrient overload through both hyperplasia and hypertrophy of adipocytes (Figure 5). The cellular composition of AT includes endothelium, immune cells, and adipocytes (Halberg, Wernstedt-Asterholm, & Scherer, 2008). As adipocytes enlarge during obesity, the local blood supply may become insufficient, resulting in tissue hypoxia (Cinti et al., 2005). Hypoxia is proposed to induce adipocyte necrosis and macrophage infiltration into adipose tissue, which in turn triggers macrophage-mediated overproduction of pro-inflammatory mediators such as TNF-α, IL-6 and adiponectin. (Karastergiou & Mohamed-Ali, 2010). A previous study clarifies the association between BMI and a low-grade inflammation in adolescents found an elevation of IL-6 level associates with increased BMI in both males and females (Wärnberg, Moreno, Mesana, & Marcos, 2004). Circulating inflammatory mediators, including IL-6, have been theorized to significantly contribute to the development of various diseases, such as coronary heart

disease, heart failure, atherosclerosis, type 2 diabetes mellitus, and lung cancer (Danesh et al., 2008; Hansson, 2005; Sansone & Bromberg, 2012). Therefore, IL-6 plays a pivotal role in the *acute-phase inflammatory* response. It stimulates the liver to produce CRP and fibrinogen, triggers the release of white blood cells and platelets from the bone marrow, and activates endothelial cells, contributing to hemostasis (Ellulu et al., 2017; Hansson, 2005).

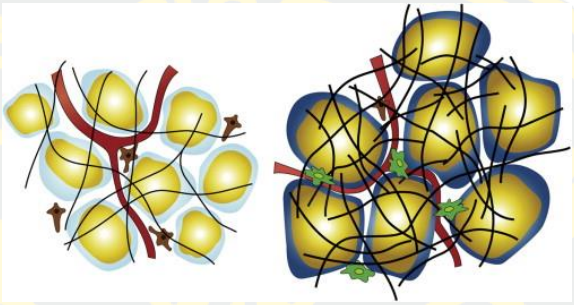


Figure 5 White adipose tissue in lean (left) compare to obese (McAllister et al.) state. Adipocytes are depicted with yellow triglyceride droplets and blue cytoplasm. In the lean state, the light blue cytoplasm indicates normoxia, whereas the dark blue cytoplasm in the obese state signifies a hypoxic condition. Preadipocytes are represented in brown, macrophages in green, blood vessels and endothelial cells in red, and the extracellular matrix in black (Halberg et al., 2008).

3.2 Obesity and C-Reactive Protein Level

CRP is a sensitive biomarker of systemic inflammation synthesized by the liver. As a nonspecific acute-phase reactant, it is traditionally employed to detect acute injury, infection and inflammatory conditions (Backes, Howard, & Moriarty, 2004). The association between obesity and elevated serum levels of CRP has been extensively elucidated through underlying pathophysiological mechanisms. The liver plays a central role in the inflammatory response by metabolizing free fatty acids and circulating triacylglycerols, which stimulates AT to release cytokines such as IL-6. Subsequently, IL-6 induces hepatocytes to express and secrete CRP, thereby linking adipose tissue inflammation to systemic inflammatory markers (G. C. Brooks, Blaha, & Blumenthal, 2010). Cross-sectional studies have investigated the relationship between obesity and CRP levels. For instance, Klisic et al. (2014) measured CRP and metabolic markers in normal-weight and overweight postmenopausal women, reporting significantly higher levels of CRP and triglycerides in the overweight group compared to their normal-weight counterparts (Klisic et al., 2014). Similarly, research by Dayal et al. (2014) examined the association between anthropometric measurements and CRP in children. Using multiple logistic regression analysis, they found that each

one-unit increase in body mass index (BMI) was associated with a 37% increase in the odds of elevated CRP levels (Dayal, Jain, Attri, Bharti, & Bhalla, 2014).

According to the American Heart Association and the Centers for Disease Control and Prevention in 2002, CRP test is a straightforward blood assay that poses minimal risk to patients. However, CRP levels can be influenced by various factors, including medications and physiological conditions. For example, hormone therapy, pregnancy, oral contraceptives, and chronic inflammatory conditions such as arthritis are known to elevate CRP concentrations. Conversely, cholesterol-lowering statins and anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac and naproxen, may reduce CRP levels. (Pearson et al., 2003).

3.3 Obesity and Leptin Dysregulation

Leptin is a 16-kDa hormone predominantly produced and secreted by mature adipocytes (Zhang et al., 1994). Leptin, whose secretion is stimulated by insulin, plays a critical role in the regulation of food intake, body weight, and reproductive function. Additionally, it is involved in fetal growth, pro-inflammatory immune responses, angiogenesis, and lipolysis (De Vos, Saladin, Auwerx, & Staels, 1995; Farr, Gavrieli, & Mantzoros, 2015; Saladin et al., 1995). Leptin regulates appetite and metabolism by inhibiting the synthesis and release of neuropeptide Y within the arcuate nucleus of the hypothalamus (Stephens et al., 1995). Leptin inhibits neural pathways stimulated by orexigenic signals to reduce energy intake, while simultaneously activating anorexigenic pathways to suppress appetite (Ahima, 2008; Fruhwürth, Vogel, Schürmann, & Williams, 2018). The interaction between leptin signaling and primary feeding regulation can be conceptualized as follows: leptin enhances the transcription of pro-opiomelanocortin, leading to the synaptic release of α-melanocyte-stimulating hormone. This peptide binds to melanocortin receptors on target neurons, promoting appetite suppression. Concurrently, leptin inhibits the synthesis of neuropeptide Y and agouti-related peptide in neurons, thereby reducing agouti-related peptide's antagonistic effects on melanocortin receptors and further facilitating the anorexigenic response. (Cowley et al., 2001; Elias et al., 1999).

The effects of leptin are akin to other acute-phase reactants. Leptin enhances the release of several inflammatory cytokines, including TNF-α, IL-6 and IL-12, (La Cava & Matarese, 2004). Conversely, exposure to inflammatory stimuli such as TNF-

α and IL-1 enhances leptin expression in adipose tissue and elevates circulating leptin levels, thereby establishing a feedback loop that perpetuates inflammation (Landman et al., 2003). This feedback mechanism illustrates leptin's role in sustaining low-grade chronic inflammation, as pro-inflammatory mediators upregulate leptin alongside other acute-phase reactants, thereby promoting persistent inflammatory states (Obradovic et al., 2021). The effects of leptin are diverse; it stimulates the expression of IL-1Rα, CD39, CD69, and CD71. (Gabay, Dreyer, Pellegrinelli, Chicheportiche, & Meier, 2001) and the production of proinflammatory cytokines TNF-α and IL-6 (Santos-Alvarez, Goberna, & Sánchez-Margalet, 1999) in macrophages. The quantity of macrophages in white adipose tissue positively correlates with obesity, with obese individuals exhibiting a higher macrophage infiltration in adipose tissue (Figure 6) (Weisberg et al., 2003; Xu et al., 2003).

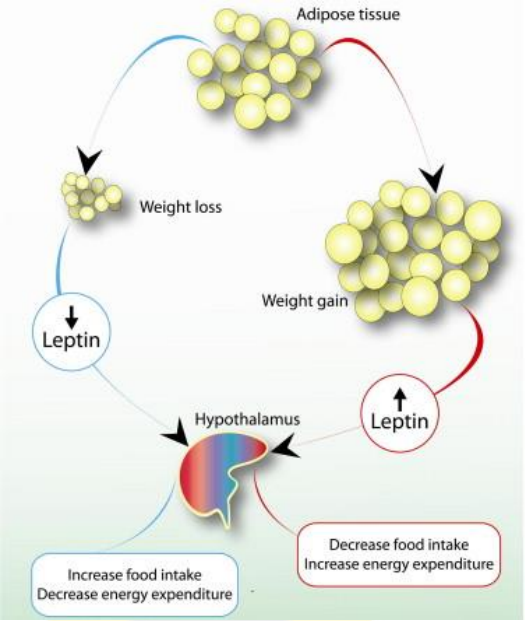


Figure 6 Biology of leptin.
Source: (Ricci & Bevilacqua, 2012).

3.4 Obesity and Adiponectin Dysregulation

Adiponectin is a protein hormone secreted by adipocytes that has garnered significant attention due to its beneficial effects on inflammation, atherosclerosis, insulin resistanc and e type 2 diabetes mellitus. (Goldstein & Scalia, 2004); thus, it links the adipose tissue directly with the cornerstones of metabolic abnormalities (Alvarez, Alpert, & Brodsky, 2004). Adiponectin is a peptide hormone

composed of 247 amino acids (Pischon & Rimm, 2006) that circulates in the bloodstream at relatively high concentrations, ranging from 2 to 20 µg/ml (Oh, Ciaraldi, & Henry, 2007). Numerous studies have demonstrated a significant decrease in serum adiponectin levels associated with weight gain and obesity (Ricci & Bevilacqua, 2012). A previous study compared adiponectin levels between normal-weight and obese postmenopausal women, reporting significantly lower adiponectin concentrations in the obese group. Furthermore, the study identified associations between obesity and metabolic abnormalities, including dyslipidemia and altered leptin levels (Jaleel, Jaleel, Rahman, & Alam, 2006). Another cross-sectional study conducted in a healthy Estonian population aged > 19 years examined the association between metabolic risk factors and obesity. The results demonstrated a negative correlation between adiponectin levels and obesity in both males and females. Additionally, adiponectin was positively correlated with high-density lipoprotein cholesterol and inversely correlated with fasting blood glucose, total cholesterol, and triglyceride levels (Figure 7) (Eglit, Ringmets, & Lember, 2013).

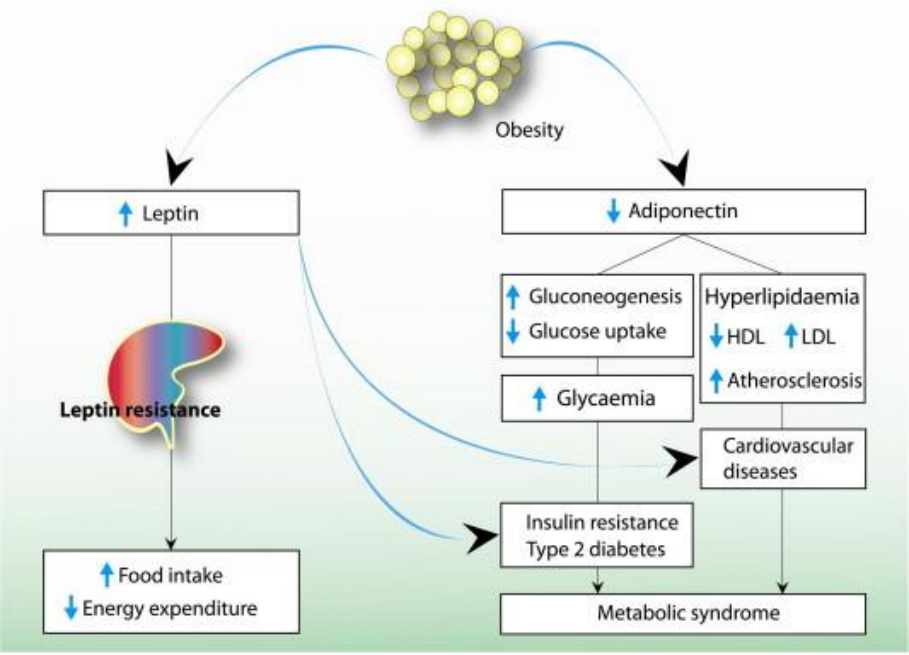


Figure 7 The Implications of leptin resistance and adipokine dysregulation in obesity-related metabolic syndrome.

Source: (Ricci & Bevilacqua, 2012)

4. Obesity and Oxidative Stress

Under both physiological and pathological conditions, adipokines stimulate the production of reactive oxygen species, leading to oxidative stress, which subsequently disrupts the regulation of adipokine secretion (Fernández-Sánchez et al., 2011). Multiple mechanisms contribute to the generation of oxidative stress in obesity (Figure 8). Notably, oxidative stress and pro-inflammatory processes are closely interconnected (Hensley, Robinson, Gabbita, Salsman, & Floyd, 2000). Activation of immune cells results in the production of free radicals, while oxidative stress itself further promotes
chronic inflammatory state.

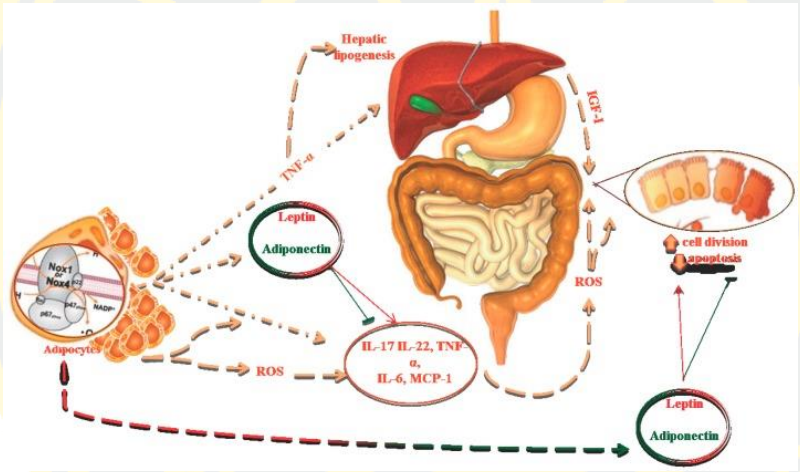


Figure 8 Pathophysiological mechanisms underlying increased cancer susceptibility in obesity
Source: (Marseglia et al., 2014).

Firstly, excessive adipose tissue serves as a source of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which stimulate macrophages and monocytes to increase the production of reactive oxygen and nitrogen species. Therefore, an increase in concentration could be responsible for elevated OS (Fonseca-Alaniz, Takada, Alonso-Vale, & Lima, 2007). Reactive oxygen species (ROS) further stimulate the release of pro-inflammatory cytokines and upregulate the expression of adhesion molecules and growth factors, including connective tissue growth factor, insulin-like growth factor I (IGF-I), platelet-derived growth factor, and vascular cell adhesion molecule-1 (VCAM-1) (Lavrovsky, Chatterjee, Clark, & Roy, 2000) via redox-sensitive transcription factors, especially NF-κB and the NADPH

oxidase pathway (Charlton et al.) (Shoelson, Herrero, & Naaz, 2007). NADPH oxidase (NOX) is a membrane-bound enzyme complex that transfers electrons from NADPH to molecular oxygen, serving as a major source of ROS production in adipocytes. The superoxide radicals (O_2^-) generated by NOX are subsequently converted into hydrogen peroxide (H_2O_2), a longer-lived and membrane-permeable ROS. Hydrogen peroxide, in turn, stimulates the expression of IL-4 and IL-6 genes, as well as cytokine secretion, through an apurinic/apyrimidinic endonuclease/redox factor-1, dependent signaling pathway. Supporting these observations, experimental models have shown that silencing oxidant sources such as NOX4 effectively inhibits ROS generation induced by palmitate and glucose, underscoring the critical role of NADPH oxidases as a prominent non-mitochondrial source of ROS in adipocytes (Frossi, De Carli, Daniel, Rivera, & Pucillo, 2003). Nevertheless, a dynamic crosstalk exists between NADPH oxidases and mitochondria. Mitochondria serve not only as targets for ROS generated by NOX but also as significant sources of ROS themselves, which can further activate NADPH oxidase activity (Dikalov, 2011). Mitochondria-targeted antioxidants have been shown to suppress mitochondrial ROS production, which in turn attenuates NOX activity (Dikalova et al., 2010). Susceptibility to oxidative damage is even greater in obese individuals due to depleted antioxidant sources, including superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), vitamin A, vitamin E, vitamin C, and β-carotene (Amirkhizi et al., 2010). Compared to normal-weight individuals, obese patients exhibit significantly lower SOD activity (Ozata et al., 2002). Furthermore, studies have demonstrated that antioxidant supplementation could reduce oxidative stress (OS) and reactive oxygen species (ROS), decrease the risk of obesity-related complications, and restore the expression of adipokines (Furukawa et al., 2004).

Secondly, while elevated FFA levels are physiologically observed during periods of active growth, excessive fat accumulation in obese individuals leads to a pathological increase in serum FFA levels, impairing glucose metabolism (Rzheshevsky, 2013). This favors the accumulation of energy substrates (fats and glucose) in hepatic, muscular, and adipose tissues (Tereshin, 2007), promoting higher mitochondrial and peroxisomal oxidation. This status leads to increased synthesis of free radicals (FRs), OS, mitochondrial DNA injury, depletion of ATP (Duvnjak et al.,

2007), and lipotoxicity involving various adverse effects of fatty acids on cellular structures (Goossens, 2008). Cellular damage triggers the elevated production of pro-inflammatory cytokines, such as TNF-α, which further amplifies ROS generation in tissues and accelerates lipid peroxidation (Khan, Naz, & Yasmeen, 2006).

Thirdly, adipose tissue functions as a source of bioactive adipokines, including leptin, adiponectin, visfatin, resistin, apelin, and plasminogen activator inhibitor type 1, that play pivotal roles in both the physiological and pathological regulation of oxidative stress (Marseglia et al., 2014).

Additionally, leptin and adiponectin, which are secreted by differentiated adipocytes, exhibit significant anti-inflammatory and anti-atherogenic properties, respectively. Adiponectin, in particular, inhibits monocyte adhesion to endothelial cells, the transformation of macrophages into foam cells, and endothelial cell activation, while also enhancing nitric oxide production in endothelial cells (Ouedraogo et al., 2007).

Previous studies have been shown that free radicals may adversely affect survival of cell because of membrane damages through the oxidative damage of lipid, protein and irreversible DNA modification (Mishra, 2004; Valdecantos, Pérez-Matute, & Martínez, 2009). Markers of oxidative damage induced by ROS include lipid peroxidation products, such as thiobarbituric acid reactive substances and hydroperoxides, as well as **protein oxidation markers**, such as protein carbonyls (Olusi, 2002; Uzun, Konukoglu, Gelisgen, Zengin, & Taskin, 2007). Additionally, oxidative damage is intensified by the reduced activity of **antioxidant enzymes**, such as SOD, catalase (CAT), glutathione S-transferase (GST), and glutathione peroxidase (GPx), which serve as critical free radical scavengers under oxidative stress conditions (Blokhina, Virolainen, & Fagerstedt, 2003). Malondialdehyde (MDA) and F2-isoprostanes (F2-IsoPs) are well-established byproducts of **polyunsaturated fatty acid peroxidation** and serve as reliable biomarkers of oxidative stress.

5. Obesity and Immune Response

Obesity is characterized by the chronic low-grade activation of the innate immune system (Engin, 2017). There are strong evidences indicating that excess adiposity negatively impacts immune function and host defence, which are found

higher rates of infections, in obese individuals (Khanna & Rehman, 2021; Milner & Beck, 2012; Muscogiuri et al., 2021; Rojas-Osornio, Cruz-Hernández, Drago-Serrano, & Campos-Rodríguez, 2019). Excess body fat is associated with alterations in leukocyte counts, characterized by elevated levels of neutrophilsl, eukocytes, monocytes, and lymphocytes, but reduced B- and T-cell mitogen-induced proliferation (Figure 9). Moreover, other studies have indicated that the production of antibodies following vaccination is reduced in obese patients (Martí, Marcos, & Martínez, 2001; Sheridan et al., 2012).

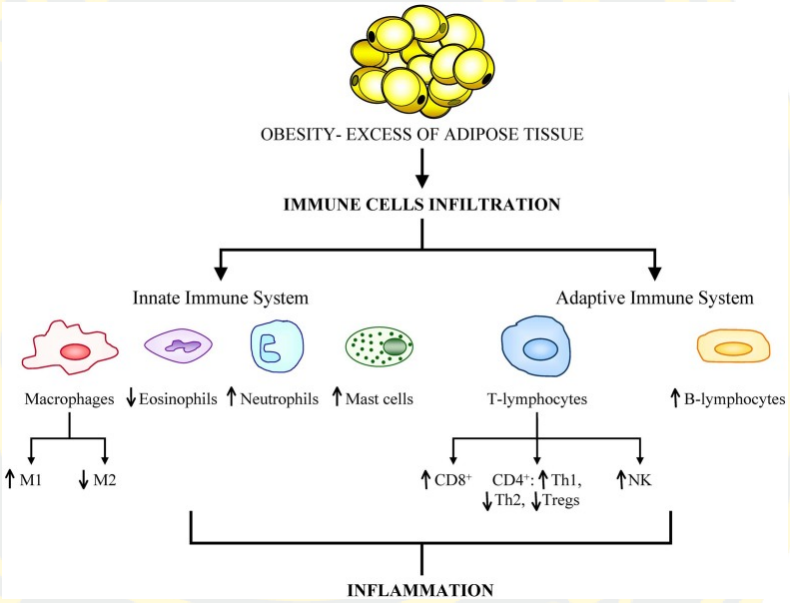


Figure 9 Obesity is associated with a great infiltration of cells from both the innate and adaptive immune systems.

Source: (V. Catalán, Gómez-Ambrosi, Rodríguez, & Frühbeck, 2013)

Obesity and metabolic syndrome are linked to stress and dysfunction in metabolic tissues, including adipose tissue, liver, skeletal muscle, and pancreas. The systemic physiological dysfunction resulting from obesity-related complications leads to fat accumulation in primary lymphoid organs (such as bone marrow and thymus), resulting in a breakdown of tissue architecture and integrity. Changes induced by obesity in lymphoid tissues are further associated with an altered distribution of leukocyte subsets and populations, along with increased numbers of leukocytes exhibiting pro-inflammatory phenotypes. Disruptions in the immune system caused by obesity impair immunity and contribute to the progression of metabolic

dysfunction and chronic disease. Chronic diseases, in turn, can perpetuate dysfunction throughout the immune system (Figure 10) (Andersen, Murphy, & Fernandez, 2016).

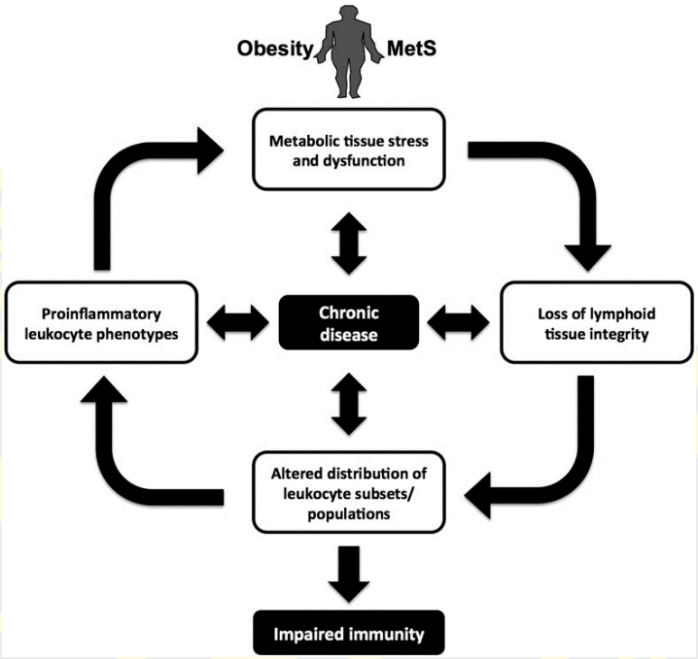


Figure 10 The impact of obesity and MetS on immune system function. MetS, metabolic syndrome. Source: (Andersen et al., 2016).

Obesity is characterized by an increased infiltration of macrophages and other immune cells into adipose tissue, largely as a result of tissue remodeling triggered by adipocyte apoptosis. These immune cells secrete pro-inflammatory cytokines, which contribute to the development of insulin resistance commonly observed in individuals with obesity (Grant & Dixit, 2015). Figure 11 illustrates the altered secretion of adipokines, cytokines, and fatty acids by hypertrophied adipocytes. This alteration affects macrophage activity, leading to further release of pro-inflammatory cytokines and a stimulation of adipocyte lipolysis. Additionally, adipocytes undergo hypoxia and cellular stress, exacerbating the local inflammatory response and resulting in adipocyte dysfunction and metabolic changes, particularly insulin resistance.

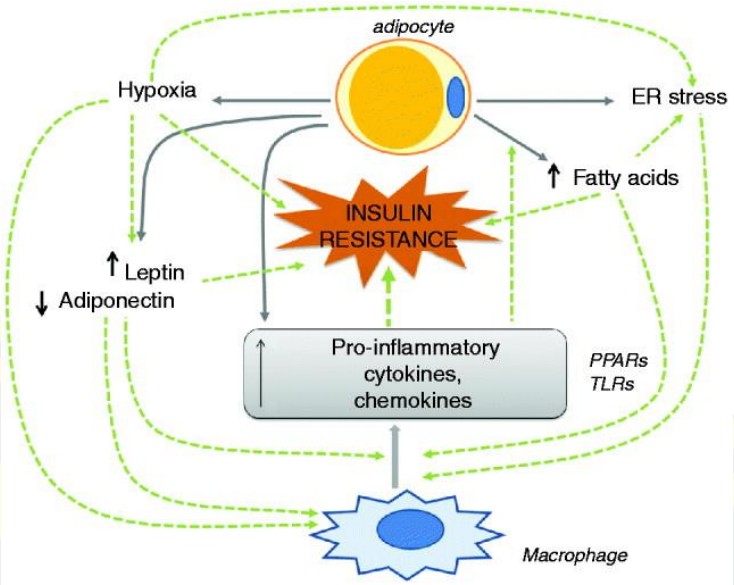


Figure 11Diagram of the proposed relationships between adipocytes and macrophages in the context of inflammation and immune alterations in obesity.
Dashed arrows indicate stimulatory events; solid arrows indicate production and release of molecules. Source: (de Heredia, Gómez-Martínez, & Marcos, 2012)

6. Pathophysiological Efftes of Overweight and Obesity

6.1 Anatomical Effect

In individuals with a sustained positive energy balance, excess adiposity typically develops gradually over time. Increasing of lipids, mainly triglycerides (Hopewell et al.), in adipost tissue occurs in conjunction with volume accrets in skeletal, liver and other tissues and organ. A weight-stable individual with obesity, compared to a normal-weight counterpart, typically demonstrates increased fat and lean mass, elevated resting energy expenditure, higher cardiac output and blood pressure, and an expanded pancreatic β-cell mass (J. E. Hall et al., 2010; Heymsfield, Gonzalez, Shen, Redman, & Thomas, 2014). Insulin secretion in both the fasting state and after a glucose load increases linearly with BMI (Ferrannini et al., 2004).

Subcutaneous adipose tissue harbors the majority of stored lipids across various anatomical sites. Adipocytes in subcutaneous adipose tissue are predominantly white adipocytes, primarily responsible for triglyceride storage and the secretion of leptin, adiponectin, and other adipokines (Shen et al., 2003; Tchkonia et

al., 2013). Visceral adipose tissue constitutes a smaller lipid storage compartment compared to subcutaneous adipose tissue. Notably, omental and mesenteric fat depots are mechanistically implicated in the metabolic disturbances and adverse health outcomes commonly associated with obesity (Shen et al., 2003; Tchkonia et al., 2013). Adipose tissue surrounds the kidney, and the blood pressure increase due to renal compression may contribute to the hypertension often observed in obese patients (J. E. Hall et al., 2010). Obesity often entails an increase in pharyngeal soft tissues, which can obstruct airways during sleep and lead to obstructive sleep apnea (Ashrafian et al., 2015). Excess adiposity also increases a mechanical load on peripheral joints that makes a risk factor for the development of osteoarthritis in obese people (Goldring & Otero, 2011). Elevated intra-abdominal pressure is a contributing factor to the increased risk of gastroesophageal reflux disease and esophageal adenocarcinoma in individuals with overweight or obesity (Hampel, Abraham, & El-Serag, 2005).

6.2 Physiological Effect

. AT is an importance complex endocrine organ that plays many roles in metabolism and secretes several adipocyted-derived factors (cell-signaling proteins or energy-regulating proteins) known as adipokines. AT modulates energy expenditure, appetite, insulin sensitivity, bone metabolism, reproductive and endocrine functions, inflammation, and immunity, while also serving as a reservoir for triacylglycerols (Dixon & Peters, 2018). Adipokines and hormones are synthesized by adipocytes, with their synthesis rates and physiological effects influenced by both the quantity and distribution of adipose tissue. Excessive secretion of pro-inflammatory adipokines, such as leptin, by adipocytes and macrophages within adipose tissue contributes to a chronic low-grade systemic inflammatory state observed in some individuals with obesity. The hydrolysis of triglycerides within adipocytes releases free fatty acids (FFAs), which are subsequently transported via plasma to peripheral tissues for metabolic utilization. Plasma FFA levels are often elevated in obesity (Tchkonia et al., 2013). dditionally, *lipids* in adipose tissue are stored not only as triglycerides but also within liposomes, small cytoplasmic organelles located near mitochondria (Heymsfield, Hu, Shen, & Carmichael, 2015). The accumulation of excess lipid intermediates, such as ceramides, in non-adipose tissues can induce lipotoxicity,

resulting in cellular dysfunction and apoptosis. Consequently, elevated concentrations of inflammatory cytokines, FFAs, and lipid intermediates in non-adipose tissues contribute to *impaired insulin signaling* and the development of *insulin resistance* commonly observed in individuals with overweight or obesity. Insulin resistance is particularly associated with excess intra-abdominal adipose tissue (Tchkonia et al., 2013). This metabolic and anatomical interplay represents one of the key pathophysiological mechanisms underlying obesity-related dyslipidemia, characterized by elevated fasting plasma triglycerides, increased low-density lipoprotein cholesterol, and reduced high-density lipoprotein cholesterol, as well as type 2 diabetes, obesity-related liver disease, and osteoarthritis (Heymsfield & Wadden, 2017). Moreover, elevated bioavailable levels of IGF-1 and other tumor-promoting molecules have been implicated in the pathogenesis of cancer (Wolin, Carson, & Colditz, 2010).

Chronic overactivity of the sympathetic nervous system is observed in some individuals with obesity and may contribute to several pathophysiological processes, including hypertension (J. E. Hall et al., 2010). Elevated blood pressure, along with the constellation of abnormalities related to insulin resistance, obesity-associated dyslipidemia, and type 2 diabetes, underlies the pathogenesis of heart disease, stroke, and chronic kidney disease. Figure 12 illustrates key pathways through which the mechanical, metabolic, and physiological consequences of excess adiposity promote the development of these chronic comorbidities.

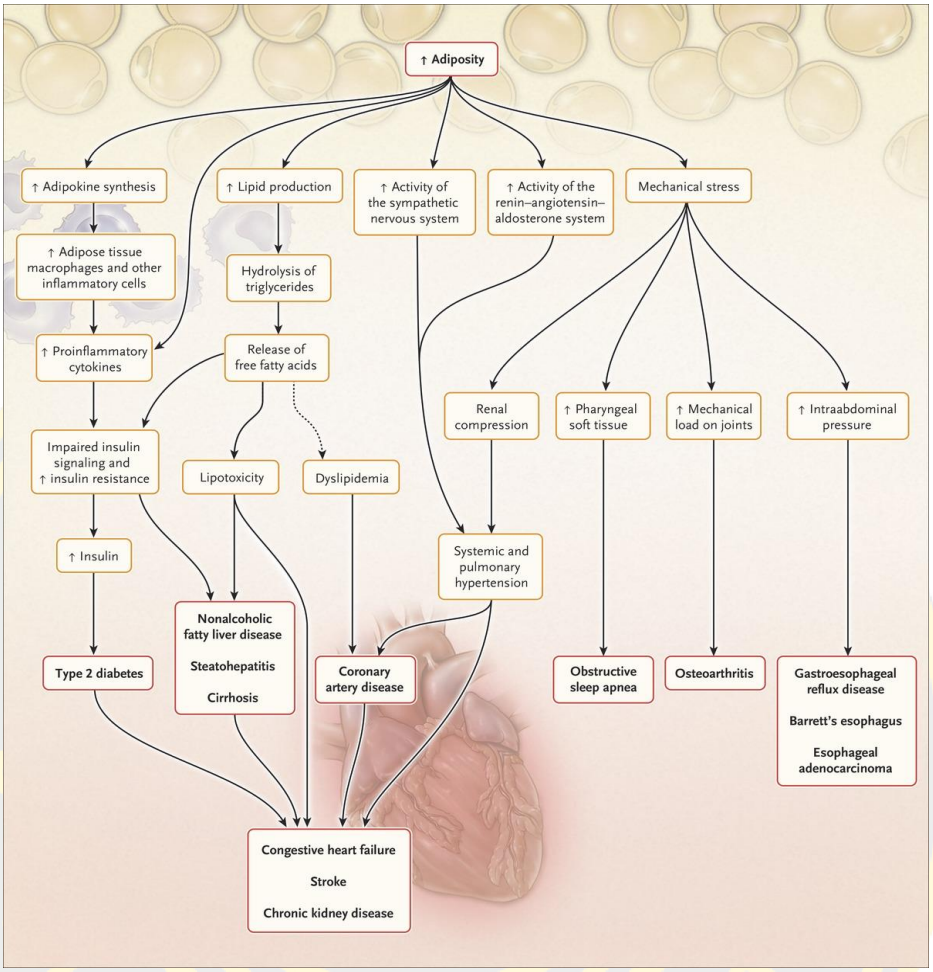


Figure 12 Pathways linking excess adiposity to risk factors and chronic diseases. The dashed arrow denotes an indirect association.
Source: (Heymsfield & Wadden, 2017)

7. Obesity and Respiratory Function

7.1 Adipose Tissue Inflammation and Its Impact Pulmonary Function in Obesity

Obesity significantly influences immune cell populations within adipose tissue. Notably, adipose tissue macrophages are markedly increased, which may impact pulmonary function (Figure 13). Furthermore, an expansion of adipose tissue mass correlates with enhanced mast cell proliferation. Mast cells, key mediators of allergic responses, originate in part from adipose tissue, which serves as a reservoir for mast cell progenitors (Poglio et al., 2010). Compared to lean individuals, obese subjects exhibit a higher mast cell burden, suggesting that obesity-induced mast cell

proliferation could represent an additional mechanism contributing to airway disease in obesity (Dixon & Peters, 2018; Liu et al., 2009).

Leptin also plays an important role in the regulation of ventilatory drive (Bassi et al., 2014; Polotsky et al., 2004). Given leptin's role, it may contribute to the pathogenesis of airway disease. Visceral fat leptin expression strongly correlates with airway hyperresponsiveness, and elevated serum leptin levels are inversely associated with lung function in obese women (Hickson et al., 2011; Sideleva et al., 2012). Both high BMI and increased serum leptin are strongly linked to asthma in adults (Sood, Ford, & Camargo, 2006). However, the BMI–asthma association remains significant even after adjusting for leptin, indicating that leptin is not the sole mediator. Contrarily, some studies report no difference in serum leptin levels between obese asthmatics and obese non-asthmatics (Sideleva et al., 2012). These conflicting findings may reflect differences in study populations and asthma phenotypes (Dixon & Peters, 2018).

Adipokine expression differs in the adipose tissue of obese patients with asthma compared to those without asthma, with adiponectin levels significantly decreased and leptin levels elevated in obese asthmatics (Sideleva et al., 2012).

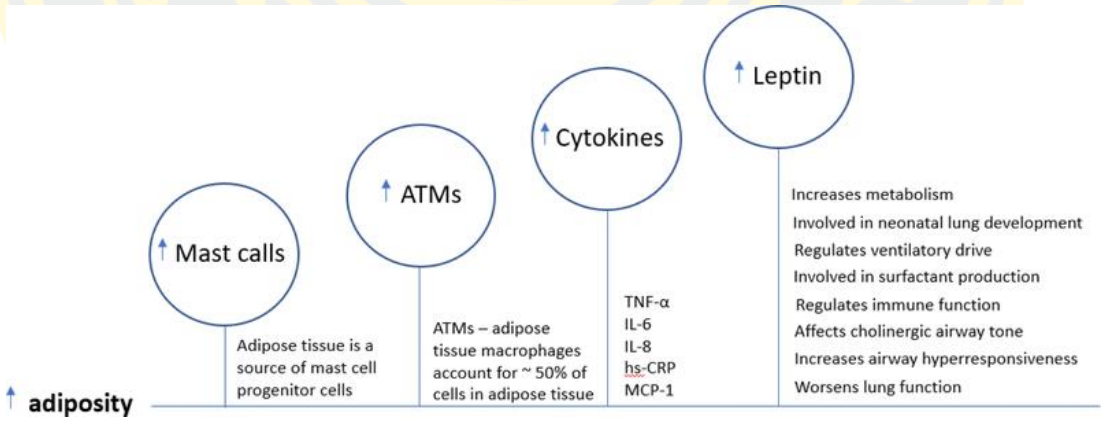


Figure 13 Immune cells and adipokines increased in obesity impact lung function. Source: (Dixon & Peters, 2018).

7.2 Mechanical Changs of the Lung and Chest Wall in Obesity

The mechanics of the lungs and chest wall are significantly altered in obesity, mainly due to fat deposits in the mediastinum and abdominal cavities. These alterations reduce the compliance of the lungs, chest wall and entire respiratory system (Hedenstierna & Santesson, 1976; Naimark & Cherniack, 1960; Pelosi et al.,

1998; Schachter et al., 2001; J. T. Sharp et al., 1964). Its contribute to the pulmonary symptoms of obesity such as dyspnea, orthopnea and wheeze (Ferretti, Giampiccolo, Cavalli, Milic-Emili, & Tantucci, 2001; Schachter et al., 2001; Sin et al., 2002). The decrease in respiratory system compliance (resulting in increased stiffness) also affects the breathing pattern. Normally, air flows into the lungs because of the negative pressure gradient in the pleural space. However, in obesity, increased fat accumulation in the thoracic and abdominal cavities restricts the downward movement of the diaphragm and the outward expansion of the chest wall, causing slight increases in intra-abdominal and pleural pressures (Behazin, Jones, Cohen, & Loring, 2010; Sugerman, Windsor, Bessos, & Wolfe, 1997). This modification of the breathing pattern leads to a significant decrease in both the expiratory reserve volume (ERV) and the resting lung volume, known as the functional residual capacity (FRC). The reduction in FRC correlates with obesity severity: overweight individuals and those with mild and severe obesity, but without asthma, show decreases in FRC of approximately 10%, 22%, and 33%, respectively (Jones & Nzekwu, 2006). Tidal volume is slightly reduced in obese individuals; however, a modest increase in respiratory rate compensates for this shallow breathing, resulting in a significant rise in overall minute ventilation (Burki & Baker, 1984; Chlif, Keochkerian, Choquet, Vaidie, & Ahmaidi, 2009; Sampson & Grassino, 1983).

7.3 Changes in Lung Volume and Airflow in Obesity

Obesity significantly reduces FRC and ERV, but has minimal impact on residual volume (RV) and total lung capacity (TLC) (Collet et al., 2007; Jones & Nzekwu, 2006; Lavrovsky et al., 2000). Several studies have shown slight reductions in TLC as BMI increases; however, TLC generally remains well-preserved even in severe obesity (L. C. Collins, Hoberty, Walker, Fletcher, & Peiris, 1995; Jones & Nzekwu, 2006; Ray, Sue, Bray, Hansen, & Wasserman, 1983; Watson & Pride, 2005). RV is typically normal in individuals with obesity, and the RV-to-TLC ratio, which indicates gas trapping, is usually normal or slightly elevated. (Jones & Nzekwu, 2006; Watson & Pride, 2005).

Measurements of static lung volumes along with transpulmonary and transdiaphragmatic pressures have deepened our understanding of how obesity affects lung mechanics and volumes. A landmark study measuring lung volumes in the seated

position found that esophageal and gastric pressures at FRC were significantly higher in obese individuals compared to healthy controls matched for age, gender, and height. Similar findings were observed in the supine position, with BMI positively correlating with both gastric and esophageal pressures (Steier, Lunt, Hart, Polkey, & Moxham, 2014).

Dynamic pulmonary function measures, such as FEV_1 and FVC are slightly reduced in individual with obesity, but FEV_1/FVC ratio is usually unaffected, unless BMI is greater than 62 kg/m^2 (Biring et al., 1999; Lazarus et al., 1997; Schachter et al., 2001; Sin et al., 2002; Zerah et al., 1993). When ERV decreases, while vital capacity (L. Dinan, T. Savchenko, et al.) remains normal, inspiratory capacity (IC) will be increased (Salome et al., 2008). Inspiratory capacity is found both higher no significant differences in obese individuals compare with non-obese individuals (Costa, Barbalho, Miguel, Forti, & Azevedo, 2008; Zerah et al., 1993).

Body fat distribution has a stronger impact on pulmonary function than overall weight or BMI (Leone et al., 2009; Ochs-Balcom et al., 2006). A large population-based study of 121,965 individuals found that increased abdominal obesity is a risk factor for reduced FEV_1/FVC, abdominal obesity predicted FEV_1 and FVC independent of BMI (Leone et al., 2009). Taken together, these findings suggest that obesity does not significantly affect the ability of patients to fully inflate or deflate their lungs but does reduce resting lung volumes.

7.4 Airway Narrowing and Closure in Obesity

Obesity's mechanical effects cause airway narrowing and closure, increasing respiratory system resistance. Compared to healthy-weight individuals, airway narrowing in obesity is linked to airway closure and airway hyperresponsiveness (AHR) (Chapman, Berend, King, & Salome, 2008). Airway narrowing and closure lead to gas trapping and uneven ventilation (Pellegrino et al., 2014). often indicated by an elevated residual volume to total lung capacity ratio (RV/TLC) (Naoum, Kritharides, Ing, Falk, & Yiannikas, 2017).

Although other markers like RV and closing capacity typically remain normal in obesity (Hedenstierna, Santesson, & Norlander, 1976; Watson & Pride, 2005), airway closure can occur during normal breathing when functional residual capacity (FRC) drops to or below closing capacity (Hakala, Mustajoki, Aittomäki, &

Sovijärvi, 1995; Hedenstierna et al., 1976; Milic-Emili, Torchio, & D'Angelo, 2007). This is likely due to mechanical lung compression (Jones & Nzekwu, 2006), reducing mechanical support between airways and lung tissue (Mead, Takishima, & Leith, 1970; Pelosi et al., 1998) , which may cause slight FEV1 reductions in obese asthmatics (Schachter et al., 2001). Increased abdominal obesity is associated with airway closure in lung regions near the diaphragm, impairing airflow distribution, especially when supine (Engel & Prefaut, 1981).

8. Obesity and Cardiorespiratory Fitness

In severe obesity often have reduced cardiorespiratory fitness (Amati et al., 2008; Gallagher et al., 2005; Lee et al., 1999; Miller et al., 2012). Low CRF is associated with lower energy expenditure (Arciero et al., 1993; Shook et al., 2014), higher body mass index (BMI) (Gallagher et al., 2005; Miller et al., 2012) and increased waist circumference (Dyrstad et al., 2019). Since lower CRF can lead to reduced daily activity levels and decreased energy expenditure during activities, improving CRF may help promote weight loss (Blair et al., 2001; De Souza et al., 2010; Katch et al., 1991). In line with this, improvements in CRF have been associated with decreased amounts of subcutaneous fat, visceral fat, liver fat and total fat mass, as well as decreased waist and hip circumference (Rosenkilde, Nordby, & Stallknecht, 2016; Whyte, Gill, & Cathcart, 2010). The most commonly used measure of CRF is maximal oxygen consumption (VO_2max). Each liter of oxygen consumed releases approximately 5 kcal, depending on the work intensity (Katch et al., 1991). Therefore, at any given relative work intensity, a higher VO_2max corresponds to greater energy expenditure and improved CRF.

9. Anthropometric and Other Measurements of Obesity

Even though, the BMI is associated with important health outcomes and widely used both research and clinical practices but also provides a major source of criticism. BMI fails to reflect several important factors, including the distribution of adipose tissue and muscle mass (Williams et al., 2015). Thus, other measurement

methods must be combined including: waist circumference, waist-to-hip ratio, skinfold thickness, bioelectrical impedance and visceral adiposity index.

9.1 Waist Circumference

The waist circumference (Fawcett & Barroso) can be used alone as an indicator of obesity-related health risk, as abdominal obesity is the main concern (Canoy, 2008; de Koning, Merchant, Pogue, & Anand, 2007). Although BMI and WC are correlated, WC is better measure of visceral adiposity which can be varied within BMI. Because adiposity is the greater risk for obesity-related disease, the WC or the waist-to-hip ratio can be an importance measure for health risk assessment (Després, 2012). Furthermore, risk criteria for adults based on more specific WC have been developed. Table 4 is based on data where waist circumference was measured at the level of the iliac crest (G. A. Bray, 2004; Janssen, Katzmarzyk, & Ross, 2004; Medicine, Riebe, Ehrman, Liguori, & Magal, 2018).

Table 4 Waist circumfernce in adult and risk criteria.

Risk category*	**Waist circumference (cm)**	
	Women	**Men**
Very low	< 70 cm	< 80 cm
Low	70-89 cm	80-99 cm
High	90-110 cm	100-120 cm
Very high	> 110 cm	> 120 cm

*Disease risk for type 2 diabetes, hypertension and cardiovascular diseases.

Source (G. A. Bray, 2004; Medicine et al., 2018).

9.2 Waist-to-hip Ratio

The waist-to-hip ratio (WHR) is the circumference of the waist divided by the circumference of hips and has traditionally been used as a simple method for assessing body fat distribution and identifying individual with higher amounts of abdominal fat. Health risk increases as WHR increase and the standards for risk vary with age and sex (Duren et al., 2008; Pi-Sunyer, 2004). For example, health risk is very high for young men when WHR is > 0.95 and for young women when WHR is >0.86 (Medicine et al., 2018).

9.3 Bioelectrical Impedance Analysis

The bioelectrical impedance analysis (Muscogiuri et al.) also referred to simply as bioelectrical impedance, is a widely used method for estimating body composition (McAllister et al.). Based on a two-compartment model, fat mass and fat-free mass (FFM), BIA measures the resistance to a small electrical current as it passes through the body's water content. Electrodes placed on the extremities detect changes in electrical conductivity, and the lowest resistance values are used to estimate total body water (TBW), from which total body FFM is calculated (Figure 14) (Kyle et al., 2004).

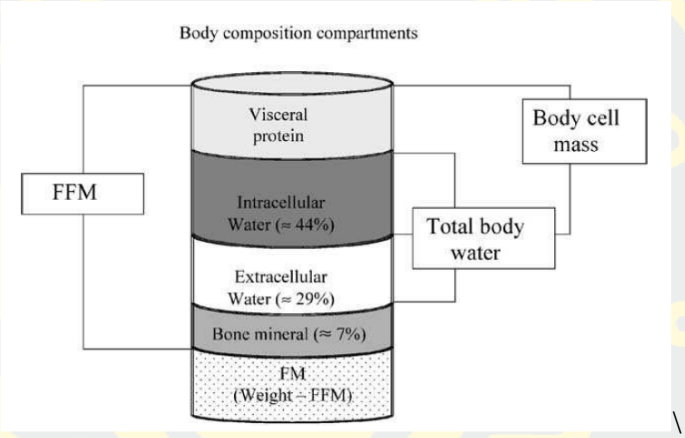


Figure 14 Schematic diagram of fat-free mass, total body water (TBW), intracellular water (ICW), extracellular water (ECW) and body cell mass (BCM).
Source: (Kyle et al., 2004).

9.4 Visceral Adiposity Index

The visceral adiposity index (VIA) has been recently strongly used to estimate the visceral adiposity dysfunction associated with cardiometabolic risk. VIA is a mathematical model that uses both anthropometric (BMI and WC) and functional (triglycerides (TG) (in mmol/l) and high-density lipoprotein (HDL) cholesterol (in mmol/l)) simple parameters (Amato et al., 2010). The VIA formulation as below.

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88 \times BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89 \times BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

10. Management of Overweight and Obesity

Recommendations for treating overweight and obesity are based on evidence showing that excess weight is linked to increased morbidity and mortality, as well as elevated risk factors for non-communicable diseases (NCDs). Therefore, weight loss can help manage conditions worsened by overweight and obesity and may reduce the risk of developing such diseases. Classical guidelines outline three main goals for weight management: (I) prevent further weight gain, (II) reduce body weight, and (III) maintain the reduced body weight over the long term. ("Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health," 1998; "Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014).

Various modalities can be used to address overweight and obesity. To assess their effectiveness in promoting weight loss, reducing abdominal fat, and improving cardiorespiratory fitness, evidence from randomized controlled trials (RCTs) was reviewed. These trials considered dietary therapy, physical activity or exercise, behavior therapy, combined therapy or lifestyle therapy, pharmacotherapy and bariatric surgery ("Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health," 1998; "Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014).

10.1 Dietary Therapy

Many randomized controlled trials have evaluated the effectiveness of various diets on weight loss, including low-calorie diets (LCDs), very low-calorie diets (VLCDs), and low-fat diets (LFDs) with different macronutrient compositions. Classical evidence shows that LCDs can reduce total body weight by an average of 8% over 3 to 12 months and decrease abdominal fat, as measured by waist circumference. However, improvements in cardiorespiratory fitness (VO2max) are generally not seen in overweight or obese adults who lose weight on LCDs without increasing physical activity. VLCDs produce greater initial weight loss compared to LCDs, but long-term weight loss (>1 year) does not differ significantly between the two. LFDs without targeted calorie reduction promote weight loss by lowering overall caloric intake, and when combined with caloric restriction, lead to greater weight loss

than low-fat diets alone. Overall, evidence suggests that LCDs are effective for weight loss in overweight and obese individuals, and reducing fat intake as part of an LCD is a practical approach to lowering calorie consumption ("Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health," 1998; "Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014).

10.2 Exercise or Physical Activity

Many randomized controlled trials (RCTs) have evaluated the effects of physical activity on weight loss, abdominal fat (measured by waist circumference), and cardiorespiratory fitness (VO2 max). Most interventions involved cardiovascular endurance exercises, such as aerobic dancing, brisk walking, jogging, running, cycling, swimming, and skiing, often with warm-up and cool-down periods. Some programs included dynamic calisthenics. Exercise intensity was personalized, typically ranging from 60% to 85% of maximum heart rate or around 70% of VO2 max. Sessions were held 3 to 7 times per week, lasting 30 to 60 minutes each. Programs varied between supervised and home-based formats. Adherence was reported inconsistently, and most studies did not estimate caloric expenditure or control for calorie intake. Intervention durations ranged from 12 weeks to 1 year. Evidence suggests that physical activity in overweight and obese adults: 1) Produces modest weight loss independent of dietary calorie reduction 2) Modestly reduces abdominal fat 3) Improves cardiorespiratory fitness independently of weight loss 4) May aid in maintaining weight loss over time ("Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health," 1998; "Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014).

10.3 Behavioral Therapy

Behavior therapy involves strategies based on learning principles, such as reinforcement, to help individuals overcome barriers to adhering to dietary changes and increasing physical activity. A key recommendation is the regular monitoring of food intake, physical activity, and body weight, which can be supported by smartphone applications, activity trackers, and cellular-connected scales ("Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in

adults," 2014; Steinberg et al., 2013). Participants typically review their progress on a weekly basis with a trained interventionist, who offers encouragement, goal-setting, and problem-solving strategies. Evidence indicates that behavior therapy, when combined with other weight loss strategies, provides additional short-term benefits (up to 1 year) in supporting weight loss. However, without ongoing intervention, these benefits do not appear to persist over the long term (3 to 5 years) ("Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health," 1998; "Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014).

10.4 Lifestyle and Combined Therapies

Numerous RCTs have investigated the effects of combining a reduced-calorie diet with increased physical activity on body weight. Control groups in these studies typically received either dietary intervention or physical activity alone. The evidence suggests that the combined intervention is more effective than either component alone in producing weight loss, reducing abdominal adiposity, and improving cardiorespiratory fitness, as measured by VO_2max. However, improvements in VO_2max have not been consistently demonstrated to occur independently of weight loss Primary care practitioners commonly provide guidance on dietary and physical activity modifications; however, they often lack the resources or time to deliver high-intensity behavioral counseling interventions (Wadden, Butryn, Hong, & Tsai, 2014). Referring patients to high-intensity community-based interventions constitutes a valuable strategy for enhancing weight management support. YMCA programs increasingly offer a version of the Diabetes Prevention Program (Ackermann et al., 2015) and commercial weight loss programs can be recommended if their safety and efficacy have been documented in peer-reviewed publications ("Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014). *Telephone-delivered lifestyle interventions* have been shown to produce weight loss outcomes comparable to those achieved through in-person counseling, supporting the development of weight-management call centers (Appel et al., 2011). *Web-based interventions* that incorporate personalized feedback from interventionists also present a viable alternative; however, they typically result in only

50% to 66% of the weight loss observed with face-to-face counseling (Harvey-Berino et al., 2010). Despite this limitation, web-based programs offer the advantages of broader accessibility and reduced costs, thereby enhancing their potential for population-level impact (Heymsfield & Wadden, 2017).

10.5 Pharmacotherapy

Pharmacotherapy is recommended as an adjunct to a reduced-calorie diet and increased physical activity for the long-term management of overweight and obesity (Apovian et al., 2015; Garvey et al., 2016; Yanovski & Yanovski, 2014). Medications, using Dexfenfluramine, Sibutramine, Orlistat, Lorcaserin, Liraglutide, Naltrexone-bupropion or Phentermine/fenfluramine-topiramate may be considered for adults with a BMI of 30 kg/m^2 or higher, or a BMI of 27 kg/m^2 to 29 kg/m^2 with at least one weight-related coexisting condition. This treatment has been demonstrated to induce significant weight loss in obese adults when administered for durations ranging from six months to one year (Apovian et al., 2015; Heymsfield & Wadden, 2017). When combined with lifestyle interventions, pharmacotherapy and behavioral modifications produce additive effects on weight reduction and should be implemented concurrently. Furthermore, the integration of pharmacotherapy with lifestyle changes may aid in the long-term maintenance of weight loss (Apovian et al., 2015; Garvey et al., 2016; Yanovski & Yanovski, 2014). Current evidence supports the use of weight loss medications only as components of a comprehensive weight management program that includes dietary modification and increased physical activity. This is particularly relevant for patients with a BMI of 30 without any concurrent obesity-related risk factors or diseases, or for those with a BMI of 27 who have accompanying obesity-related risk factors or diseases.

Previous studies report the percentages of participants in randomized controlled trials who achieved weight loss of at least 5% or at least 10% of their initial body weight one year after undergoing either a high-intensity lifestyle intervention or pharmacotherapy, which was typically combined with low-to-moderate-intensity lifestyle counseling (fewer than two sessions per month). The percentages are cumulative, meaning that those who lost at least 5% of their weight include participants who also lost at least 10%. For example, in the Look AHEAD study, 68% of participants achieved a weight loss of at least 5%, of whom 37% attained a weight

loss of at least 10%. These findings are consistent with the lifestyle intervention trials (Association, 2007), the Diabetes Prevention Program trial (Group, 2002), and the study conducted by Teixeira et al. ("Expert Panel Report: Guidelines (2013) for the management of overweight and obesity in adults," 2014). The selected studies were chosen based on their fair to good quality ratings according to the Guidelines (2013) for the Management of Overweight and Obesity in Adults (2014) and because their trial data are reported as categorical weight loss outcomes. Additional categorical weight-loss data from the Diabetes Prevention Program trial were provided by the Diabetes Prevention Program Research Group. The median percentages of participants achieving weight loss of at least 5% or 10% with each of the five medications approved for long-term weight management were derived from a meta-analysis conducted by Khera et al. (2016) (Khera et al., 2016). Furthermore, data on the percentage of participants achieving at least 15% weight loss at one year were available from the Look AHEAD study (16%), the Diabetes Prevention Program trial (11%), liraglutide (14%), phentermine–topiramate (32%), and naltrexone–bupropion (14%) (Heymsfield & Wadden, 2017).

10.6 Surgical Interventions: Bariatric Surgery

Bariatric surgery, which refers to surgical weight-loss procedures, is indicated for individuals with class III obesity (BMI ≥ 40 kg/m²) or for those with a BMI of 35 to 39.9 kg/m² who have one or more obesity-related comorbidities (Sturm & Hattori, 2013). Although more effective than lifestyle and pharmacologic interventions, these procedures are associated with greater risks (Garvey et al., 2016; Schauer, Mingrone, Ikramuddin, & Wolfe, 2016) Currently, three primary types of bariatric surgery are performed. Laparoscopic adjustable gastric banding, considered the least invasive and safest technique, involves the placement of an inflatable silicone band around the gastric fundus to create a small pouch, typically measuring approximately 30 milliliters in volume. This restrictive procedure is reversible and does not involve anatomical alteration of the gastrointestinal tract. Roux-en-Y gastric bypass entails the creation of a small gastric pouch (less than 50 milliliters) in the upper gastric fundus, which is anastomosed to a Roux limb of the jejunum. This procedure combines restriction of food intake with intestinal bypass, circumventing

approximately 95% of the stomach, the duodenum, and a substantial portion of the jejunum. The vertical sleeve gastrectomy, a more recently developed technique, involves resection of approximately 70% of the stomach, resulting in accelerated gastric emptying (Purnell, 2018; Schauer et al., 2016). Evidence recommends bariatric surgical intervention as a viable option for carefully selected patients with clinically severe obesity (BMI >40 kg/m² or >35 kg/m² with comorbid conditions) when less invasive weight loss methods have proven unsuccessful and the patient faces a high risk of obesity-related morbidity and mortality.

For present study, we selected an appropriated treatment were ***"High intensity home-based exercise intervention with remoted individual supervised via telemedicine****". Because there were sufficient evidences, better short- and long-term adherence compared to the lower intensity home-based or higher intensity onsite-based exercises* (Appel et al., 2011; Heymsfield & Wadden, 2017; A. C. King, Haskell, Young, Oka, & Stefanick, 1995) *and was suitable for the serious COVID-19 pandemic situation.*

11. Exercise Recomendations for Overweight and Obesity

There is dose-response relatioship between physical activitires (PA) levels and the magnitude of weight loss. The American College of Sports Medicine (ACSM)' s position stand on PA and weight loss concluded that 1) < 150 min/week of PA promotes minimal weight loss, 2) >150 min/week of PA results in modest weight loss of 2-3 kg, and 3) >225-420 min/week results in of 5-7.5 kg weight loss. Based on the scientific evidenves, the ACSM makes the following an exercise training recommendations for individuals with overweight and obesity as follow.

The objectives of exercise during the active weight loss phase are twofold: 1) to optimize caloric expenditure to facilitate weight loss, and 2) to incorporate exercise into the individual's routine, laying the groundwork for sustained success during the weight loss maintenance phase. The ACSM recommends that the duration of moderate to vigorous intensity physical activity should initially progress to at least 30 minutes per day, totaling at least 250 minutes per week (>2,000 kcal/week), performed on 5 to 7 days per week, as outlined in Table 5. Additionally, target a

minimal reduction in body weight of at least 3%-10% of initial body weight over 3-6 months (Medicine et al., 2018).

Table 5 ACSM recommendations for individuals with overweight and obesity.

	Aerobic	Resistance	Flexibility
Frequency	More than 5 days/week	2 to 3 days/week	2 to 3 days/week
Intensity	Initial intensity should be moderate (40% to 59% VO_2R or HRR); progress to vigorous (>60% VO_2R or HRR) for greater health benefits.	60% to 70% of 1-RM gradually increase to enhance strength and muscle mass.	Stretch to the point of feeling tightness or slight discomfort.
Time	30 min/day (150 min/week) increase to 60 min/day or more (250 to 300 min/week).	2 to 4 sets of 8 to 12 repetitions for each the major muscle group.	Hold static stretch for 10 to 30 seconds and 2 to 4 repetitions of each exercise.
Type	Prolonged, rhythmic activities using large muscle groups.	Resistance machines or free weights.	Static, dynamic or PNF.

1-RM, one repetitions maximum; HRR, heart rate reserve; PNF, proprioceptive neuromuscular facilitation; VO_2R, oxygen uptake reserve.

12. High Intensity-interval Training (HIIT)

12.1 Definition and Its Benifits

The popularity of high intensity interval exercise which is often termed intermittent or HIIT is on the rise. HIIT training involves performing repeated bouts of exercise at an intense effort interspersed by low intensity exercise or periods of rest with varied recovery times. The exercise sessions may vary in duration from 5 seconds to 8 minutes and are conducted at intensities between 80% and 95% of an individual's estimated maximal heart rate. Recovery periods may fluctuate in duration,

resulting in total exercise sessions lasting between 20 and 60 minutes (Campbell & Rutherford, 2018; Roy, 2013).

HIIT training can be readily adapted for individuals across various fitness levels and with special conditions, such as overweight and diabetes. It can be implemented across a variety of exercise modalities, including cycling, walking, swimming, aqua training, elliptical cross-training, and various group exercise classes. HIIT provides comparable fitness benefits to continuous endurance exercise but requires less time. This is attributed to HIIT's tendency to burn more calories than traditional exercise, particularly through increased post-exercise energy expenditure.The post-exercise period is referred to as "Excess Post-exercise Oxygen Consumption (EPOC)", denoting the excess post-exercise oxygen consumption. Excess post-exercise oxygen consumption (EPOC) typically lasts for about 2 hours following an exercise session, during which the body restores itself to pre-exercise levels, leading to increased energy expenditure. Due to the intense contractile demands of HIIT, EPOC is generally modestly elevated compared to traditional exercise, contributing an additional 6 to 15% of calories to the total exercise energy expenditure (Campbell & Rutherford, 2018; Roy, 2013).

The primary advantage of high-intensity exercise lies in its ability to achieve significant energy expenditure within a shorter timeframe. This is crucial because when energy expenditure is equated, weight reduction is comparable to exercising for 300 minutes per week at moderate intensity or 200 minutes per week at vigorous intensity. Previous studies have reported distinct effects on body fat distribution between high-intensity and aerobic exercise training. After 24 weeks of high-intensity exercise, abdominal obesity decreased by 4.6 cm (range: 6.2 to 3.0 cm), compared to a 3.6 cm reduction (range: 5.1 to 2.2 cm) following an equivalent duration of aerobic training. Considering that a 5 cm reduction in abdominal circumference is associated with a 9% lower mortality risk, these findings have important clinical implications. Furthermore, increasing exercise intensity may provide additional health benefits beyond increased energy expenditure (Campbell & Rutherford, 2018).

Research shows that total time spent in high-intensity exercise is crucial for physiological benefits. Alternating high and low intensity intervals helps sustain effort

longer than continuous exercise. HIIT benefits include improved fitness, insulin sensitivity, lipid profiles, blood pressure, fat oxidation, metabolism, weight loss, fat reduction, and exercise adherence. Key studies have advanced understanding of HIIT's effects in healthy and clinical populations (ACSM, 2014; Atakan et al., 2021; Campbell & Rutherford, 2018; Roy, 2013). Relevant training studies are summarized in Table 6. .

Table 6 HIIT studies in overweight and obesity.

Study	Number	Intervention	Intensity	Duration	Control	Study End Point: VO_2max (ml.min.kg)	Study End Point: BMI (kg/m ^{2})
(Abdelbasset et al., 2020)	47 (20 females ,27 males)	HIIT (bicycle Ergometer) (40 min, 3/week) MICT (bicycle Ergometer) (3/week)	5 minute warm up involving cycling exercise without resistance, followed by 3 sets of 4 minutes cycling sessions at 80% to 85% of the VO_2max with 2 minutes interval at 50% of the VO_2max between sets, 5 minutes of cool down	8 weeks	Normal level of physical activity	-	CON: from 35.9±5.3 to 36.2±5.5 HIIT: from 36.3±4.5 to 34.1±3.1 MICT: from 36.7±3.5 to 34.3±34.3
(Cheema, Davies, Stewart, Papalia, & Atlantis, 2015)	12 (7 females 5 males)	HIIT (Boxing; 50 min) (4/week)	5 min warm up HIIT 2:1 and >75% HRR vs rest/pacing	12 weeks	50 minutes brisk walking (4 times/week)	CON: from 29.0±6.4 to 28.8 ±8.0 HIIT: from 27.9±2.4 to 32.5 ±5.0	CON: from 30.8±2.6 to 30.7 ±3.0 HIIT: from 32.0±5.9 to 30.5 ±4.0
(Higgins, Fedewa, Hathaway, Schmidt, & Evans, 2016)	60 females	SIT (cycle ergometer) (3/week)	4 minuntes warm up 30 seconds 'all out" sprints, 4 minutes active recovery. 5 repetitions in week 1, 2, 6 repetitions in week 3, 4 and 7 repetitions in week 5, 6	6 weeks	20 to 30 minutes cycling at 60-70% HRR	MICT; from 26.9±4.5 to 28.8 ± 4.3 SIT; from 29.1±4.8 to 33.2± 4.4	-
(Jung, Bourne, Beauchamp, Robinson, & Little, 2015)	32 (27 females, 5 males)	HIIT (25 min) (walking, elliptical machine, treadmill or cycling) (3/week)	3 min warm up 10x1 min 90% HRpeak 2 min cool down	10 days + 4 weeks	20 to 50 min continuous 65% HRpeak	HIIT: from 20.7±3.3 to 22.6 ±4.1 MICT: from 20.8±5.2 to 22.0 ±4.6	HIIT: from 29.8±5.5 to 29.9 ±5.1 MICT: from 32.1±4.1 to 31.9 ±3.7
(Keating et al., 2015)	48	HI (cycling) (3/week)	30 to 45 min 60, 70% VO2peak	8 weeks	Low to moderate intensity and high volume (Brisk walking) 45 to 60 min 50% VO_2peak	HI: from 21.9±4.8 to 24.9±5.5 LO: from 24.9±3.5 to 27.2±2.8	HI: from 36.3±5.9 to 35.8± 5.9 LO: from 33.9±3.1 to 33.4±3.1
(Landaeta-Díaz et al., 2013)	45 (30females, 15males)	MeDE (diet +exercise) (ergometer) (3/week)	30 minutes 80% of HRmax	12 weeks	Diet calori restriction	MeDE: from 18.87±5.59 to 27.31±4.70 MeD: from 19.99±5.72 to 22.38±6.98	MeDE: from 37.05±3.22 to 33.79±3.21 MeD: from 38.44±6.5 to 36.35 ±6.12
(Lunt et al., 2014)	49 (36 females, 13 males)	AIT: aerobic interval training (walking) MVIT: maximal volitional intensity training	AIT: 4min HIIT (85-95% HRmax)/3 min walking 4 repetitions (40 minutes) MVIT: 30 seconds volitional intensity/4 minutes walking, 3 to 6 repititions (25 to 40 minutes)	12 weeks	Walk: 10 minutes warming up 5 minutes cool down 33 minutes walk (65-75% HRpeak)	WALK: from 26.5±5.3 to 25.2 ±3.6 AIT: from 24.2±4.8 to 25.6 ±4.8	WALK: from 32.4±2.9 to 32.3 ±2.9 AIT: from 32.1±3.1 to 32.1 ±3.0

Study	Number	Intervention	Intensity	Duration	Control	Study End Point: VO_2max (ml.min.kg)	Study End Point: BMI (kg/m ^{2})
		(3/week)	10 minutes warming up 5 minutes of cool down			MVIT: from 25.0±2.8 to 25.2 ±3.4	MVIT: from 32.4±2.9 to 32.3 ±2.9
(Mezghanni et al., 2012)	31 females	High intensity aerobic training (walking and jogging)	G75: 20 to 55 minutes 75% HRR	12 weeks	Moderate intensity aerobic training G50: 20 to 55 minutes 50% HRR OR Control		CON: from 33.2±1.8 to 33.3±1.7 G75: from 32.9±1.8 to 30.5±2.4 G50: from 34.1±3.6 to 32.9±3.8
(Reljic, Frenk, Herrmann, Neurath, & Zopf, 2021)	123	HIIT: cycle ergometers MIIT: cycle ergometers	HIIT: 2 minutes warm up, 5 interval bouts of 1 minute at 80–95% HRmax interspersed with 1 minute of low intensity recovery and a 3 minutes cool-down phase (total session time: 14 min) MIIT: cycle ergometers	12 weeks	CON: inactive	HIIT: from 2.51±0.6 to 2.75±0.68 MIIT: from 2.06±0.56 to 2.12±0.55 CON: from 2.24±0.87 to 2.09±0.92	HIIT: from 38. ±6.8 to 37.1±6.8 MIIT: from 35.7±5.0 to 34.9±4.9
(Robinson et al., 2015)	39	HIIT (treadmill, cycle, elliptical)	HIIT: 3 minutes warm up 4x 1:1 85 to 90 % Wpeak/20% Wpeak to 10x 1:1 85 to 90% Wpeak / 20% Wpeak Cool down (32.5% Wpeak)	2 weeks	20 to 50 minutes of continuous activity at 32.5% Wpeak	HIIT: from 20.4±3.4 to 21.9±4.0 MICT: from 20.6±4.9 to 22.1±4.7	HIIT: from 32.9±6.6 to 32.6±6.7 MICT: from 31.4±4.1 to 31.3±4.0
(Roxburgh, Nolan, Weatherwax, & Dalleck, 2014)	29 (19 females, 10 males)	CMIET+ single bout of HIIT (treadmill and cycling) (5 times/week)	4 sessions CMIET +1 session HIIT: 60s 100%VO2max With 150 s recovery 8 to 12 repetitions	12 weeks	CMIET: 15 min walking and 15 minutes cycling (45-60%HRR) Control: normal activity level and no exercise	CMIET+HIIT: from 32.7±9.2 to 36.0±11.5 CMIET: from 33.2±4.0 to 34.5±6.1 CON: from 30±4.6 to 28.3±6.5	CMIET+HIIT: from 30.7±6.3 to 30.6±6.1 CMIET: from 29.6±4.7 to 29.4±4.7 CON: from 29.2±4.2 to 29.5±4.4
(Skleryk et al., 2013)	16 males	Sprint interval training (Obesity & World Health) (ergometer) (6 sessions)	8 ɯseconds to 12x10 seconds 'all out' sprints	2 weeks	Traditional exercise recommendations(TER) 30 min 65% VO_2max (10 sessions)	SIT: from 29.7±3.7 to 29.3±5.3 TER: from 26.3±5.7 to 26.3±6.2	SIT: from 32.2±5.9 to 32.2±5.9 TER: from 35.2±5.1 to 35.2±5.1

12.2 Physiological Effects

Generally, high intensity interval exercise, such as the Tabata protocol, typically involves eight sets performed at 170% of VO2max intensity, with 10-second rest intervals (Tabata et al., 1996), enhances mRNA expression, particularly of proteins involved in mitochondrial biogenesis and protein synthesis in skeletal muscle (Figure 15) (I. Tabata, 2019). Exercise at intensities exceeding 130% of VO2max increases oxygen delivery to muscle mitochondria by approximately 100-fold; however, despite the substantial rise in blood flow to contracting skeletal muscle, partial hypoxia occurs. This heightened metabolic demand surpasses the available energy supply, resulting in elevated levels of adenosine monophosphate, lactic acid, inorganic phosphate, and other metabolites.For improved oxygen delivery, hypoxia-Inducible Factor and vascular endothelial growth factor induction would initiate the development of enhanced vascularization, especially with active recovery between exercise bouts (P. Wahl et al., 2013). Notably, incorporating active rest between exercise sets enhances the effects of the regimen compared to passive rest. Active rest promotes lactate clearance and glycogen resynthesis, thereby improving overall exercise outcomes. (Choi, Cole, Goodpaster, Fink, & Costill, 1994). Similar results have been observed in young athletes performing four maximal-effort sprints of 300 m, three sprints of 100 m, one of 400 m, and two of 200 m. All applied methods led to elevated lactic acid levels; however, intermittent workouts (3 × 100, 2 × 200 m running) seemed to outperform continuous workouts of the same total distance. This was evident in their enhanced ability to produce energy through the lactate system (Saraslanidis et al., 2009).

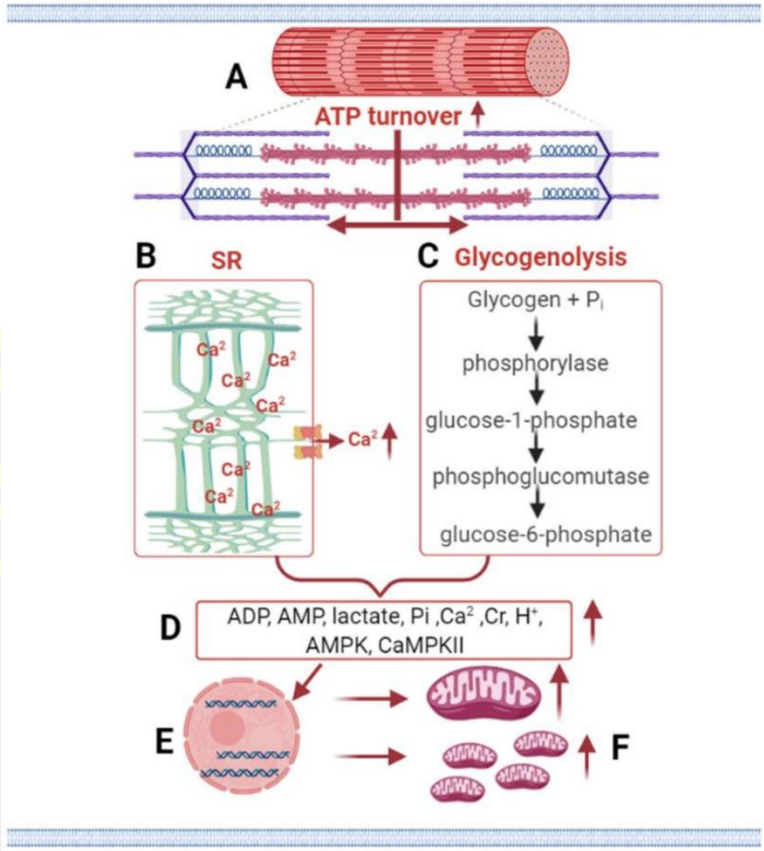


Figure 15 Signaling pathways driving greater mitochondrial adaptations in high-intensity versus lower-intensity exercise.

Higher-intensity exercise demands greater ATP turnover (A) and increases calcium release from the sarcoplasmic reticulum (B). Carbohydrate oxidation, mainly from muscle glycogen, predominates (C), causing accumulation of metabolites like ADP, AMP, lactate, Pi, creatine, calcium, H^+, AMPK, and CaMKII (D). This triggers enhanced gene expression (E), leading to increased mitochondrial protein synthesis and mitochondrial content (F). Source: (Atakan et al., 2021).

When examining the acute effects of high-intensity interval cycling and high-volume cycling on the hormonal profile of well-trained cyclists, it was found that high-intensity work increased circulating levels of growth hormone and cortisol compared to high-volume exerciseThe acidosis induced by high-intensity exercise may contribute to the elevation of these hormones, which are integral to protein synthesis, turnover, repair, and metabolic regulation. Additionally, acute high-intensity exercise results in increased circulating levels of microRNAs, which may play a critical role in modulating vascular function and anabolic adaptive responses

(Kilian et al., 2016). High-intensity resistance exercise results in increased circulation of testosterone, suggesting an enhanced anabolic process. However, it's worth noting that longer resting periods between sets, such as 3 minutes, are superior to shorter 1-minute rest periods for experiencing the long-term effects of elevated testosterone (Senna et al., 2016). Additionally, active rest combined with high acute intensity eccentric exercise can readily cause microdamage to sarcomeres, leading to muscle soreness. Interestingly, acute high-intensity exercise may confer benefits for patients with type 1 or type 2 diabetes. This exercise modality induces increased production and accumulation of lactic acid, which is believed to help preserve cognitive function and enhance awareness of hypoglycemia (Rooijackers et al., 2017). Moreover, the production of nitric oxide metabolites with this intensity of exercise could be important for the health-promoting effects of the Tabata protocol (Campbell & Rutherford, 2018; I. Tabata, 2019).

Meta-analysis studies have consistently demonstrated that despite lower training volume, HIIT yields a similar or even greater increase in VO_2max across various populations, including adolescents, healthy adults, and individuals with obesity, cancer, and metabolic syndrome, when compared to MICT. This indicates that HIIT is a time-efficient intervention for enhancing aerobic capacity compared to MICT. The observed increase in VO_2max is typically attributed to several factors, including increased stroke volume (SV), maximal cardiac output, maximal arteriovenous oxygen difference (a-vO2 diff), skeletal muscle oxidative enzyme capacity, capillary density, heightened red blood cell volume, and hemoglobin mass, resulting in an augmented oxygen-carrying capacity. (Figure 16) (Atakan et al., 2021).

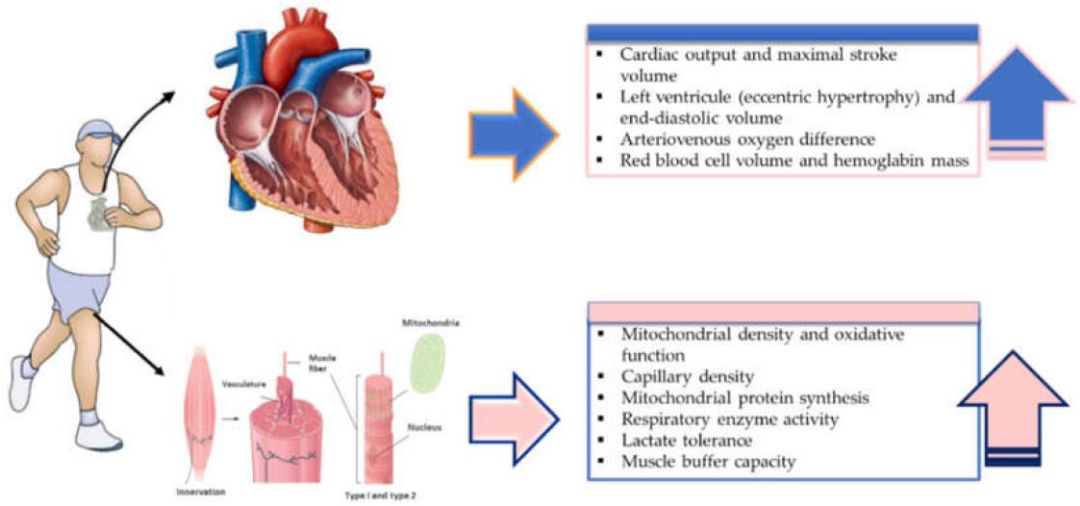


Figure 16 Central and peripheral adaptations to exercise interval training. Source: (Atakan et al., 2021).

12.3 Effect of HIIT on Weight Loss

Exercise is a critical intervention for weight loss due to its capacity to reduce body mass, increase fat-free mass, and maintain or elevate resting metabolic rate. Numerous studies have demonstrated that HIIT can effectively promote weight loss in sedentary overweight and obese individuals. For instance, a 2-week HIIT intervention led to significant reductions in waist circumference and subcutaneous adipose tissue in overweight sedentary men. Similarly, a 12-week HIIT program produced notable decreases in total abdominal, trunk, and visceral fat among overweight young males. Another study reported that 16 weeks of HIIT (4×4 minutes at ~90% HRmax, with 3-minute recovery intervals at 70% HRmax) resulted in a 3% reduction in body weight and a 5 cm decrease in waist circumference in sedentary overweight individuals with metabolic syndrome (Alahmadi, 2014).

In a longer-term study, Tjønna et al. observed reductions in total fat mass by 0.9 kg at 3 months and 2.4 kg at 12 months following HIIT intervention. More recently, a 6-week low-volume HIIT protocol (10×60 seconds at ~90% HRmax, 60 seconds recovery) in overweight/obese women yielded significant improvements in body composition, including decreased abdominal and whole-body adiposity and increased leg lean mass as measured by DEXA. Conversely, some studies have reported no significant changes in weight or body composition following HIIT in sedentary overweight/obese populations (Tjønna et al., 2009). For example, Skleryk et

al. found no body composition changes after a 2-week HIIT program involving 10-second maximal cycling efforts, suggesting this duration may be insufficient compared to protocols using longer intervals (Skleryk et al., 2013). Similarly, Astorino et al. reported no body weight changes after 12 weeks of HIIT consisting of 60-second intervals at 75–95% HRmax with 75-second recoveries (Astorino, Schubert, Palumbo, Stirling, & McMillan, 2013). Two plausible explanations for the absence of weight loss in some exercise interventions include compensatory increases in energy intake stimulated by exercise-induced appetite and reductions in non-exercise activity thermogenesis to offset the additional energy expenditure (N. A. King et al., 2007; Melanson, Keadle, Donnelly, Braun, & King, 2013).

Overall, current evidence on the effects of HIIT on weight and body composition in sedentary overweight and obese individuals remains limited, with generally modest weight loss observed. While HIIT shows promise as an effective intervention, further research with longer durations—ideally beyond 12 weeks—is necessary to clarify its efficacy (Alahmadi, 2014).

12.4 Effect of HIIT on Immune Function

A Systematic Review with Meta-Analysis of acute and chronic effects of interval training (IT) (i.e., HIIT) on the immune system found that IT might acutely reduce leucocyte function. In terms of chronic effects, IT has been demonstrated to enhance immune function without significantly affecting leukocyte counts (Souza et al., 2021).

Most studies have reported transient increases in total leukocyte count lasting up to 6 hours following high-intensity interval training (HIIT). However, one study found no change in leukocyte count following HIIT with either passive or active recovery. Fry et al. (1992) observed a significant rise in leukocyte count immediately after HIIT at 120% of $\dot{V}O_2max$, but not at 90% (Fry, Morton, Crawford, & Keast, 1992). Regarding leukocyte subsets, nine studies reported immediate post-exercise increases in total lymphocyte counts, while two studies showed no change. Additionally, five interventions demonstrated a decline in lymphocyte count between 30 minutes and 6 hours post-exercise. Neutrophil counts consistently increased after HIIT, with elevations noted immediately and persisting for up to 5 hours; some studies

also reported delayed increases between 1 and 3 hours. Monocyte counts typically rose immediately post-exercise, although one study found no change (Figure 17). For mixed leukocyte populations, two studies reported acute increases in eosinophil and basophil counts, whereas another observed increased granulocyte count. In contrast, one study found no change in eosinophils, and a study by Wahl et al. reported no change in basophils and a decrease in eosinophils following HIIT. (Patrick Wahl, Mathes, Bloch, & Zimmer, 2020).

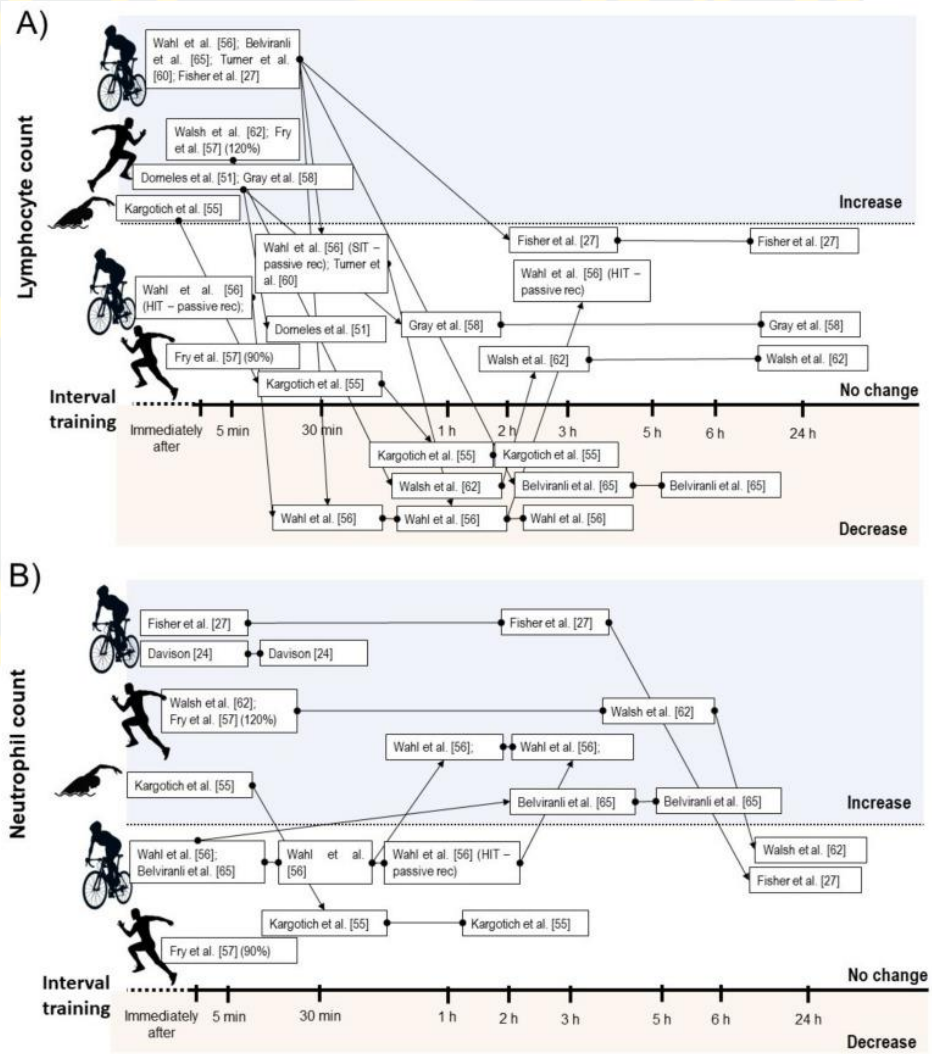


Figure 17 Time-course illustration of lymphocyte (A) and neutrophil (B) counts following an acute high-intensity interval training session.
Source: (Souza et al., 2021).

A qualitative analysis of the chronic effects of IT on immune outcomes indicates that three studies involving HIIT reported no significant changes in total leukocyte count. Regarding leukocyte function, one study observed increases in peripheral T helper subsets, particularly memory regulatory T cells, following HIIT. Additionally, three studies demonstrated enhanced neutrophil function, while two studies reported improvements in lymphocyte function. Conversely, a study involving three consecutive days of exhaustive HIIT sessions found a significant increase in lymphocyte migration and apoptosis after the final session (Souza et al., 2021).

The main findings of this systematic review concerning acute immune responses to IT are as follows: (1) IT induces transient leukocytosis lasting up to 6 hours (2) IT results in lymphocytosis followed by transient lymphopenia within the same timeframe and (3) IT leads to a temporary impairment in lymphocyte and neutrophil function (Pearson et al.) In contrast, chronic IT interventions (ranging from 1 to 24 weeks) show no significant changes in total leukocyte count but are associated with favorable adaptations in lymphocyte, monocyte, and neutrophil function (Souza et al., 2021). Overall, while the acute immune response to IT is well-characterized, further research is warranted to elucidate the long-term immunological adaptations.

12.5 Effect of HIIT on Pulmonary Function

There is very rare study of HIIT affects respiratory or pulmonary function. Andrade et al. studied an acute effects of HIIT session and endurance exercise on pulmonary function and cardiorespiratory coupling. They studied in 4 females and 4 males (BMI 22.0 ± 2.4 kg/m^2) were exposed to endurance exercise (20 min at 80% maximal heart rate) and HIIT (1 min of exercise at 90% maximal HR per 1 min of rest, 10 times) compared with self-control condition. Results revealed no significant effects of HIIT on pulmonary function (Andrade et al., 2020). Rawashdeh et al. investigated the effects of high-intensity aerobic exercise on pulmonary function in physically inactive male individuals. They studied in 72 inactive male individuals (mean weight 79.67 ± 12.56 kg. no BMI data) were given a pulmonary function test. The test protocol involved conducting three trials per session, starting with five minutes of exercise and increasing by ten minutes every three sessions, up to a maximum duration of 25 minutes. Participants exercised three times per week over a three-week period. The findings suggested that greater exercise intensity or longer

duration may be necessary to elicit significant improvements in pulmonary function parameters, including MVV, FEV_1, and FEV_1/FVC. Overall, the results indicate that high-intensity aerobic exercise on a treadmill positively influences pulmonary function in sedentary healthy individuals (Arwa Rawashdeh, 2018).

13. Tabata Training and Protocol

Tabata training derives its name from Izumi Tabata, who conducted research on changes in both the aerobic and anaerobic systems following HIIT using his proprietary protocol, which was first published in 1996 (Tabata et al., 1996). Tabata training is defined as training or exercise performed at an intensity that exhausts subjects during the 7^{th} or 8^{th} sets of exercise bouts, each set consisting of 20 seconed of exercise followed by a 10-second rest period (I. Tabata, 2019). Tabata training was originally developed for bicycling exercises. However, similar protocols have been adapted to other forms of exercise, including running and various bodyweight-bearing exercises such as burpees and squat jumps (I. Tabata, 2019; Tabata et al., 1997; Tabata et al., 1996).

13.1 Effects of Tabata Training on Body's Aerobic and Anaerobic Energy-releasing Systems

Previous study conducted a comparison between two intermittent bicycle exercise protocols, Tabata training and traditional intermittent training. Results indicated that during the exhaustive intermittent exercise of Tabata training (with an exercise intensity of approximately 170% VO_2max, consisting of 7–8 bouts of 20-second exercise with a 10-second rest between bouts), the accumulated oxygen deficit equaled the anaerobic capacity. Consequently, the Tabata training appeared to exert maximal stress on the anaerobic energy system. Furthermore, the Tabata training maximally engaged the oxygen delivery system, as evidenced by the fact that the oxygen uptake measured during the latter part of the Tabata training did not differ from the subjects' VO2max (Tabata et al., 1997).

Aerobic training, comprising a 1-hour prolonged bicycle exercise at 70% VO2max, was found to increase VO2max without affecting a maximal accumlated oxygen deficit (MOAD). In the last session of the Tabata protocol, oxygen uptake reached VO_2max (a measure of aerobic capacity), while the accumulated oxygen

deficit of the training exercise equated to the MAOD (a measure of anaerobic capacity). The effectiveness of specific training on a particular aspect of fitness may vary based on how much it challenges the subject's fitness level. Given that humans possess only two energy-releasing systems and the Tabata protocol maximally stresses both systems, training using this protocol can be considered one of the most comprehensive methods for aerobic and anaerobic training. As a result, in line with the specificity of training and its impact on energy release, Tabata training enhances both VO_2max and MAOD (Tabata et al., 1996).

13.2 Effect of Tabata Training on Muscle

Previous research has reported on skeletal muscle adaptation to Tabata training. Following 6 weeks of Tabata training, there were significant increases in the enzyme activities of citrate synthase and phosphofructokinase. This suggests that the training might have boosted protein expressions, potentially influencing both the aerobic and anaerobic energy-releasing systems. Consequently, in relation to these energy-releasing systems, peripheral adaptations were observed post-Tabata training. These heightened enzyme activities likely played a role in the increases in both VO_2max (9.2%) and MAOD (20.9%) (Miyamoto-Mikami et al., 2018).

One of the key mechanisms underlying the enhancement of MAOD following Tabata training, is the improved buffer capacity of recruited muscles (J. T. Sharp et al., 1964). This heightened capacity enables greater formation of muscle lactate, leading to increased glycolytic ATP production during high-intensity exercises. Shark et al. demonstrated a notable 37% increase in muscle buffer capacity after an 8-week sprint training regimen, which likely accounts for the majority of the MAOD elevation post Tabata training. Moreover, carnosine is recognized as a minor contributor (5–10%) to muscle buffer capacity (Sahlin, 2014). In this regard, it is noteworthy that Tabata training led to increased mRNA and protein levels of carnosine synthase 1 (Miyamoto-Mikami et al., 2018), suggesting a potential elevation in the body's carnosine content akin to that observed after Tabata training (de Salles Painelli et al., 2018).

13.3 Effect of Tabata Training on Peripheral Blood Circulation

Endurance training has been found to increase capillary density (Hermansen & Wachtlova, 1971). Cocks et al. demonstrated that Sprint Interval Training and

endurance training are equally effective in enhancing skeletal muscle capillarization, increasing the body's endothelial nitric oxide synthase content, and reducing aortic stiffness (Cocks et al., 2016). This study revealed that Tabata training led to increased expression of eNOS, responsible for nitric oxide production, which may subsequently dilate arteries. This suggests that Tabata training may enhance arterial function via a mechanism akin to conventional aerobic training, potentially reducing the risk of cardiovascular events.

13.4 Tabata Training in Obesities and Inactive Person

Tabata training demands a high level of effort (Foster et al., 2015). A study involving recreationally active women revealed an increase in perceived enjoyment of weight-bearing High-Intensity Interval Training (HIIT) from pre- to post-training, suggesting that prolonged exposure to such training may enhance individuals' enjoyment (Funch et al., 2017). Additionally, dropout rates in studies involving obese pre-adolescent boys (Chuensiri et al., 2018) and inactive adolescent volunteers (Logan et al., 2016) were relatively low, indicating tolerability and positive acceptance of HIIT. However, contrasting results from another investigation suggest that training at high intensities may not be enjoyable for everyone (Ekkekakis, Hall, & Petruzzello, 2008), warranting a psychological inquiry into subjects' enjoyment of Tabata training.

Previous Tabata training review suggests that an exploring potential adverse effects of Tabata training and other forms of HIIT is essential, along with devising strategies to mitigate these effects through diet, supplements, alternative conditioning methods, or other interventions. Furthermore, to develop evidence-based training protocols, more foundational research on HIIT, including Tabata training, is necessary to elucidate the mechanisms underlying its beneficial effects on both athletic and health-related outcomes, ultimately contributing to an enhanced quality of life (Izumi Tabata, 2019).

14. Home-based HIIT

Traditionally, resistance training is performed separately from aerobic exercise, typically on two to three nonconsecutive days per week. The ACSM recommends 8 to 12 repetitions per major muscle group at an intensity of 60 to 70% of 1-repetition maximum (1RM), adjusted to the participant’s training level, with 2 to

4 sets and 2 to 3 minutes of rest between sets for adequate recovery. Aerobic training guidelines advise 150 minutes per week of moderate-intensity exercise (40 to 59% VO_{2max}) for 30 to 59 minutes per session or 250–300 minutes per week of vigorous-intensity exercise (>59% VO_2max) for 60 minutes per session. While effective, these traditional protocols may be impractical for time-constrained adults due to their duration and certain limitations in demonstrated effectiveness (Murphy & Schwarzkopf, 1992; Scott, Leighton, Ahearn, & McManus, 2011).

High-Intensity Circuit Training (HICT), which combines body-weight resistance exercises with aerobic components in a high-intensity, limited-rest format, has gained popularity due to its efficiency and practicality for time-constrained individuals. This hybrid approach integrates aerobic and resistance training, delivering substantial health benefits in significantly less time than traditional exercise programs (Gibala et al., 2006; LaForgia, Withers, & Gore, 2006; Little, Safdar, Wilkin, Tarnopolsky, & Gibala, 2010; Tabata et al., 1996; Wernbom, Augustsson, & Thomeé, 2007). Utilizing body weight as resistance removes barriers related to access to gym equipment and facilities, increasing its accessibility.

When crafting a HIIT program, it's essential to consider the duration, intensity, and frequency of the work intervals, as well as the length of the recovery intervals. The intensity during the high-intensity work interval should exceed 80% of the estimated maximal heart rate, with participants perceiving the effort as "hard" to "very hard". The intensity of the recovery interval should be maintained at 40-50% of the estimated maximal heart rate. The relationship between the work and recovery intervals is crucial, as many studies employ specific ratios of exercise to recovery to optimize various energy systems within the body. For instance, a 1:1 ratio might involve a 3-minute high-intensity bout followed by a 3-minute low-intensity recovery bout. These 1:1 interval workouts typically consist of intervals lasting 3, 4, or 5 minutes, followed by an equal recovery period (ACSM, 2014).

To overcome the limitations of traditional exercise protocols and offer an effective, time-efficient program suitable for the COVID-19 pandemic context, our study employed home-based high-intensity interval training (HIIT) utilizing body weight as resistance. This approach integrated aerobic and resistance exercises into a single bout lasting approximately 4 minutes, following the Tabata protocol (20

seconds of exercise alternating with 10 seconds of rest). Each session included a 4-minute recovery period, resulting in a total session duration of 8 minutes (exercise:rest = 4 minutes:4 minutes) (I. Tabata, 2019; Tabata et al., 1996). Participants completed four repetitions of this 8-minute bout. Because body weight was the sole source of resistance, the program could be performed anywhere without the need for equipment.

15. Ecdysteroids and Its Phamacological Effects

"Ecdysteroids" is a growth steroid hormone which is produed by insects, shrimp, crabs and invertebrates in Arthropoda phylum and other phylum. The hormone is often referred to as molting hormone because it is found in all stages of these insects growth. The hormone controls the biochemical and physiological processes of insects which from the stage of embryo to pupa and from the chrysalis continue to molt to become insects. The hormone is also responsible for controlling various processes of invertebrates both molting shape change and control the reproductive process. Including, the hormone is also involved in metabolic and excretion processes. In addition, Ecdysteroids is also found in plants that are in the bare seed group, the fern group and the flowering plant group. Ecdysteroids of plant is also called "Phytoecdysteroids". Previous studies found that the plants produce phytoecdysteroids to fight insects. Because if insects eat plants that contain phytoecdysteroids, the hormone will harm the insects themselves (อภิชาติ สุขสำราญ, 2542).

Previous studies found that Ecdysteroids is found in a few insects because the insects use in very small quantities of the hormone. Horn and colleuge extracted 1 ton of crayfish (Jasus lalandei) and extracted 20-hydroxyecdysone (20E) (one form of Ecdysteroids) (Figure 18) in the amount of only 2.3 mg (Horn, Middleton, Wunderlich, & Hampshire, 1966). Nakanishi et al. extracted *Podocarpus nakaii* (one kind of plant) for find anti-cancer compounds. Instead, three Ecdysteroids namely ponasterones A, B, and C (Figure 18 (2,3,4)) were found more than in animals. It mean that, when extracting only 900 g of the leaves of this plant, a total weight of 6.6 g of Ecdysteroids was obtained (Nakanishi, Koreeda, Sasaki, Chang, & Hsq, 1966). This is consistent with study of Takemoto et al that found a relatively high levels of

20-hydroxyecdysone (20E) in the roots of the plant *Achyranthes fauriei*, which have diuretic properties. Now, the 20E is considered an important mainstream of bioactive compound and is found a lot of the 20E of the Ecdysteroids group (Figure 18 (5)) (Baltaev, 2000; Takemoto, Hikino, Hikino, Ogawa, & Nishimoto, 1969).

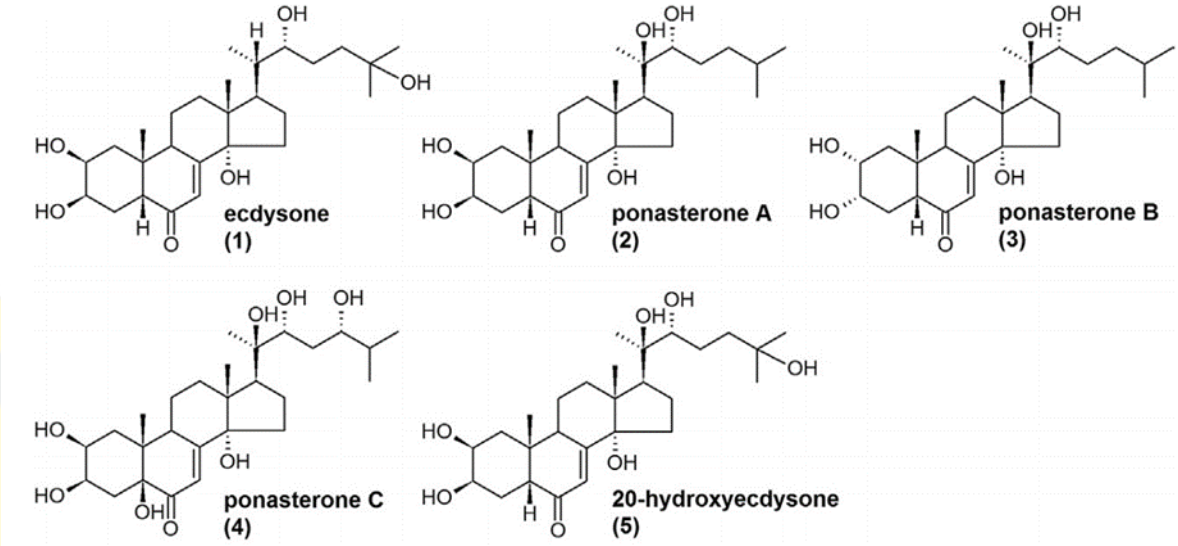


Figure 18 Chemecal structure of Ecdysteroids extracted from plants and animals. Source: (Bajguz, Bąkała, & Talarek, 2015).

The discovery of Ecdysteroids and many studis of the its structure and biological functions. It is seem important in terms of theory and practice. Because Ecdysteroids are involved in many functions of insects such as reproductive function and growth function etc. Therefore, Ecdysteroids may be useful in controlling the quantity and severity of insect populations. In addition, Phytoecdysteroids may have many medicinal and pharmacological efftects without causing toxicity to humans and vertebrates.

15.1 Chemical Structure of Phytoecdysteroids in Plants

Ecdysteroids comprise a class of steroids with a polyhydroxy-lated cyclopentano (α) perhydrophenanthrene ring system as shown in figure 18 The phytoecdysteroids are composed of 5 β-cholestanol is a steroid skeleton and a 6-ketone ring B with the hydroxyl group at C-14. The chemical structure of Phytoecdysteroids is very diverse. It depends on the number of carbons present in the molecule (19, 21, 24, 27, 28, 29 carbon atoms). However, most Phytoecdysteroids are cholesterol derivatives. Thus, the carbon is C-27 and the hydroxyl group is at C-14 α

position (Báthori, Tóth, Hunyadi, Márki, & Zádor, 2008). This hydroxyl group that results in the heterogeneity of the chemical structure of Phytoecdysteroids. Depending on the number, location, and direction that connects other substances in its structure. Most of the hydroxyl groups are found at C-2 β, C-3 β, C-14 α, C-20R and C-22R positions. The location of its hydroxyl group is necessary for the bioavailability effects of Ecdysteroids. For example, Ponasterone A (25-deoxy-20E) (Structures are shown in figure 18 (2)). Now, more than 1,000 structures of natural Phytoecdysteroids have been discovered and found in small quantities in plants. Most of the structures found are slightly different, found in small quantities in plants and is also a same chemical structure but its biologically effects do not as high as 20E (L. Dinan et al., 1999).

Phytoecdysteroids have been found in more than 100 families of terrestrial plants, of which about 5-6 percent were found to have high levels of the hormone. Phytoecdysteroids are naturally occurring compounds found in a variety of plant species, including both herbaceous and perennial plants. Within the group of bare seed plants, phytoecdysteroids have been identified in nine families, while twenty families within the fern group are known to contain these compounds. Additionally, phytoecdysteroids are present in flowering plants, encompassing both monocotyledonous and dicotyledonous species. A total of 176 plant Phytoecdysteroids have been identified in 28 families, 66 genera, and of these, 147 were identified as 20E. Phytoecdysteroids are extracted from many parts of plants such as seeds, fruits, flowers, stamens, leaves, bark, stems, roots and rhizomes. The distribution of Phytoecdysteroids depends on a plant parts and a stage of growth. The hormone may be subject to change depending on a seasonal factor, location the plants are planted, transport and cycle of synthesis. Therefore, the amount of Phytoecdysteroids in a plant part may be diference and fluctuations throughout the growth of the plant which this different quantity may be found from 0.000001% - 10% of dry weight (Bandara et al., 1989). Phytoecdysteroids can be extracted in large quantities in the roots of the fern and a bark and roots of other plants such as the group of seeds plants and the group of seeds bark etc (Adler & Grebenok, 1999; G. T. Brooks, 1985). In addition, many studies also found that almost all plants produce Phytoecdysteroids but there are a problem in the accumulation of this hormone. Thus,

sometimes, this hormone is not detected in many plant species (Laurence Dinan, 2009; L. Dinan, P. Bourne, et al., 2001; L. Dinan et al., 1999; L. Dinan, T. Savchenko, et al., 2001). Previous study found the highest concentration of 20E in plants is 3.2% of dry weight of the stems of *Diploclisia glaucescens* (Bandara et al., 1989). Therefore, when compared, amount of Ecdysteroids are found in plants higher than in animals.

Drawing from the traditional utilization of certain plants, dried plant parts (or their extracts) are commercially available as dietary supplements (refer to Figure 19), primarily marketed for their purported anabolic properties. These supplements are targeted towards humans (including bodybuilders and athletes) as well as animals (such as horses and dogs). Typically, these supplements do not contain pure 20E but rather a more or less complex mixture.

Figure 19 Examples of dietary supplements containing (or claimed to contain) 20E (Ecdysteroids).

15.2 Pharmacological Action of Ecdysteroids

A lot of researches that study the pharmacological effects of Ecdysteroids in plants (also call Phytoecdysteroids) on vertebrates and humans. Compounds of Phytoecdysteroid are widely used. The first study, in the 1960, study the toxicity of Phytoecdysteroid exposure in rats showed that Phytoecdysteroid were low toxic to mammals (LD50 >6 g/kg body weight). This trial is the first study

leading to the pharmacological effects of Ecdysteroids on mammal. A study on the pharmacological effects of Ecdysteroids exposured showes that Ecdysteroids stimulate a protein synthesis process in laboratory animals. The rats were exposed to 20E or other Ecdysteroids derivatives, then, these rats synthesis more protein in liver (L. Dinan et al., 1999; Seidlova-Wuttke, Ehrhardt, & Wuttke, 2010). However, the pharmacological effects of Phytoecdysteroids are currently unclear. From the results of previous studies, there are found that Phytochemicals are effective against bacteria and fungi, regulating physiological processes to bring homeostasis (adaptogenic), immunoprotective, anti-inflammatory, anti-diabetic, anabolic and hepatoprotective, wound-healing and antitumor. As a result, there are many uses of Ecdysteroids compounds in terms of preventing or reducing the risk of disease and in promoting health in both general people and athletes. Ecdysteroids have antioxidant effect and is often mixed into various food products (Cahlíková et al., 2011). The plant sources that are often used for medicinal purposes are plants of the families *Achyranthes* and *Cyathula*. It is also found in spinach and quinoa seeds (Laurence Dinan, 2009).

The anabolic properties have been investigated in small-scale human trials over the past 35 years (Table 7), Especially noteworthy are the earlier studies utilizing the standardized proprietary preparation Ecdysten®—pills containing 5 mg of pure 20E extracted from Rhaponticum carthamoides. However, detailed reports for most of these studies are lacking. The administration of these molecules was frequently coupled with protein supplements (such as whey proteins) and rigorous physical exercise, complicating the assessment of the isolated effects of the ecdysteroids themselves.

Table 7 Human studies on anabolic properties of ecdysteroids.

Author(s)	Aim	Age	Numbers	Dose	Duration	Output(s)
(Gadzhieva, Portugalov, Paniushkin, & Kondrat'eva, 1995)	Anabolic effect	Runners 15–25	20 (4 arms)	-	21 days	Reduction of subcutaneous fat, muscle mass increase
(Azizov, Seĭfulla, Ankudinova, Kondrat'eva, & Borisova, 1998)	Physical capacity	Athletes	44	-	20 days	Increase of working capacity by 10–15%
(Emirova, 2004)	Physical capacity	Athletes	10/arm	-	3 weeks	A combination of ecdysten and cytamins increases bench press performance and endurance
(Wilborn et al., 2006)	Physical capacity	20.5 ± 3 years	45 males	30 mg/day *	8 weeks	No observed effects on body composition, anabolic/catabolic hormonal status, or physical performance
(Safarova, 2016)	Physical capacity	Athletes	64 males	5, 10, then 15 mg/day	10 days each	Muscle mass increase (+5%), fat mass decrease, strength increase (+12%)
(Isenmann et al., 2019)	Anabolic effect	Athletes 25.6 ± 3.7 years	46	12/48 mg/day **	10 weeks	Increase in body weight (ca. 3 kg), muscle hypertrophy and improved performance

* The stated quantity is based on the information provided by the dietary supplement supplier and has not been independently verified. ** The measured amount was determined; however, the absence of other anabolic substances in the dietary supplement utilized was not confirmed.

15.3 Ecdysteroids on Inflammation and Immune Function

Phytoecdysteroids such as 20E, cyasterone, turkesterone and viticosterone E have the effect of reducing inflammation and increase the functioning of the immune system. From previous studiy found that obese and overweight individuals ,who is chronic low-grade inflammation, is identified by monocyte chemotactic protein-1, interleukin-6 and plasminogen activator inhibitor-1. (PAI-1) in the blood increased that caused by stimulation through TLR4-mediated signaling pathway (Wong et al., 2009). While the production of anti-inflammatory agents is reduced, TLR-4 is an important mechanism influencing immune function, both innate immunity and adaptive immunity. Exposure to 20E has effect reduce the amount of mRNA involved in The TLR4-mediated signaling pathway results in 20E having an anti-inflammatory effect (Lafont & Dinan, 2003).

15.4 Ecdysteroids and Metabolic Syndrom

Effects of Ecdysteroids on metabolic syndrome is found in ovariectomized rats that is a postmenopausal women model. They were orally treated with 3 doses of Ecdysteroids (18, 56 or 116 mg/day/animal) and compared with positive controls received 159 micro g estradiol. Ecdysteroids do not stimulate uterine weight. In ovariectomized rats, treatment with ecdysteroids results in reduced fat accumulation and increased muscle mass. Serum levels of thyroid-stimulating hormone, thyroxine, and triiodothyronine remain unchanged following ecdysteroid administration, whereas estradiol treatment increases thyroxine and decreases triiodothyronine levels. At the lowest dose, ecdysteroids reduce serum low-density lipoprotein (LDL) cholesterol without elevating serum triglycerides, a response observed in E2-treated rats. At the highest ecdysteroid dose, serum high-density lipoprotein (HDL) cholesterol is significantly higher than in control animals. In conclusion, ecdysteroids exert beneficial effects on adipose and muscle tissues and may have potential to prevent metabolic syndrome and sarcopenia via a non-estrogenic mechanism in postmenopausal women. (Seidlova-Wuttke et al., 2010). Studies have shown that Ecdysterone can be used for cardiovascular system protection. This is linked directly with tissue metabolism related to depression of heart and vessel function. Ecdysterone would be used against age related illnesses (for example, obesity related to the metabolic syndrome, arteriosclerosis, hypertension, osteoporosis, menopause and andropause troubles (Cahlíková et al., 2011).

15.5 Ecdysteroids and Glucose Metabolism

There are previous studies on the effect of edosteroids on glucose metabolism. Yoshida et al. study the effect of ecdysterone on hyperglycemia in experimental animals. Following the administration of ecdysterone to alloxan-diabetic mice, the blood glucose level decreased to approximately half of the value observed prior to ecdysterone administration. Moreover, treatment with ecdysterone stimulated the incorporation of glucose into protein in normal mouse liver and into glycogen in both normal and mildly diabetic mouse liver tissues (Yoshida, Otaka, Uchiyama, & Ogawa, 1971). Ecdysterone also stimulates tissues to use more glucose (increased sensitivity of tissues to insulin). Phytoexdysteroids have been proposed as antidiabetic

drugs and it may be more or less effective depending on blood sugar levels (L. Dinan & Lafont, 2006).

15.6 Ecdysteroids and Lipid Metabolism

Ecdysteroids can reduce blood lipid levels by reduce the formation of cholesterol and increase the breakdown of cholesterol mechanism. Syrov and colleagues investigated the effects of phytoecdysteroids on bile-secretory function in both normal liver and experimental hepatitis models. Oral administration of a 5 mg/kg dose markedly stimulated bile secretion in normal rats following a single dose of cyasterone and after 7 days of treatment with ecdysterone and cyasterone. The results demonstrated a significant improvement in the chemical composition of bile, characterized by increased levels of bile acids and bilirubin, along with a reduction in cholesterol content (V. N. Syrov, Nabiev, & Sultanov, 1986) which is related to oxysterol. Thus, Ecdysterone plays a role in the process of producing and breaking down cholesterol in variuos tissues. As a result of this mechanism, Ecdysteroids may also have an anti-atherosclerotic effect. Ecdysterone ejection increases in 14C-acetate incorporation into triglycerides. A concomitant decrease in free fatty acids and diglycerides is observed in liver and adipose tissue of rats (R. E. Catalán et al., 1985).

15.7 Ecdysteroids and Cardiovascular Function

Ecdysteroids can prevent an ischemic heart disease and arrhythmia by through the expression enhancement mechanism of vascular endothelial growth factor (VEGF) which controls the proliferation and migration of endothelial cells in the mamal vascular wall (L. Dinan & Lafont, 2006). Several studies have shown the effect of Ecdysteroids on the anti-ischemic therapy (Maĭmeskulova & Maslov, 2000). Previous study took Ecdysteroids to rabbits with atherosclerosis (induced by took the high cholesterol diet). The result of this study found an increased the activity of the enzyme Na^+/K^+ ATPase in the myocardium (Lafont & Dinan, 2003).

15.8 Ecdysteroids and Musculoskeletal Function

Ecdysteroids are in naturally foods are relatively low such as a large amounts of spinach or quinoa seeds that would provide only <1 mg of Ecdysteroids which is insufficient to used in human body. The recommended dosage for athletes to build muscle is 100-1000 mg per day (Lafont & Dinan, 2003). Previous study

compared the enhancing effect of Ecdysteroids with metandrostenolon (a powerful anabolic steroid is commonly used by bodybuilders) in animal. The result shows an increased muscle mass and muscle strength (Lafont & Dinan, 2003). Gorelick-Feldman and colleagues investigated the effects of phytoecdysteroids on skeletal cells in mammalian tissues using an in vitro cellular assay to measure protein synthesis. The results showed that phytoecdysteroids increased protein synthesis by up to 20%. In vivo studies further demonstrated that ecdysteroids enhanced grip strength in rats. Additionally, plant extracts containing ecdysteroids elicited comparable effects (Gorelick-Feldman et al., 2008) Isenmann and colleagues investigated the effects of ecdysterone-containing supplements on exercise performance in humans. In a 10-week strength training intervention involving 46 young men, varying doses of ecdysterone supplements were administered to evaluate their performance-enhancing potential. The results demonstrated a significantly greater increase in muscle mass among participants receiving ecdysterone. Corresponding hypertrophic effects were also observed in vitro in C_2C_{12} myotubes. Importantly, participants supplemented with ecdysterone showed significantly greater improvements in one-repetition maximum bench press performance. No adverse changes were detected in biomarkers of liver or kidney toxicity. These findings support the efficacy and safety of ecdysterone supplementation for enhancing sports performance (Isenmann et al., 2019). Parr and colleagues compared the anabolic effects of ecdysterone to well-characterized anabolic agents. The hypertrophic effects were assessed by measuring fiber size in the rat soleus muscle and the diameter of C2C12-derived myotubes. Ecdysterone demonstrated a pronounced hypertrophic effect on soleus muscle fiber size, which was notably greater than that observed with metandienone (Dianabol), estradienedione (Trenbolox), and the selective androgen receptor modulator (SARM) S1, all administered at an equivalent dose of 5 mg/kg body weight for 21 days (Parr et al., 2015a).

On the other hand, ecdysteroids had been or being presently investigated in clinical trials in order to assess their potential use as a medicine for treating parasitoses or several diseases (Dinan, Dioh, Veillet, & Lafont, 2021). They are also

currently being assessed in a clinical trial on SARS-CoV-2 patients with regard to their lung-protective activity (Dioh et al., 2021).

CHAPTER 3
RESEARCH METHODS

1. Study design

The study was a randomize control trail (RCT). The study was a prospective, experimental study. Participants were randomized and allocated into high intensity interval training group (HIIT), Asparagus stem extract supplement group (ASP), HIIT combined with asparagus stem supplementation (COM) group, or control group (CON). This study was designed following the SPIRIT guideline which used the CONSORT statement (Figure 20) for clinical trials (Hopewell et al., 2022).

The present study received ethical approval from the Burapha University Institutional Review Board (BUU-IRB), approval ID: G-HS018/2565(C1), and was registered with the Thai Clinical Trials Registry (TCTR), registration ID: TCTR20220518001. All participants met the eligibility criteria and provided written informed consent prior to participation.

2. Study site

This study had been conducted at the Exercise and Nutrition Innovation and Sciences Research Unit (ENIS RU) Laboratory in Faculty of Allied Health Sciences, Burapha University, Chonburi province, Thailand. Participant had conducted the 12-week interventions outside of the laboratory setting.

3. Participants

Volunteers with overweight or obesity and live in Mueang district, Chonburi province were recruited in this study.

3.1 Inclusion criteria

1) Male or female, age range 18 to 30 years
2) Body mass index > 22.9 kg/m^2 (World Health Organization. Regional Office for the Western, 2000)

3.2 Exclusion criteria

1) Daily supplementation with drugs or supplementations

2) Having food allergy, especially shoots or bulbs, i.e., asparagus, bamboo shoots, green onions, onions, leeks, garlic bulbs, and chives.
3) Having drug allergy.
4) Having lithium drug i.e. lithium carbonate.
5) Pregnancy or bleed feeding
6) Regular smoking (> 30 packs-years)
7) Regular alcohol drinking (>1 cup/day)
8) Having drugs or diseases of cardiovascular, liver, renal, musculoskeletal, infectious, cancer, neurological, or psychiatric disease

3.3 Withdrawal criteria

1) Having adverse symptoms during the tests i.e., nausea, vomiting, fainting
2) Having study-related serious adverse effects during study i.e., admission from any symptoms as a result of exercise or supplement
3) Intention to withdraw from the study

4. Sample size

The study would compare the means among four groups consisting of CON group, HIIT group, ASP group and COM group. Sample size for each group was calculated using a sample size formula for a comparison of more than two groups as follows (Julious, 2004):

$$n = \frac{2(Z_{\alpha/2c} + Z_{\beta})^2 \sigma^2}{\Delta^2}$$

where: n = Sample size, α = α error and β = β error, σ = Estimated standard deviation (SD), Δ = Effect size, c = Number of pairs

The sample size was calculated by means of tumor necrosis factor-alpha (TNF-α) according to the study of Soltani et al. which investigated the effect of 10-week combined all-extremity HIIT on immune function in obese young females (Soltani, Marandi, Kazemi, & Esmaeil, 2020). Mean difference in TNF-α between experimental group and control group was 16.87 and standard deviation was 13.87 (Gogtay, 2010). With α error = 0.05 and power of the test = 0.80. Sample size was obtained as follows:

$$n = \frac{2(Z_{0.05/2(4)} + Z_{0.80})^2 (13.87)^2}{(16.87)^2}$$

$$= \frac{2(2.58 + 0.84)^2 (13.87)^2}{(16.87)^2}$$

$$= 15.80$$

Number of the sample with 10% drop out was 18 per group. Therefore, seventy-two participants with overweight or obesity were required.

5. Recruitment of participants

Participants were recruited form Mueang district, Chonburi province, Thailand. Study leaflets were placed on online social media platform such as FACEBOOK and LINE application, on boards throughout the university and through direct invitation by researcher. The study information included the research title, qualifications of volunteers, a short brief of study process, and contact channels via the researcher's telephone number and LINE application. The time frame for recruitment of volunteers were started on June 2022 until March 2023. Eligible volunteers who enroll in the study were randomized and allocated using a computer program.

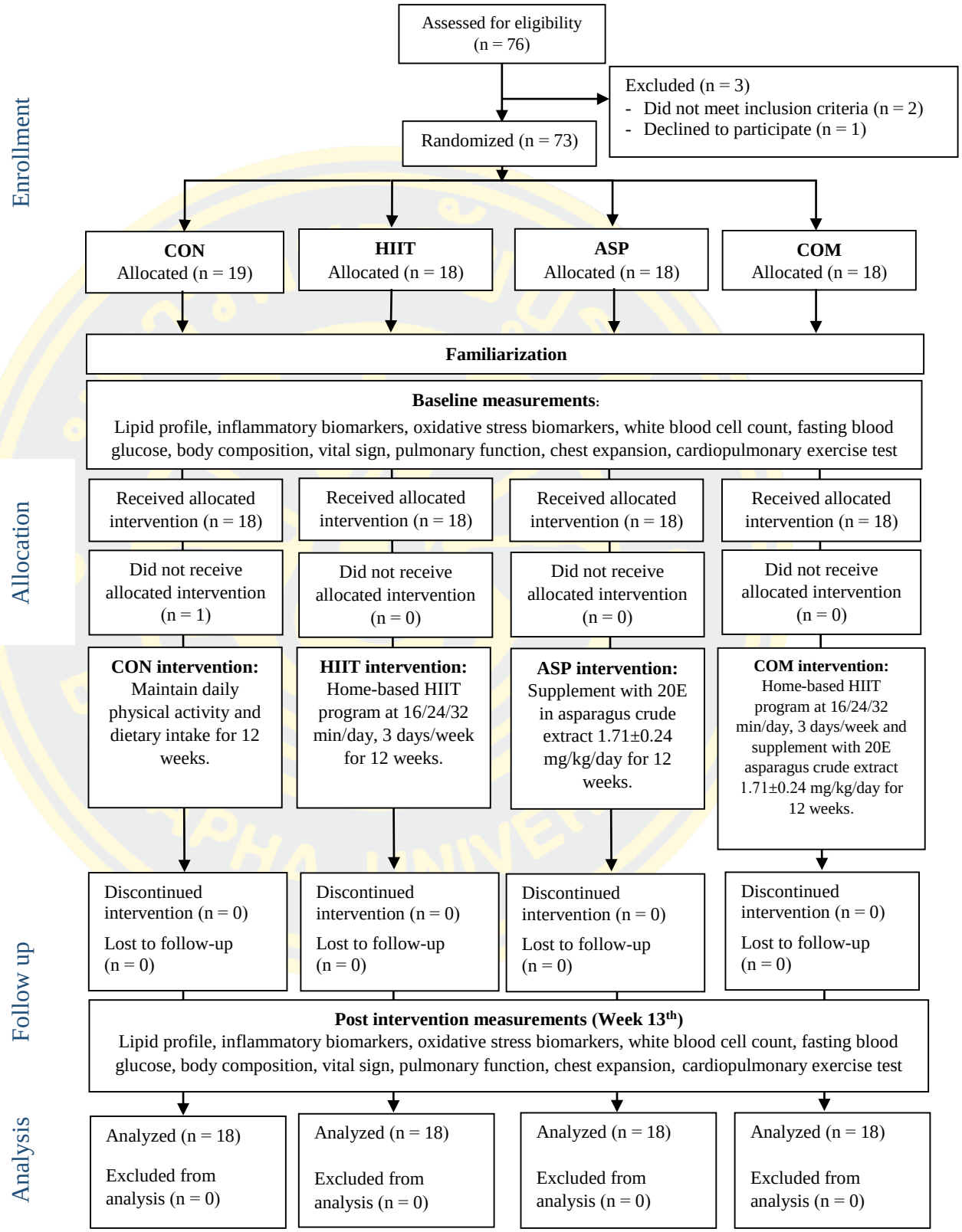


Figure 20 CONSORT flow diagram

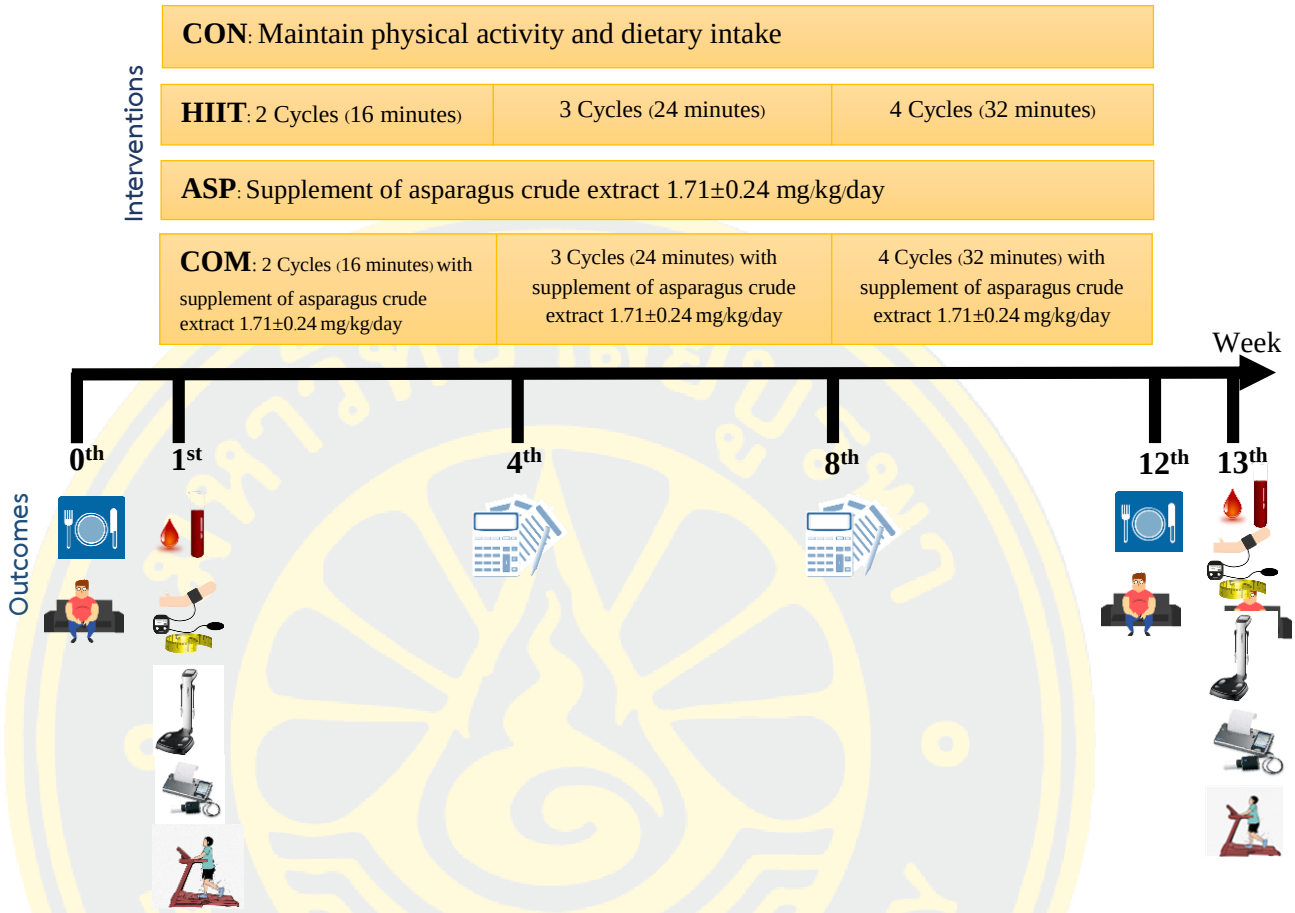


Figure 21 Timeline of outcomes measurement

6. Study procedure

6.1 Study visits

Volunteers who interest to participate to the study contacted researcher via telephon, LINE application, or face to face. They were given objectives, procedures of the study and asked to signed a consent form. They also were scheduled a convenient date and time to be given screening tests. On the screening day, participants were measured body composition and asked to answer the Beacke Habitual Physical Activity questioneire (Thai version) .

Eligible participants came to the labolatory for 3 visits to participate familialization test, baseline measurements and follow up measurements at 12 weeks (Figure 21). At the first visit, at least 7 days after the the screening test, they were tested for familiarization with the virtual procedures. Before the visit 2 , participants were asked to refrain alcohol and smoking at least 24 hours, and any food or drink for

at least 8 hours (8-hour fasting). Participants also were asked to sleep at least 6 hours or as usual and to refrain from performing strenuous exercise for 72 hours. During experimental period, participants in each group had been performed their given intervention or program for 12 weeks.

6.2 Randomization

All eligibility volunteers were stratified blocked randomized into CON group, HIIT group, ASP group, or COM group using Microsoft Excel. Seventy-two numbers of participants were randomized into 1, 2, 3, or 4 regarding sequence of participation, sex (male or female), BMI (overweight, obesity), and physical activity level (active/athletes or sedentary). The randomization process had been conducted by researcher.

6.3 Blinding

This study was non-blinded. Same researcher had been randomized and allocated eligible participants and collected and analyzed data before and after experiments. However, medical technicians who collect blood sample and analyze blood parameters (lipid profile, white blood cell counts, inflammatory biomarkers and oxidative stress biomarkers) were blinded to the participant groups.

6.4 Experiments

Participants in each group were asked to perform as follows:

1) Participants in the CON group were asked to maintain their daily physical activity and dietary intake.

2) Participants in the HIIT group were instructed to perform a home-based exercise program for 16, 24, or 32 minutes per day, three days per week, over a 12-week period.

3) Participants in the ASP group were asked to supplement with asparagus stem crude extract capsule at 1.71±0.24 mg/kg/day daily after meal (1 or 2 capsule for breakfast and 2 capsules for dinner) for 12 weeks, too (L. Dinan et al., 2021).

4) Participants in the COM group were asked to perform home-based exercise program at 16/24/32 min/day, 3 days/week and supplement with asparagus stem crude extract capsule at 1.71±0.24 mg/kg/day daily after meal (1 or 2

capsule for breakfast and 2 capsules for dinner) for 12 weeks, too (L. Dinan et al., 2021).

Outcome including lipid and sugar levels, white blood cell count, inflammatory and oxidative stress biomarkers, and cardiopulmonary fitness were measured at baseline and at the end of the 12th week. Besides that, habitual physical activity was followed using Beacke Habitual Physical Activity Questionnaire (Thai version) (Baecke, Burema, & Frijters, 1982; Jalayondeja et al., 2015). Moreover, compliance with and adherence to the program or intervention had been followed every week via Microsoft Team ™.

7. Asparagus stem crude extract capsule

The root of asparagus was extracted and used as supplement in present study. Normally, asparagus's root contains sclerenchyma, lignin, and thicken vascular cell walls which is not appropriated for consumption. Thus, it was extracted for yielding the 20E. Participants supplemented the 20E in form of capsule. Each capsule contains 500 mg of dried asparagus stem tissue which consisting of 32.2 mg of 20E active ingredients (Wilborn et al., 2006).

Figure 22 The dried asparagus's root.

Figure 23 Asparagus's root tissue powder.

The root of asparagus was crudely extracted by crushing 300 g of dried asparagus's root tissue and brought it in a beaker. Then, add 95% ethanol (v/v) volume for about 1.5 liters and soaked for 3 days. Consequently, there were separated to the residue and solution. The solution was refrigerated at 4 °C. While the residue was re-extracted by adding 95% ethanol (v/v) volume for 1.5 liters and soaked for 3 days. Then, the solution was re-mixed with the residue and brought them into an

evaporator. A dried weight was obtained after the evaporation. The root extract was prepared at 20,000 µg/L concentration by mixing HPLC-grade methanol at a ratio of 1 ml per 1 g of extraction, and was filtered through a nylon membrane filter with a pore size of 0.4 µm. The HPLC was used to measure the amount of substance 20-hydroxyecdysone which was obtained in each preparation set. The HPLC technique used in this study was modified from the extraction method of Snogen et al. (2007) using ethanol solution. The 20-hydroxyecdysone samples were analyzed by the HPLC at a volume of 20 µL with a column flow rate of 1 mL/min and a column temperature of 40 °C. Finally, the UV-Vis detector was used to detect the 20-hydroxyecdysone samples and compare with the standard substance of 20-hydroxyecdysone chromatogram. This process had been repeated for 3 times. Standard quality and safety was checked by the Innovation and Health Industry Support Division Department of Medical Sciences for determimimg microbial contamination. The GC-MS technique of Central Laboratory (Thailand) Co., Ltd. Investigated and guaranteed other substances in the asparagus stem tissue.

To prepare asparagus capsules, the dried asparagus roots were filled into capsule which each capsule containing 500 mg in sterile condition. These asparagus capsules were then stored at a temperature -20 degree Celsius. Each capsule contained 32.2 mg of the compound 20E per gram of dry weight (Barakat Denben, Siriporn Sripinyowanich, Ratree Ruangthai, & Jatuporn Phoemsapthawee, 2023).

8. HIIT program

HIIT was designed as home-based program. Participants had been performed the exercise for 3 days/weeks for 12 weeks. In the first 4 weeks, participants exercised for 16 minutes (2 cycles). The exercise time was increased to 24 minutes (3 cycles) in the 5 to 8 weeks. Furthermore, the exercise time also was increased to 32 minutes (4 cycles) in the 9 to 12 weeks. Each 4-minute cycle, participants exercised for 20 seconds alternating by 10 seconds completely rest (Tabata protocol). Between each cycle a 4-minute active rest was inserted. During this, participants were asked to maintain movement by swinging arm at 40-50% maximum rating of perceived exertion (Salome et al.). The exercise included squat jumps with toes touch, alternated reverse lunges, mountain climbers, and burpees with

toes touch. High intensity was determined from submaximal exercise test which target at 80-90% maximum RPE. Before and after exercise session, participants were asked to warm up and cool down for 5 and 5 minutes, respectively. (Figure 25). Participants were given exercise diagram sheet to learn how to exercise. They were followed compliance with and adherence to the HIIT program every week via telephone, LINE application, or video call.

The HIIT program in this study was found to be safe and suitable for individuals who are overweight or obese, as evidenced by a pilot study. The pilot study was carried out in 2 obese volunteers, one male and one female, with body mass index 35.35 and 27.01 kg/m^2, respectively. The volunteers undertook exercise protocol include; 10-minute warm up, 4-minute Tabata protocol (cycle 1), 4-minute active recovery by arm swing exercise, 4-minute Tabata protocol (cycle 2), 4-minute active recovery by arm swing exercise, and 5-minute cool down phase. Feasibility was evaluated by change in heart rate measured during exercise and by 10-scale of satisfaction of exercise program. An electrocardiogram (ECG) and a rating of perceived exertion had been recorded for safety. Results of this pilot study was found that our exercise protocol can increase heart rate to 78.58±2.49% (95%CI 76.28 - 80.89) % of maximum heart rate (Figure 24) that was in a range of vigorous intensity exercise (77-95% maximum heart rate) according to ACSM guideline. Satisfaction levels of both volunteers were 8/10. There was no adverse event during study and nor found abnormal ECG significant changed during exercise and recovery periods.

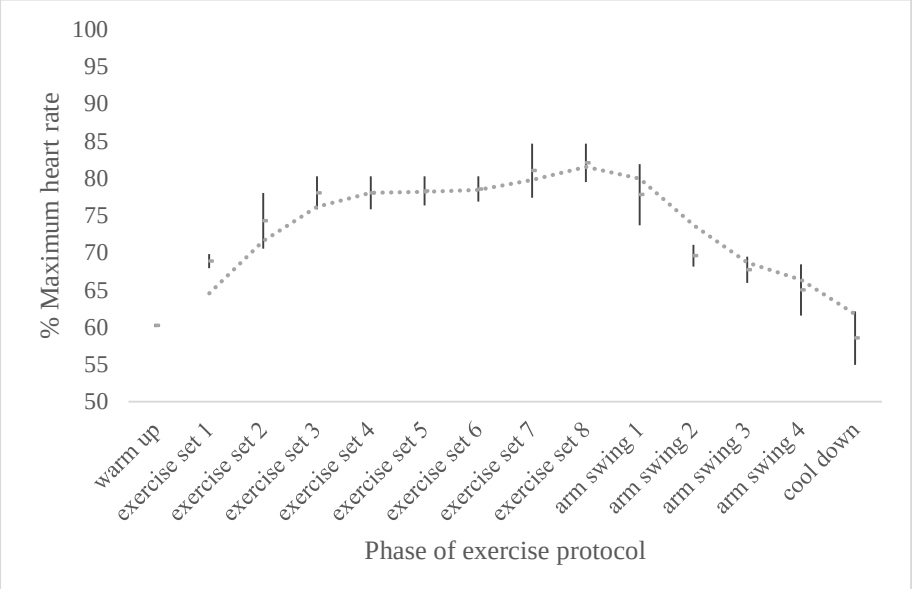


Figure 24 Mean changed of percent maximum heart rate of two obesity during exercise followed the HIIT protocol in pilot study.

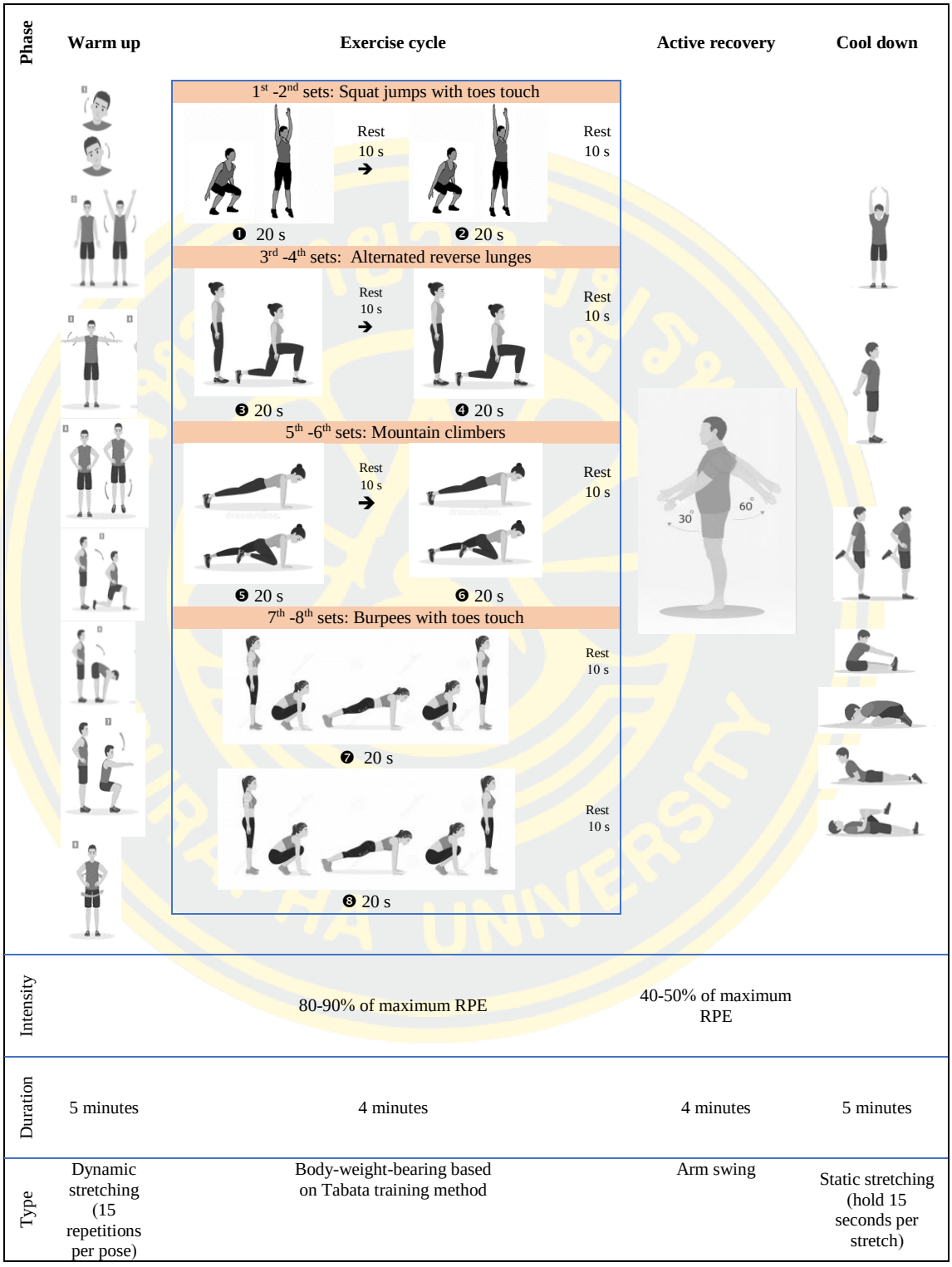


Figure 25 Home-based HIIT protocol, duration, intensity and type of exercise.

9. Control group

Participants in the control group were asked to maintain their daily physical activity and dietary intake. However, at the end of the 12-week study period, the participants were taught HIIT including intensities and frequencies to perform at their leisure time and were given our supplementation depending on their intention.

10. Telemonitoring

Telemonitoring by Microsoft Team ™ application was used to follow HIIT program participation and 20E supplementation entire the 12 weeks. This had been performed by an experienced physiotherapist who checked for accuracy and provide feedback and support. For any situations that might occur during study period participants could contact the researcher and information had been recorded.

11. Outcome measurement

The primary outcomes of the study were changed in white blood count, inflammation, and oxidative stress before and after 12-week HIIT, Asparagus supplement, and combined interventions. The secondary outcomes were changes in blood lipid and sugar levels, pulmonary and physical capacities, and body composition. Both primary and secondary outcomes were measured before and after the interventions. Table 8 summaries the outcomes measurements to be made and the time points at which they had been investigated during the study.

Table 8 Parameters and timepoints measures of each measurement.

Parameters	Timepoints measures
Primary outcome	
Immunology: White blood cell count Inflammatory biomarkers: TNF-alpha, IL-6 Oxidative stress biomarkers: Malondialdehyde, Protein carbonyl	Baseline, post-intervention
Secondary outcomes	
Lipid profile: triglyceride, LDL, HDL, total cholesterol	Baseline, post-intervention
Fasting blood glucose	Baseline, post-intervention
Liver functions: ALT, AST (only in 20E and HIIT+20E groups)	Baseline, post-intervention
Pulmonary function: FEV_1/FVC, FEV_1%, TV, ERV, IRV, IC, MIP, MEP, Chest expansions (upper chest, middle chest, lower chest)	Baseline, post-intervention
Physical fitness: VO_2peak	Baseline, post-intervention
Vital sign: HR, BP, RR, SpO_2	Baseline, post-intervention
Physical activity level and dietary intake	Baseline, post-intervention
Body composition and VIA	Baseline, post-intervention

12. Data collection

12.1 Blood sampling and analysis

Intravenous blood sample for about 10 ml were collected for analyzing immune function (complete white blood cells count), inflammation (IL-6, TNF-alpha), oxidative stress (malondialdehyde, protein carbonyl), lipid profile (triglyceride, LDL, HDL, and total cholesterol), fasting blood glucose. For detect any toxicity of asparagus root supplementation, liver function (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)) also analyzed only in ASP and COM groups.

Blood samples were collected in the morning during both pretest and posttest periods (for posttest, following a 72-hour break from the 12-week interventions) from the median cubital vein into vacuum blood collection tubes, including two ethylenediaminetetraacetic acid (EDTA) tubes, two lithium heparin tubes and a glucose tube (MediPlus, Taipei, Taiwan) by an experienced medical thecnitian team.

One lithium hepaine tube, EDTA tube and glucose tube were sent to the N-health medical laboratory, an international standard lab, within 2 hours for

analysis the complete white blood cells count, lipid profile (triglyceride, LDL, HDL, and total cholesterol), AST, ALT and fasting blood glucose.

The collected blood form another EDTA tube and a lithium heparine tube were centrifugedimmeditedly after collection at 3,500 revolutions per minute for 5 minutes, and the plasma and serum were then collected and stored at -20 ˚C until further study.

The concentrations of IL-6 and TNF-α in serum were measured using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the manufacturer's protocol. The human IL-6 ELISA kits (3460-1HP-2 ELISA Pro: Human IL-6, Mebtech, Sweden) and the human TNF-α kits (3512-1HP-2 ELISA Pro: Human TNF-alpha, Mebtech, Sweden) were purchased from Biomed Diagnostics (Bangkok, Thailand). A microplate spectrophotometric reader (SpectraMax ABS, Moledular Device LLC, USA) was used to determine the optical density at 450 nm. The measuremnets were performed by experienced medical technicians at Department of Medical Technology, Faculty of Allied Health Sciences, Burpha University, Thailand. The standard curves of IL-6 assay and TNF-α assay had R-squared values of 0.9998 and 0.9999, recpectively.

Plasma samples in EDTA-treated tubes were analyzed for malondialdehyde. This study employed thiobarbituric acid (TBA) as a fluorescence-generating agent to derivatize MDA, followed by analysis of the resulting MDA-TBA adduct using a previously established HPLC-fluorescence technique (Nielsen, Mikkelsen, Nielsen, Andersen, & Grandjean, 1997). Our study utilized HPLC separation, which effectively minimized interference from TBA-reactive substances (TBARS), leading to enhanced specificity and accuracy in MDA analysis (Moselhy, Reid, Yousef, & Boyle, 2013). The process of MDA analysis was as follows.

The 150 μL plasma samples were mixed with 10% trichloroacetic acid, 5 mM EDTA, 8% sodium dodecyl sulfate and 500 ppm of butylated hydroxytoluene. This mixture was then incubated for 10 minutes at room temperature, followed by the addition of 535 μL of 0.6% thiobarbituric acid and further incubation. Afterward, the mixture was boiled in a water bath for 30 minutes. Upon cooling to room temperature, it was centrifuged at 10,000 rpm for 5 minutes. The absorbance of the supernatant was measured at 532 nm using a spectrophotometer. A standard curve was generated using

appropriate concentrations of 1,1,3,3-tetraethoxypropane, ranging from 0.33 to 9.89 μM. The standard curves of MDA assay had R-squared values of 0.99675.

Protein carbonyl (PC) measurement used a convenient colorimetric assay for the measurement of oxidized proteins. Protein samples were derivatized by making use of the reaction between 2,4-dinitrophenylhydrazine (DNPH) and protein carbonyls followed protocols of Levine (Levine et al., 1990). The process of PC analysis was as follows.

Diluted plasma (400 μL) was transferred to two microtubes, one serving as the sample tube and the other as the control tube. To the sample tube, 500 μL of 15 mM DNPH in 3.6 M HCl was added, while the control tube received 500 μL of 3.6 M HCl. Both tubes were then incubated in the dark at room temperature for 1 hour, with each tube being vortexed brieftly every 15 minutes during the incubation. Afterward, 600 μL of 25% trichloroacetic acid was added to both tubes, which were then vortexed. The tubes were placed on ice and incubated for 15 minutes. Following this, both tubes were centricuged at 10,00 rpm for 5 minutes at 4 ˚C. The supernatant was discarded, and the pellet was resuspended in 600 μL of 10% trichloroacetic acid. After another round of votexing and placed on ice for 15 minutes, the tubes were centricuged again at 10,00 rpm for 5 minutes at 4 ˚C. The supernatant was discarded and the pellet was washed in 600 μL of mixure containing (1:1) ehylacetate/ethanol. After vortexing and standing on ice for 15 minutes, the tubes were centrifuged at 10,000 rpm, and the supernatant was discarded. This washing process was repeated twice. Subsequently, the pellet was dried at 60 °C for 30 minutes, and the protein pellet was resuspended in 400 μL of 6 M guanidine hydrochloride by vortexing. The tubes were then incubated in a water bath at 37 °C, with vortexing every 15 minutes, and centrifuged at 2,500 rpm at room temperature for 10 minutes. Afterward, 200 μL of supernatant from both tubes was transferred to wells of a 96-well plate, and the absorbance was measured at 360 nm using a spectrophotometer. For the protein concentration measurement, a mixture of 10 μL of diluted supernatant with 4990 μL of deionized water was prepared, and 50 μL of this mixture was then reacted with 200 μL of Bradford solution. After incubating at room temperature for 15 minutes, 200 μL of supernatant from both tubes was transferred to wells of a 96-well plate, and the absorbance was measured at 620 nm using a spectrophotometer, with bovine serum

albumin used as a standard (ranging from 0.05 to 1 mg/mL) and Bradford solution as the blank. The protein carbonyl content (unit: nmol/mg protein) was calculated using the equation: OD at 360 * 80.16 / Conc. Protein (mg/ml).

12.2 Pulmonary functions

12.2.1 Static lung volumes (TV, TC, ERV, IRV) and dynamic lung capacity (FEV_1, FVC, FEV_1/FVC) were measured by a portable, automated spirometer (MicroLab, Micro Medical®, USA). Participants were asked to take a maximum inspiration and slowly and completely exhale (slow vital capacity) and to take a maximum inspiration and fast and completely exhale (forced vital capacity). The measurement procedures adhered to the standard guidelines outlined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (Graham et al., 2019).

12.2.2 Inspiratory and expiratory muscles strength were determined by maximum inspiratory mouth pressure (MIP) and maximum expiratory mouth pressure (MEP), respectively, by a portable, respiratory pressure meter (MicroRPM, CareFusion, USA). Participants were asked to take a maximum inspiration and fast and completely exhale for MEP and to take a maximum expiration and completely inhale for MIP. The procedure of measurement followed the standard guideline of the ATS/ERS Statement ("ATS/ERS Statement on respiratory muscle testing," 2002).

12.2.3 Chest expansions were circumferentially measured by a standard centimeter tape at three levels that are the 3rd intercostal space, the 5th intercostal space and the tip of zyphoid process (Debouche, Pitance, Robert, Liistro, & Reychler, 2016; Preeyaphorn Songsorn, 2014). The difference between deep expiration and deep inspiration had been measured for two times. Three trails were given at each level and average of three readings were noted. Participants in sitting position with elbows slightly flexed so that the hands rested on their hips. Intratester reliability of upper-, middle-, and lower-chest expansion measurements were evaluated with five obese participants with average age 22.40 ± 1.34 years and BMI 31.46 ± 2.89 kg/m^2. Participants in sitting position with elbows slightly flexed so that the hands rested on their hips. The difference between deep expiration and deep inspiration had been measured and the two trails were given at each level and average of two readings were noted. Each participant had been performed the measurements

for 3 days. The intraclass correlation coefficient (ICC) show good intratester reliabilities of upper and lower chest expansions (ICC = 0.88 and 0.83, respectively) and moderate intratester reliability for middle chest expansion (ICC = 0.72) (Koo & Li, 2016).

12.3 Cardiorespiratory fitness

A progressive incremental exercise test to volitional fatigue on a motorized treadmill were performed to determine peak oxygen consumption (VO_2peak). Participant were instructed to perform a 5 minutes warm up at 0% gradient. A Bruce treadmill protocol be used (Medicine et al., 2018). This protocol was divided into successive 3-minute stages, with each stage increasing both speed and gradient to enhance work output. For example, stage 1 was performed at 1.7 miles per hour and a 10% gradient, while stage 2 at 2.5 mph and 12% gradient. Heart rate were measured throughout the test using chest-belt heart rate monitor. RPE also had been asked every 2 minutes during the test using the 6–20 Borg scale. The test was terminated upon the participant reaching volitional fatigue and/or the occurrence of any test termination criteria, as specified by the ACSM guidelines for VO_2peak testing;

I) Reached > 90% of maximum heart rate, *or*

II) Reached a modified Borg scale 17 out of 20 *or*

III) Reached a visual analog scale of fatiques 7 out of 10, *or*

IV) Reached respiratory exchange ratio > 1.15, or

V) Found ST elevation (> 1 mm) in leads without preexisting Q waves, *or*

VI) Sustained ventricular tachycardia or another arrhythmia, including second- or third-degree AV block, *or*

VII) Signs of poor perfusion: light-headedness, confusion, ataxia, pale, cyanosis, nausea or cold and clammy skin.

From the test, HR and RPE at 50% and 80% HRmax were calculated to determine the intensities of program.

12.4 Body composition

Body composition (body mass, BMI, muscle mass, %body fat, fat mass, water mass, protein, mineral and visceral fat level) was measured by a

bioelectrical impedance analyzer (In Body 270, Body Composition Analyzer, Korea). The visceral adiposity index (VIA) was calculated form formulation as below.

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88 \times BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89 \times BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

12.5 Vital sign

HR, blood pressure (BP), respiratory rate (RR), and partial oxygen saturation (SpO_2) were measured in the supine position by a bed side monitor (Vismo PVM-2701, NIHON KOHDEN Corporation, Japan). Mean of three measurements were taken and rest 1 minute apart.

12.6 Physical activity level

To ensure that the results of this study will be less affected by other concurring factors including changes in daily physical activities participants would be instructed not to change their routine physical activities and dietary intake throughout the study period. The Beacke Habitual Physical Activity Questionnaire (Thai version) (Baecke et al., 1982; Jalayondeja et al., 2015) were used to determine participants' activity levels (sedentary or active physical activity).

12.7 Feasibility

Completion, dropout rates, heart rate changeing and RPE for detect their intensity during each intervention, enjoyed and compliance with and adherence to the program and supplementation (i.e., numbers of HIIT session and numbers of asparagus capsule supplementation that particiapants in each group complete over the 12-week study period, numbers of participant who report not to achieve the desired exertion level during HIIT) had been recorded.

15. Statistical Analysis

Data were analyzed using a SPSS software program (version 23, IBM Brop., USA) and expressed as mean and standard deviation (SD) or range. Data were tested for normal distribution by using Kolmogorov–Smirnov test, and relevant parametric or non-parametric tests were then applied. The difference between group were

analyzed by one-way analysis of variance (ANOVA) and followed by Bonferroni post hoc test. Data for IL-6, TNF-α, MDA, lipid profiles, glucose level, liver enzymes, body compositions, vital sign and pulmonary function test were not normal distribution. In case of non-normal distribution, they were therefore log-transformed then were analyzed by one-way analysis of variance (ANOVA) and followed by Bonferroni post hoc test. The difference within each group between pretest and posttest were analyzed by the pair *t* test. A statistical significance was considerate at *p* value less than 0.05.

CHAPTER 4
RESULTS

1. Participant Characteristic

Seventy-six participants with overweight and obesity voluntarily participated; only seventy-three participants met the criteria and enrolled the study. Among them, only seventy-two participants were finally participated in the study. The one participant of control group declined because of an inability blood drawing. The flow chart of study enrollment is shown in Figure 20. The seventy-two (fifty-eight males, 80.60%) subjects with overweight (n=17, 76.4%) and obesity (n=55, 23.6%), body mass index 28.19±4.67 kg/m^2 (range 23.10 - 44.90 kg/m^2), age 20.65±1.91 years-old (range 18-27 years) and physical activity score 7.09±1.03 (range 5.0-9.65). They had, on average, active of physical activity level. The characteristics of participants in each group are given in Table 9. There were no statistical differences in their characteristics between the groups. Additionally, there was no significant change in the physical activity score at the posttest compared to the pretest.

Table 9 Characteristics of participants

	Control group	HIIT group	Asparagus group	Combined group
Number	18	18	18	18
Sex (n, male : female)	5:13	5:13	2:16	2:16
Age (years)	21.61±2.06	20.72±1.32	20.22±1.93	20.06±2.01
BMI (kg/m^2)	28.69±5.08	29.99±4.49	27.24±2.97	27.84±4.92
WHO BMI classification (n, overweight : obese)	2:16	5:13	5:13	5:13
Physical activity score				
- **Pretest**	7.01±1.07	7.04±0.99	7.46±1.19	6.86±0.85
- **Posttest**	6.96±0.79	7.31±1.22	7.27±0.99	7.37±1.20
Physical activity level				
- **Sedentary (n, %)**	3 (17%)	3 (17%)	3 (17%)	1 (6%)
- **Active (n, %)**	11 (61%)	12 (66%)	9 (50%)	14 (78%)
- **Athletic (n, %)**	4 (22%)	3 (17%)	6 (33%)	3 (17%)

Data are presented as number, percentage, ratio and mean±SD. BMI: body mass index; WHO: World Health Organization; HIIT: High-intensity Interval Training.

2. Effects of HIIT and Asparagus Root Supplement on Immune Response

One of the primary outcomes of the study was immune system. During the pretest period, there were no differences between the groups in the number and

percentage of white blood cell counts. After 12-week interventions in the posttest period, the eosinophil number was decreased by 132.11±50.39 /mm^3 in COM group (p<0.05) compared to the ASP group. The HIIT group also experienced a 1.61±0.63% decrease in eosinophil percentage (p<0.05) when compared to the ASP group. There were no differences in the counts of other types of white blood cells between groups (Table 10).

3. Effects of HIIT and Asparagus Root Supplement on Inflammatory Cytokines

In the pretest phase, it was observed that the two cytokines that stimulate the inflammatory process, TNF-α and IL-6, exhibited no significant differences between the groups. After 12-week interventions, participants in COM group were alleviated the IL-6 concentration by -1.75±7.36 pg/ml (p<0.05) compared to CON group, but no significant difference was found in the HIIT and ASP groups (Figure 26). However, TNF-α concentration showed a non-significant improvement in all groups (Table 11).

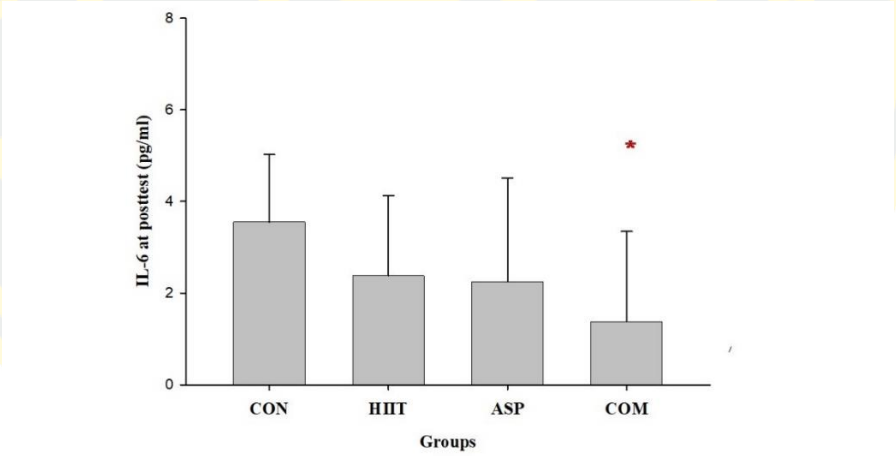


Figure 26 IL-6 concentration after 12-week interventions
of CON group, HIIT group, ASP group and COM group. *: p<0.05 vs. CON group.

4. Effects of HIIT and Asparagus Root Supplement on Oxidative Stress

The baseline levels of MDA and PC were higher in the three intervention groups compared to the control group. Consequently, it was imperative to address changed (posttest value minus pretest value) in these two oxidative biomarkers.

After the 12-week intervention, MDA levels increased by approximately 2.71±1.21 μM (p<0.05) in the ASP group when compared to the CON group.

Meanwhile, HIIT group and COM group showed no significant differences when compared to the CON group. When comparing the pretest and posttest values within each group, MDA levels increased in both the ASP group (by 3.30±1.82 µM, $p<0.05$) and the COM group (by 2.06±2.14 µM, $p<0.05$).

PC levels demonstrated a reduction of approximately 0.32±0.47 nM/mg protein in the COM group compared to the other three groups ($p<0.05$). Meanwhile, HIIT and ASP groups exhibited no significant change to CON group (see Figure 27 and Table 11). When comparing the pretest and posttest values (within-group analysis), PC levels decreased in the HIIT, ASP and COM groups (-0.10±0.17 nM/mg protein, -0.07±0.13 nM/mg protein and -0.32±0.47 nM/mg protein, $p<0.05$, respectively)

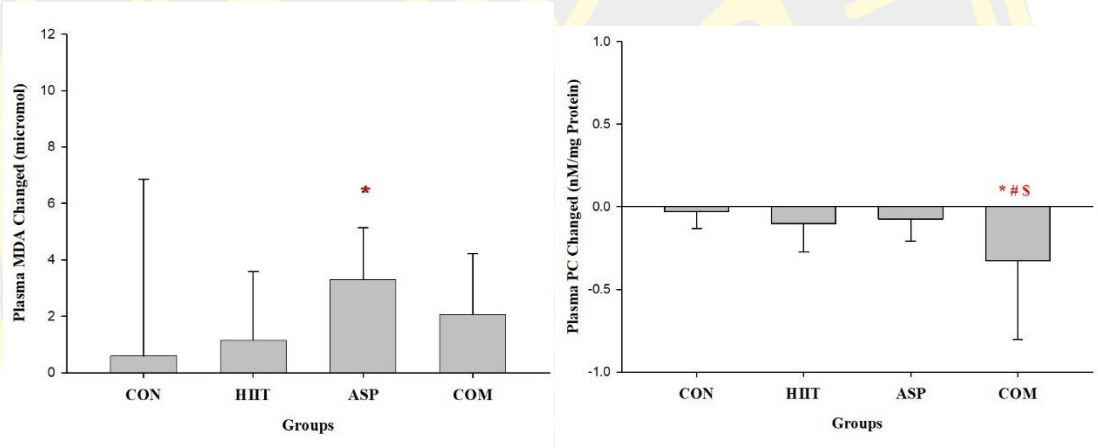


Figure 27 Plasma MDA and PC changed after 12-week interventions.

*: $p<0.05$ vs CON group; $^{\#}$: $p<0.05$ vs HIIT group; $^{\$}$: $p<0.05$ vs ASP group.

5. Effects of HIIT and Asparagus Root Supplement on Liver Function, Lipid Profile and Sugar Level

The two liver enzymes, AST and ALT, were not significantly changed between pretest and posttest periods in both Asparagus and Combined groups, indicating that asparagus root supplement consumption was safe for overweight and obese people. At the pretest period, lipid profile, including cholesterol, triglyceride, HDL, LDL, cholesterol/HDL ratio and LDL/HDL ratio, as well as fasting blood glucose, were similar at baseline in all groups.

After the 12-week interventions, significant improvements in the lipid profile of the participants were observed. The HIIT group experienced a noticeable decrease in cholesterol (13.89±16.16 mg/dL) and an increase in HDL (about 4.56±3.47 mg/dL) (p<0.05) after completing the training program, as compared to the CON group. Additionally, the ratio of cholesterol/HDL was significantly lower in both the HIIT and the COM group (0.64±0.45 and 0.44±0.91, respectively) (p<0.05) compared to the CON group. Similarly, the ratio of LDL/HDL was significantly lower in both the HIIT and the COM group (0.23±0.45 and 0.12±0.30, respectively) (p<0.05) compared to the CON group (Figure 28 and Table 12). The ASP group exhibited an increase in cholesterol (6.67±19.47 mg/dL, p<0.05), cholesterol/HDL (0.22±0.61, p<0.05), LDL/HDL (0.33±0.57, p<0.05), and a decreased in HDL (-1.72±7.92 mg/dL, p<0.05) when compared to the HIIT group.

Fasting blood glucose was reduced in both the HIIT and COM groups after the 12-week interventions by 4.39±6.70 mg/dL (p<0.05) and 4.39±6.99 mg/dL (p<0.05), respectively, when compared to the pre-training period. However, these changes were not significantly different from the CON group

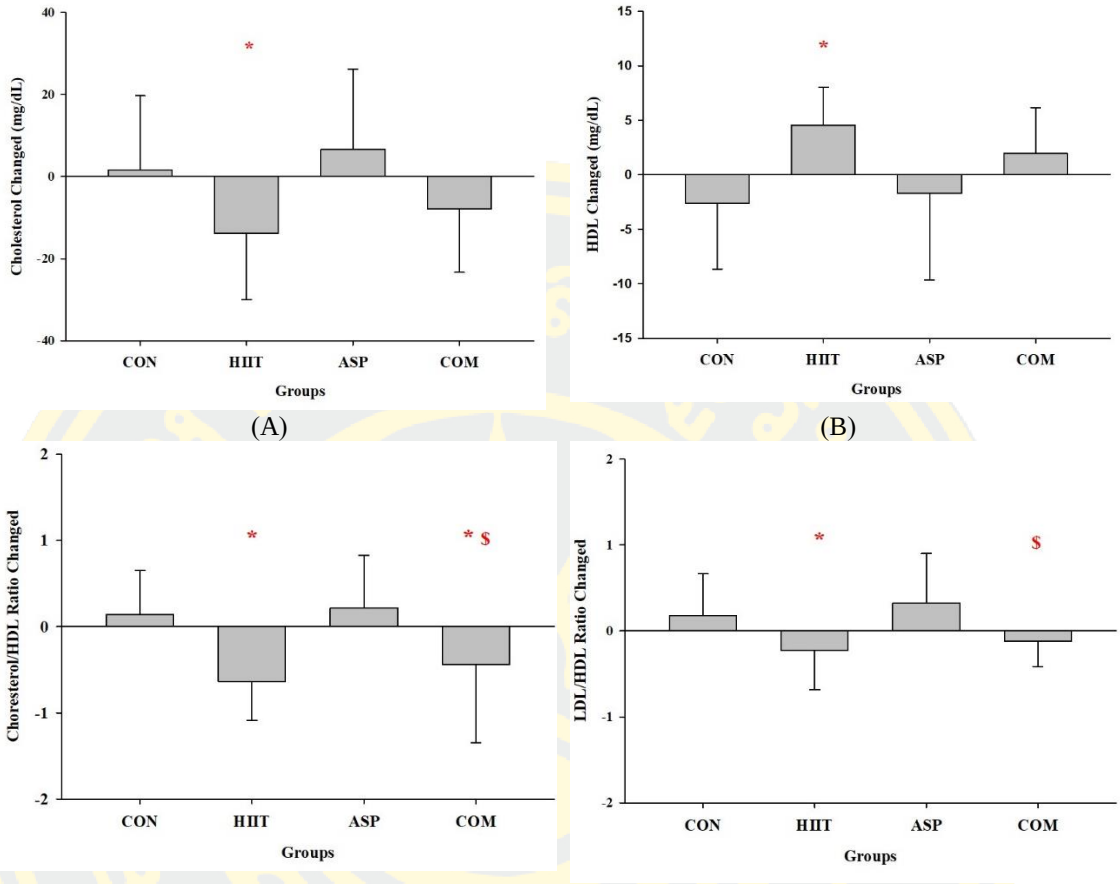


Figure 28 Changed of lipid profile parameters after 12-week interventions in CON group, HIIT group, ASP group and COM group. (A): Cholesterol changed; (B): HDL changed; (C): Cholesterol/HDL Ratio changed; (D): LDL/HDL Ratio changed. *: $p<0.05$ vs CON group; $^{\$}$: $p<0.05$ vs ASP group.

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Table 10 Mean ± Standard deviation of each types of white blood cell count in pretest and posttest of each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Total white blood cell (10^3/mm^3)	7.64±1.85	8.06±1.58	7.48±1.76	7.91±1.59	7.43±1.25	8.02±1.27	7.23±2.17	7.46±2.01
Neutrophils (%)	54.40±7.66	54.47±6.12	53.37±5.60	52.14±7.28	53.52±4.90	54.08±7.46	56.59±8.37	56.33±7.67
Neutrophils (/mm^3)	4,233±1,477	4,392±1,017	4,019±1,096	3,926±1,522	3,976±717	4,390±1,226	4,121±1,472	4,246±1,450
Lymphocytes (%)	36.43±6.76	36.53±5.78	37.25±5.65	39.01±7.08	36.79±5.57	35.79±6.37	34.82±7.35	35.01±7.17
Lymphocytes (/mm^3)	2,722±625	2,956±838	2,748±634	2,848±949	2,734±624	2,829±509	2,515±934	2,589±812
Monocytes (%)	6.25±1.19	5.96±1.13	6.55±1.63	6.16±1.01	5.72±0.95	5.74±1.41	5.97±1.84	5.87±1.53
Monocytes (/mm^3)	478±148	481±137	451±157	486±126	426±105	454±101	409±91	415±70
Eosinophils (%)	2.51±1.95	2.66±1.97	2.47±1.39	2.33±0.91	3.46±2.34	3.95±2.97 $^{\#}$	2.28±0.90	2.42±1.02
Eosinophils (/mm^3)	177±137	209±160	199±153	188±91	255±165	311±226	163±73	179±81 $^{\$}$
Basophils (%)	0.38±0.20	0.38±0.24	0.33±0.11	0.36±0.17	0.49±0.15	0.43±0.19	0.31±0.20	0.36±0.23
Basophils (/mm^3)	27±14	30±20	24±8	28±11	37±14	34±15	22±18 $^{\$}$	25±17

Data were compared between groups by the One-way ANOVA and followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. $^{\#}$: $p<0.05$ vs HIIT group; $^{\$}$: $p<0.05$ vs ASP group.

Table 11 Mean ± Standard deviation of inflammatory cytokines (IL-6 and TNF-α) concentrations and oxidative stress biomarkers (MDA and PC) in pretest and posttest of each groups.

	Control group		HIIT group		Asparagus group		Combined group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
IL-6 (pg/ml)	3.09±1.85	3.55±1.47	2.22±2.43	2.37±1.75	1.82±1.98	2.24±2.26	3.13±8.88	1.37±1.96*
TNF-a (pg/ml)	3.13±3.12	4.09±4.65	5.17±4.03	4.74±3.51	4.19±2.99	4.46±4.55	6.45±8.18	5.11±2.05
MDA (µM)	6.42±5.68	7.02±2.29	4.72±2.56	5.87±1.28	3.59±1.80	6.89±1.17 [A]*	3.43±1.34	5.50±1.97 [A]
PC (nM/mg protein)	0.08±0.14	0.05±0.05	0.15±0.18	0.05±0.07 [A]	0.12±0.14	0.05±0.04 [A]	0.52±0.38	0.16±0.29 [A]*

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group.

Table 12 Mean ± Standard deviation of liver function, lipid profile and sugar levels in pretest and posttest of each groups.

	Control group		HIIT group		Asparagus group		Combined group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Cholesterol (mg/dL)	202.50±38.44	204.06±32.44	202.61±33.95	188.72±37.25 ^{A*}	197.61±23.19	204.28±28.38	189.94±45.16	182.11±37.75 ^{A}
Triglyceride (mg/dL)	111.00±64.51	122.94±68.63	119.83±71.00	110.28±47.43	109.66±51.57	111.06±51.16	94.50±47.01	93.94±43.70
HDL (mg/dL)	55.27±10.56	52.67±9.58	51.83±16.82	56.39±15.91 ^{A*}	53.61±10.36	51.89±9.04	55.44±10.88	57.39±10.30 ^{A}
LDL (mg/dL)	135.88±34.10	138.00±29.34	138.77± 28.66	139.72±35.39	131.77±27.13	145.83±30.31 ^{A}	122.50±44.30	121.17±40.18
VLDL (mg/dL)	22.27±12.92	24.50±13.74	24.00±14.18	23.33±9.35	21.88±10.35	22.22±10.12	18.94±9.40	20.39±9.09
Cholesterol/HDL ratio	3.75±0.89	3.90±0.89	4.19±1.20	3.56±1.13 ^{A*}	3.85±1.08	4.08±1.05	3.67±1.37	3.24±0.73 $^{A*\$}$
LDL/HDL ratio	2.53±0.79	2.72±0.86	2.94±1.11	2.72±1.18	2.62±1.07	2.95±1.06 ^{A}	2.29±0.90	2.17±0.78
Glucose (Fasting)(mg/dL)	89.94±9.92	87.17±10.08	89.33±10.36	84.94±10.90 ^{A*}	102.33±69.70	99.11±47.84	86.72±7.41	83.94±6.71 $^{A\$}$
AST (U/L)	-	-	-	-	23.83±12.56	21.67±4.98	21.61±7.94	21.78±5.63
ALT (U/L)	-	-	-	-	19.47±4.58	18.67±12.12	16.36±3.85	20.22±11.27

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. ^{A}: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group; $^{\$}$: $p<0.05$ vs ASP group.

6. Effects of HIIT and Asparagus Root Supplement on Body Composition and Vital Sign

During the pre-experiment phase, there were no noticeable differences in body composition data among the four groups, as evidenced in Table 13 and Table 14. However, alterations in the waist-hip ratio were noted after 12-week intervention. Specifically, the COM group exhibited a waist-hip ratio value of 0.89±0.05, which was significantly lower than that of the CON group (0.94±0.06, $p<0.05$). Furthermore, following 12-week interventions, a trended reduction in waist circumference was observed in participants in HIIT group. The COM group had positive effects on segmental body fat as indicated by decreasing percent body fat in abdominal, right arm and left arm (76.1 ± 70.39% ($p<0.05$), 91.38 ± 43.42% ($p<0.05$), 91.52 ± 43.81% ($p<0.05$), respectively) compared to the CON group Table 14.

There were no significantly changes in weight, BMI, muscle mass, fat-free mass, body fat mass, percent body, body water, protein, mineral, VIA and basal metabolic rate between group.

When comparing the results of the intra-group analysis (posttest minus pretest), participants in the ASP group showed an increase in body weight (1.26±1.85 kg, $p<0.05$), BMI (0.76±1.46 kg/m^2, $p<0.05$), body fat mass (0.89±1.65 kg/m^2, $p<0.05$), waist-hip ratio (0.01±0.03, $p<0.05$), fat arm left (12.80±23.73%, $p<0.05$), and fat arm right (11.93±22.50%, $p<0.05$). In contrast, the COM group experienced an increase in body fat mass (1.07±1.82 kg, $p<0.05$), fat arm left (10.61±19.50%, $p<0.05$), and fat arm right (8.46±15.76%, $p<0.05$), although these increase was less than that observed in the CON group. Additionally, the CON group also increased the ratio of waist and hip (0.02±0.04, $p<0.05$).

At the pretest phase, no disparities in vital signs, including HR RR SpO_2 and BP, were detected among the participants in all four groups, as indicated in Table 15. Nevertheless, after completed of the 12-week intervention, a notable increase in SpO_2 was observed in the HIIT group, amounted to 0.89±1.28% ($p<0.05$), surpassing that of the ASP group and the COM group. In the intra-group analysis, HR decreased in the CON group (-4.78±7.34 beats/min, $p<0.05$) and the COM group (-8.11±12.74 beats/min, $p<0.05$).

7. Effects of HIIT and Asparagus Root Supplement on Pulmonary Function

According to the data in Table 16, it was initially observed that, in the pre-intervention phase, middle and lower chest expansions of participants in the COM group higher than those in the CON group. However, by the end of the 12-week interventions, these expansions had become similar to those of the CON group, with no notable differences observed in the post-experiment period among all four groups.

Regarding expiratory muscles strength or MEP, a significant increase was observed in both the HIIT group and the COM group, with values of 7.61±13.71 cmH_2O (p<0.05) and 7.11±13.05 cm H_2O (p<0.05), respectively, when compared to the CON group (Figure 29). Conversely, there were not changes in MIP, respiratory times and lung volume before and after the 12-week interventions in all four groups when compre to the CON group (Table 16).

In the intra-group analysis, MIP improved in all four groups; the CON group (4.39±3.17 cmH_2O, p<0.05), the HIIT group (6.31±9.65 cmH_2O, p<0.05), the ASP group (4.71±3.80 cmH_2O, p<0.05), the COM group (4.22±3.27 cmH_2O, p<0.05). Meanwhile, MEP improved only in the HIIT group (7.61±13.71 cmH_2O, p<0.05) and the COM group (7.11±13.05 cmH_2O, p<0.05). VC improved in both the HIIT group (0.12±0.20 liters, p<0.05) and the ASP group (0.18±0.28 liters, p<0.05). Additionally, the ASP group also shown an increase of IC (0.31±0.33 liters, p<0.05) and IRV (0.27±0.51 liters, p<0.05).

Table 17 reveals that participants in the ASP groups and the COM group experienced improvements in pulmonary function. This was evidenced by increased values for the FEV_1/FVC% and the percentage of FEV_1/FVC (%predicted). The ASP group exhibited an increase of 1.39±2.77 %predicted (p<0.05), while the COM group had increases in the percentage of FEV_1/FVC of about 2.44±7.17% (p<0.05) and increases the percentage of FEV_1/FVC %predicted of about 2.83±8.05 %predicted (p<0.05) when compared to the CON group (Figure 30).

In the intra-group analysis, the three intervention groups improved in peak expiratory flow, maximal voluntary ventilation, peak inspiratory flow, and forced expiratory time, as indicated in Table 17.

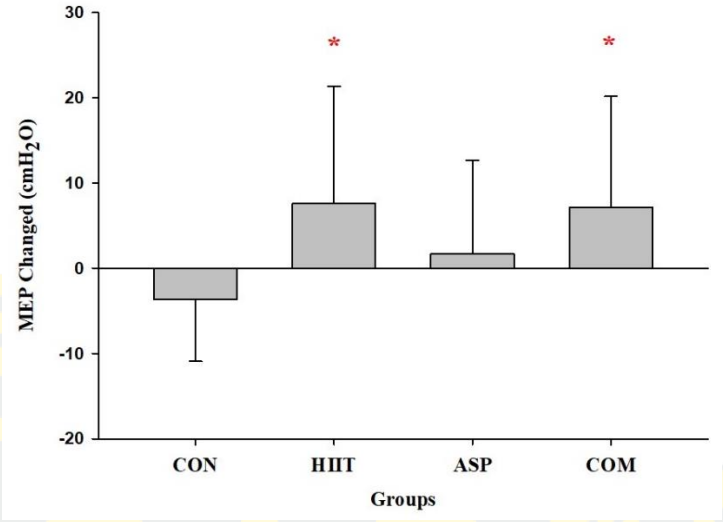

Figure 29 MEP changed after 12-week intervention.

*: $p<0.05$ vs CON group.

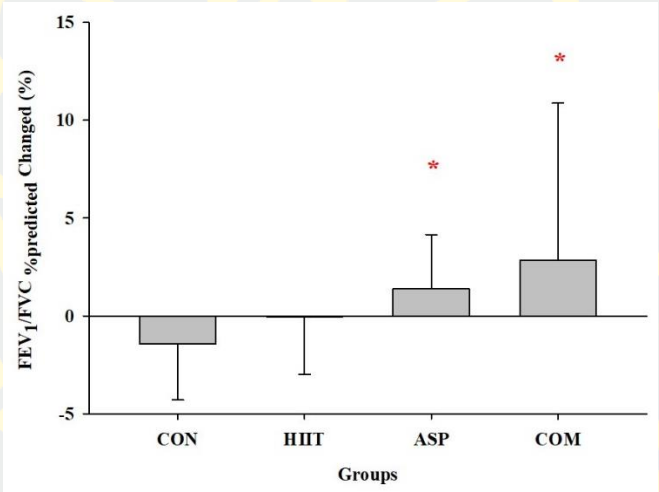

Figure 30 Changed of FEV_1/FVC%predicted after 12-week intervention.

*: $p<0.05$ vs CON group.

Table 13 Mean ± Standard deviation of body composition in pretest and posttest of each groups.

	Control group		HIIT group		Asparagus group		Combined group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Water (L)	33.70±6.61	33.51±6.61	34.31±7.19	34.55±7.45	31.21±9.95	32.98±7.44	32.28±4.74	32.01±4.59
Protein (kg)	9.06±1.83	9.03±1.84	9.23±2.01	9.33±2.09	8.83±1.90	8.88±2.01	8.67±1.31	8.59±1.26
Mineral (kg)	3.28±0.62	3.27±0.61	3.29±0.65	3.36±0.68	3.15±0.63	3.23±0.67	3.17±0.44	3.17±0.42
Weight (kg)	77.40±15.25	77.36±14.49	77.64±16.60	78.89±16.75	71.43±13.05	72.71±13.54 [A]	70.47±7.60	71.19±7.67
High (cm)	162.50±7.87	163.00±9.06	158.50±5.65	163.17±8.78	166.72±10.63	162.28±8.37	164.16±10.63	161.83±7.39
Body mass index (kg/m^2)	29.10±5.11	29.11±4.87	29.13±5.48	29.59±5.65	26.98±2.97	27.44±3.04 [A]	26.92±2.50	27.19±2.32
Skeletal muscle mass (kg)	25.37±5.52	25.25±5.55	25.88±6.08	26.14±6.27	24.60±5.79	24.79±6.09	24.14±3.97	23.96±3.84
Fat free mass (kg)	46.04±9.06	45.82±9.06	46.85±9.84	47.24±10.20	44.73±9.60	45.11±10.12	44.12±6.50	43.77±6.28
Body fat mass (kg)	31.36±10.23	31.53±9.62	30.79±11.64	31.65±11.85	26.70±6.21	27.60±6.52 [A]	26.34±5.26	27.42±4.84 [A]
Percent body fat (%)	40.07±7.38	40.44±7.14	39.02±8.98	39.54±9.21	37.44±5.53	38.04±5.64	37.37±5.79	38.52±5.10
Waist circumference (cm)	95.13±9.53	95.41±11.75	95.31±12.97	94.38±12.99	87.73±9.92	89.28±9.44	85.04±8.13	86.96±6.99
Waist-Hip ratio	0.92±0.06	0.94±0.06 [A]	0.91±0.06	0.91±0.06	0.91±0.05	0.93±0.81 [A]	0.87±0.04	0.88±0.05 *
Visceral adiposity index	4.13±2.29	3.49±1.70	3.79±2.35	4.66±3.46	4.05±2.27	4.19±2.96	3.15±2.04	3.24±2.26
Basal metabolic rate (kcal)	1364±195	1359±196	1382±212	1390±220	1336±207	1344±218	1323±140	1315±135

Group comparisons were conducted using One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using paired *t*-test.

[A]: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group.

Table 14 Mean ± SD of segmental muscles (lean) and fat areas in pretest and posttest of each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Lean arm left (kg)	2.35±0.64	2.35±0.63	2.38±0.66	2.43±0.70	2.25±0.68	2.29±0.71	2.13±0.45	2.12±0.44
Lean arm left (%)	92.20±8.17	92.11±7.06	94.80±12.72	95.98±13.50	94.29±10.57	95.11±11.85	93.70±11.39	91.28±8.17
Lean arm right (kg)	2.38±0.66	2.35±0.73	2.43±0.68	2.46±0.71	2.33±0.73	2.37±0.77	2.15±0.45	2.14±0.44
Lean arm right (%)	93.38±9.00	96.80±8.17	96.50±12.29	96.80±13.31	96.90±12.18	98.00±12.90	94.64±10.84	92.33±8.03
Lean abdomen (kg)	20.75±4.10	20.79±4.06	20.91±4.24	21.17±4.37	20.15±4.28	20.53±4.72	19.26±2.90	19.26±2.79
Lean abdomen (%)	94.56±5.16	94.80±4.49	96.00±7.26	96.50±7.84	96.43±6.54	96.84±7.07	94.91±6.04	93.84±4.67
Lean leg left (kg)	7.13±1.48	6.84±1.79	7.37±1.81	7.59±1.85	6.91±1.60	6.86±1.58	6.89±1.19	6.88±1.22
Lean leg left (%)	92.78±6.02	91.07±6.27	95.87±7.59	95.98±8.24	94.42±7.49	93.05±6.79	96.96±8.14	95.48±6.62
Lean leg right (kg)	7.20±1.50	7.05±1.50	7.40±1.86	7.44±1.89	6.99±1.64	6.95±1.23	6.94±1.21	6.91±1.23
Lean leg right (%)	93.71±6.55	91.56±6.11	96.20±8.05	96.03±8.48	95.41±7.92	94.16±7.65	97.75±8.66	95.95±6.87
Fat arm left (kg)	2.62±1.37	2.67±1.32	2.62±1.53	2.72±1.56	2.05±0.71	2.16±0.81	2.01±0.57	2.11±0.55
Fat arm left (%)	324.87±161.29	329.38±154.56	311.13±176.58	322.76±185.43	238.18±82.89	250.98±86.59 [A]	221.68±69.66	237.85±57.61 [A] *
Fat arm right (kg)	2.60±1.38	2.63±1.32	2.56±1.52	2.68±1.54	2.00±0.71	2.12±0.79	1.97±0.57	1.78±0.58
Fat arm right (%)	321.72±161.12	324.39±153.33	305.64±173.77	319.14±183.73	231.97±79.50	243.91±83.90 [A]	218.86±69.60	233.01±61.63*
Fat abdomen (kg)	15.20±3.84	15.58±3.89	14.91±5.06	15.27±5.02	13.38±3.10	13.92±3.15	12.84±2.41	13.39±2.34
Fat abdomen (%)	316.30±88.06	324.01±87.20	302.69±107.17	309.74±108.02	267.72±59.22	278.18±57.99	250.50±56.68	264.51±47.47 [A] *
Fat leg left (kg)	4.82±1.89	4.69±1.58	4.69±1.75	4.85±1.90	4.02±0.85	4.09±0.89	4.17±0.85	4.31±0.74
Fat leg left (%)	225.03±80.70	219.67±68.57	214.47±81.03	221.43±88.23	179.91±34.4	182.68±36.53	179.79±42.07	189.36±29.13
Fat leg right (kg)	4.85±1.93	4.72±1.59	4.72±1.78	4.88±1.94	4.05±0.86	4.11±0.91	4.20±0.85	4.34±0.73
Fat leg right (%)	226.24±82.10	220.53±69.47	215.90±82.53	222.94±89.88	181.18±35.05	184.03±37.26	180.94±42.05	190.31±28.90

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group.

Table 15 Mean ± Standard deviation of vital sign in pretest and posttest of each groups.

	Control group		HIIT group		Asparagus group		Combined group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Heart rate (beats/min)	77.22±9.35	72.44±11.64 [a]	77.00±9.82	74.11±9.98	74.00±15.13	74.28±8.28	78.27±9.55	70.17±8.71 [A]
Partial oxygen saturation (%)	97.77±1.21	97.94±0.87	97.50±1.29	98.39±0.70 [A]	98.05±0.80	97.78±0.88 #	98.22±0.73	98.17±1.15 #
Respiratory rate (breaths/min)	18.33±3.28	17.17±2.68	16.11±2.02	16.06±2.73	17.88±3.42	17.39±3.47	17.55±3.63	17.22±3.17
Systolic blood pressure (mmHg)	118.64±16.15	112.48±12.23	118.31±11.77	114.13±12.28	112.33±13.24	112.46±12.57	110.70±8.08	111.02±9.17
Diastolic blood pressure (mmHg)	74.40±12.54	70.65±8.14	73.94±8.54	70.57±8.73	70.81±11.46	71.72±10.36	69.77±7.16	69.24±6.59
Mean arterial pressure (mmHg)	89.15±13.03	84.59±8.72	88.73±8.99	85.09±0.06	84.65±11.34	85.31±10.58	83.41±7.16	83.17±7.10

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest of each group; [#]: $p<0.05$ vs HIIT group.

Table 16 Mean ± Standard deviation of chest expansions, respiratory muscle strength, respiratory time and lung volume and capacity in pretest and posttest of each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Chest expansion								
Upper chest (cm)	2.94±1.49	3.02±1.26	3.58±1.68	3.65±1.78	3.31±1.25	2.78±1.30 [A]	3.96±1.25	3.63±1.39
Middle chest (cm)	2.07±1.45	2.21±1.46	2.58±1.83	2.83±2.02	2.54±1.26	2.34±1.48	3.39±1.31*	2.75±1.23 [A]
Lower chest (cm)	2.89±1.52	2.88±1.56	3.44±1.61	3.71±1.86	3.85±1.46	3.68±2.08	4.68±1.66*	3.82±1.58 [A]
Respiratory muscle strength								
Maximum inspiratory pressure (cmH_2O)	30.31±8.55	34.70±6.95 [A]	28.83±6.36	35.15±9.65 [A]	27.22±7.26	31.93±6.51 [A]	29.35±6.26	33.57±6.24 [A]
Maximum expiratory pressure (cmH_2O)	67.77±13.85	64.17±14.08	60.68±13.16	68.30±18.53 [A]*	55.57±11.98	57.24±16.22	61.31±14.16	68.43±18.61 [A]*
Respiratory time								
Inspiratory time (s)	2.09±0.42	1.85±0.71	2.33±0.82	2.10±0.52	1.93±0.62	1.98±0.85	2.49±0.89	2.35±0.79
Expiratory time (s)	2.28±0.48	2.38±1.28	2.56±0.80	2.28±0.67	2.08±0.52	2.29±0.86	2.64±0.82	2.58±0.60
Total time (s)	4.38±0.76	4.23±1.91	4.89±1.44	4.39±1.05 [A]	4.01±1.07	4.27±1.65	5.13±1.68	4.92±1.30
Lung volume and capacity								
Vital capacity (L)	3.01±0.73	3.10±0.71	3.22±1.16	3.34±1.13 [A]	3.02±0.62	3.21±0.58 [A]	3.13±0.69	3.17±0.67
Inspiratory capacity (L)	1.93±0.05	2.00±0.59	2.02±0.64	2.17±0.63	1.77±0.64	2.08±0.60 [A]	1.91±0.30	1.96±0.44
Tidal volume (L)	0.96±0.38	0.86±0.54	0.94±0.47	0.99±0.39	0.84±0.35	0.88±0.43	0.99±0.41	0.95±0.47
Expiratory reserve volume (L)	1.12±0.56	1.11±0.51	1.19±0.62	1.17±0.58	1.25±0.41	1.13±0.38	1.22±0.50	1.21±0.42
Inspiratory reserve volume (L)	0.96±0.47	1.15±0.59	1.07±0.52	1.19±0.52	0.93±0.60	1.20±0.41 [A]	0.92±0.31	1.01±0.51

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group.

Table 17 Mean ± Standard deviation of pulmonary function test in pretest and posttest of each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Forced expiratory in one second (FEV_1)								
FEV_1 (L)	2.89±0.52	2.93±0.50	3.02±0.87	3.06±0.85	2.92±0.59	3.01±0.53	2.88±0.54	2.95±0.50
FEV_1 (% predicted)	95.72±9.81	97.44±9.82	98.88±11.58	100.44±11.50	99.61±15.95	101.11±13.23	99.16±14.27	101.44±10.52
Forced vital capacity (FVC)								
FVC (L)	3.19±0.65	3.29±0.64	3.39±1.08	3.44±1.04	3.28±0.64	3.34±0.58	3.26±0.58	3.26±0.66
FVC (% predicted)	93.55±8.16	96.44±9.32 ^{A}	98.50±13.09	100.11±12.41	99.83±14.68	100.00±13.55	100.77±11.55	100.67±12.46
Peak expiratory flow (PEF)								
PEF (L)	6.95±1.64	7.24±1.46	6.49±1.39	7.21±1.41 ^{A}	6.44±1.79	7.15±1.53 ^{A}	6.24±1.18	6.74±1.12 ^{A}
PEF (% predicted)	97.27±25.16	101.6±23.78^{A}	91.50±15.45	101.56±15.06^{A}	92.27±19.14	101.33±16.78	92.11±12.87	99.83±14.72^{A}
Forced expiratory in one second per forced vital capacity (FEV_1/FVC)								
FEV_1/FVC (%)	90.77±5.63	89.61±6.23	89.72±5.54	89.61±4.85	89.38±6.89	90.33±6.53	88.72±9.28	91.17±5.34 *
FEV_1/FVC (% predicted)	101.05±5.57	99.61±6.39 ^{A}	99.55±5.92	99.50±5.03	98.83±7.48	100.22±7.22*	97.77±10.14	100.61±6.00^{A}*
Forced expiratory flow at 25–75% of FVC (FEF25-75)								
FEF_{25-75} (l/s)	3.71±0.96	3.67±0.99	3.67±0.98	3.57±0.76	3.61±1.03	3.76±0.95	3.46±0.99	3.73±0.60
FEF_{25-75} (% predicted)	98.00±25.95	96.94±26.81	96.00±18.58	95.22±17.82	97.1±26.30	100.56±24.68	94.11±27.456	101.94±18.35
Maximal voluntary ventilation (MVV) (l/min)	108.43±19.59	110.0±18.73^{A}	113.46±32.73	114.92±31.86^{A}	109.84±22.43	112.88±110.60^{A}	108.14±20.25	110.60±18.80^{A}
Peak inspiratory flow (PIF) (l/s)	4.71±1.36	5.30±1.05 ^{A}	4.22±1.50	5.40±1.62 ^{A}	4.17±1.41	5.17±1.41 ^{A}	4.11±0.70	4.90±1.21 ^{A}
Forced expiratory time (s)	2.40±0.61	2.84±0.94 ^{A}	2.72±0.65	2.82±0.65 ^{A}	2.58±0.73	2.50±0.79 ^{A}	2.88±0.90	2.61±0.85 ^{A}

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. ^{A}: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs Control group.

8. Effects of HIIT and Asparagus Root Supplement on Cardiopulmonary Fitness

During the pre-intervention phase, it was established that there were no significant differences in the cardiopulmonary fitness levels of participants in all four groups. This remained consistent when assessing their performance in both the resting and the peak exercising phases, as illustrated in Table 18.

During the resting phase, participant in the CON group was shown a decrease in VO_2rest of 0.50±0.71 l/min/kg (p<0.05), while the RER increased by 0.05±0.07 (p<0.05) in the HIIT group after the12-week intervention.

Following the 12-week interventions, participants in the HIIT group exhibited enhanced endurance during the Bruce exercise stress test. This improvement is clearly reflected through an increased exercise test time of 72.33±82.15 seconds (p<0.05) when compared to the CON group. The COM group showed improvements in exercise time (64.83±76.79 seconds, p<0.05) and VO_2peak (0.72±2.92 L/min/kg, p<0.05) (Figure 31). However, no such change was observed in the ASP groups (Table 18.).

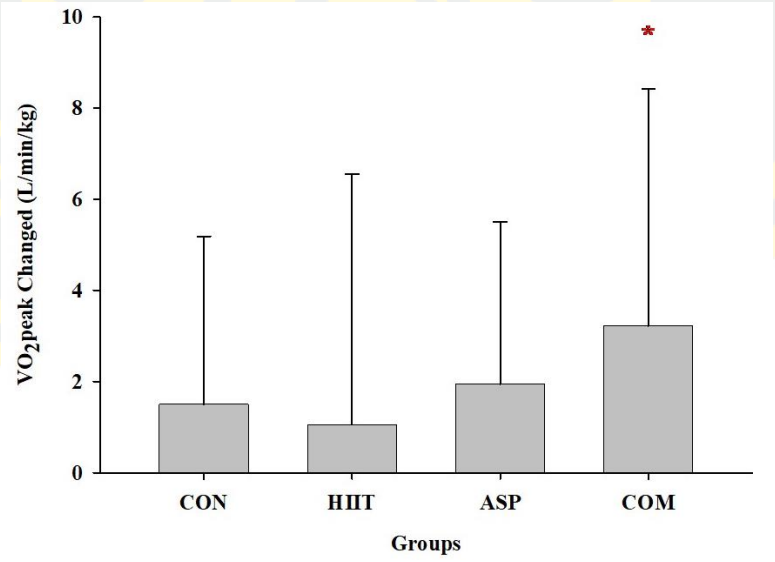

Figure 31 VO_2peak changed after 12-week intervention.

*: p<0.05 vs CON group.

9. Feasibility

The dropout rate remained 0% in both the HIIT group and the COM group. No serious adverse events occurred during the trial. Rating of perceived exertion during

homebased-HIIT program of both groups were range from 7 to 11 during the warm-up phaese, 13 to 17 during exercise phase and 9-11 during cool down phase. A few other adverse events were reported in both groups. Specifically, two individuals from the HIIT group and two from the COM group experienced leg muscle soreness and nausea during the 4th cycle of the homebase-HIIT program. None of the participants discontinued the trial.

All paricipants of both the ASP group and the COM group consumed asparagus root supplement capsules without encountering any adverse effects or complications. In addition to the 12-week interventions, there were no significant changes in daily physical activity over time, and no discernible differences were observed between the groups. Although the diets did not differ between the groups, it was observed that all groups exhibited an increased proportion of consuming fatty foods compared to the pretest period (Table 19). Furthermore, a reduction in carbohydrate intake was noted in the HIIT group, the ASP group, and the COM group. The COM group demonstrated a decrease in protein intake at posttest.

Table 18 Mean ± Standard deviation of cardiopulmonary fitness in pretest and posttest of each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Resting phase								
Heart rate (beats/min)	94.44±10.31	92.00±11.91	91.72±10.39	90.17±10.41	91.11±18.02	91.72±12.41	89.77±9.19	92.28±10.75
Respiratory rate (beats/min)	20.16±3.85	19.50±3.83	21.05±4.24	21.67±5.20	20.83±4.65	21.22±2.98	20.66±4.00	19.72±3.37
Respiratory exchange ratio	0.80±0.05	0.84±0.04	0.81±0.04	0.87±0.04 [A]	0.83±0.06	0.85±0.05	0.82±0.05	0.85±0.05
Oxygen uptake at rest (VO_{2rest}) (L/min/kg)	4.44±0.92	3.94±0.80 [A]	4.66±0.76	4.44±0.86	4.66±1.02	4.33±0.68	4.88±2.58	4.78±1.96
Maximum exercising phase								
Heart rate (beats/min)	182.22±11.59	181.44±7.90	188.01±8.88	191.00±9.57	184.55±12.07	185.78±11.87	182.16±10.78	185.78±9.33 [A]
Respiratory rate (beats/min)	52.22±10.82	54.44±10.19	54.77±10.32	62.22±12.75 [A]	57.55±13.35	59.28±11.31	55.72±11.78	57.33±11.96
Respiratory exchange ratio	1.22±0.08	1.29±0.05 [A]	1.21±0.07	1.29±0.07 [A]	1.19±0.06	1.27±0.05 [A]	1.22±0.06	1.27±0.08 [A]
Peak oxygen uptake (VO_{2peak}) (L/min/kg)	31.11±6.65	30.39±6.95	33.94±6.91	32.39±5.87	31.38±5.04	31.56±4.36	35.33±12.40	37.44±13.24 [A]*
Exercise test time (s)	691.5±75.7	729.0±72.6[A]	686.1±93.1	758.5±96.9 [A]*	736.6±74.3	768.1±51.3	711.5±73.5	776.3±95.3 [A] *

Group comparisons were conducted using the One-way ANOVA, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest of each group; *: $p<0.05$ vs CON group.

Table 19 Mean ± Standard deviation of energy intake at pretest and posttest in each groups.

	CON group		HIIT group		ASP group		COM group	
	Pretest	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**	**Pretest**	**Posttest**
Daily energy intake								
(Kcal/day)	2156±18	2326±204	2439±218	2334±200	2385±215	2043±200	2100±150	2274±119
(Kcal/day·kg)	28.86±0.93	31.30±3.57	36.13±3.65	34.26±2.54	33.36±2.89	28.75±2.87	30.48±2.14	33.36±2.22
Carbohydrate								
(g/day)	256.22±71.90	349.93±105.95	307.62±193.87	271.12±49.75	224.49±74.35	255.38±72.50	272.30±114.59	310.33±66.13
(g/day·kg)	3.28±0.59	4.71±1.59	4.14±2.35	4.04±1.02	3.24±1.18	3.59±1.04	3.98±1.82	4.53±1.10
(Kcal)	1024.88±287.60	1399.73±423.81	1230.51±775.51	1084.48±199.00	897.99±297.42	1021.53±290.01	1089.21±458.39	1241.35±264.53
(%Energy)	43.43±8.83	41.76±10.68	48.74±11.28	32.81±9.66 [A]	43.14±8.85	32.17±7.49 [A]	49.68±8.72	35.76±8.45 [A]
Fat								
(g/day)	100.72±26.07	218.65±94.65 [A]	90.92±48.01	213.60±74.88 [A]	96.78±32.91	210.38±81.24 [A]	79.61±26.50	215.39±73.51 [A]
(g/day·kg)	1.32±0.36	3.08±1.56	1.22±0.54	3.10±0.89 [A]	1.37±0.39	2.96±1.15 [A]	1.14±0.35	3.14±1.10 [A]
(Kcal)	906.56±234.65	1524.75±257.19 [A]	818.35±432.10	1922.40±674.00 [A]	871.02±296.20	1893.48±731.19[A]	716.50±238.58	1938.52±661.64[A]
(%Energy)	38.79±8.20	46.63±6.98	35.42±10.94	54.68±8.63 [A]	41.62±8.29	56.61±5.70 [A]	33.16±6.38	53.48±8.48 [A]
Protein								
(g/day)	105.00±36.85	109.37±34.75	88.78±29.90	109.68±56.21	82.52±36.44	96.72±66.36	91.73±30.52	95.52±32.01
(g/day·kg)	1.35±0.44	1.53±0.58	1.22±0.46	1.58±0.73	1.17±0.46	1.34±0.94	1.31±0.40	1.40±0.55
(Kcal)	420.00±147.42	625.25±492.02	355.13±119.61	438.72±224.84	330.09±145.77	386.88±265.46	366.93±122.10	382.08±128.06
(%Energy)	17.76±5.75	19.51±16.36	15.83±4.00	12.49±5.61	15.23±3.55	11.20±4.52	17.15±3.74	10.75±2.85 [A]

Group comparisons were conducted using the One-way ANOVA test, followed by the Bonferroni correction. Intra-group comparisons were performed using the paired *t*-test. [A]: $p<0.05$ vs pretest each group.

CHAPTER 5
DISCUSSION AND CONCLUSIONS

The objective of this study were to determine a comparative analysis of various cardiopulmonary health and disease indicators in overweight and obese individuals before and after 12-week interventions, which included the high-intensity interval training program, the consumption of asparagus root extract and a combined intrevention (COM group), as compared to control. These indicators included white blood cell counts, biomarkers of inflammation and oxidative stress, lipid and glocose levels, as well as cardiorespiratory fitness. The study was a randomized controlled trial involving a total of 72 overweight and obese participants, with 18 individuals assigned to each group.

This study is the first to investigate the effects of the 12-week HIIT-homebased program for 3 days/week, along with the consumption asparagus root extract capsules at doses 1.71±0.24 mg/kg/day (COM group). The positive results including a reduction abdominal and upper extremety fat, and an improving cholesteral/HDL ratio, LDL/HDL ratio, a decrease in the inflammatory process by reducing Il-6, a decrease in the oxidative stress biomarker by reducing protein carbonyl, and consequently, a lower count of eosinophils compared to the CON group. As a result, the combined intervention could improve the expiratory muscle strength, leading to increased forced exhalation which more reflects lung emptying. These positive effects, however, could transfer to improved exercise tolerance and cardiorespiratory fitness, by inproved VO_2peak, among the participants in the COM group.

Positive results were also observed in participants who underwent the 12-week high-intensity interval training program (HIIT group). The results for the HIIT group included improvements in HDL, a reducing cholesteral as well as favorable changes in cholesteral/HDL and LDL/HDL ratios. Consequently, the 12-week home-based HIIT program could also enhance an expiratory muscle strength and improve oxygenation. These positive effects, however, could translate into improved exercise tolerance among the participants in the HIIT group.

Consuming capsules containing asparagus root crude extract alone (ASP group) was showed to be safe for the liver, as indicated by the levels of AST and ALT enzymes and it led to an increased in pulmonary function. However, the study yielded negative results: an increase in oxidative stress, as evidenced by the elevated MDA level, a higher in eosinophils count, a decrease HDL, a high in cholesterol, cholesterol/HDL and LDL/HDL.

1. The Mechanism linkage between Immune Response, Inflammatory Biomarkers, Oxidative Stress Biomarkers and Lipid profiles of 12-week Home-based HIIT with Asparagus Root Supplementation

From the result of this study, the COM group proved to be benefit in improving one type of innate immune cell know as eosinophil counts. Also, decrease in the inflammatory process by reducing Il-6, a decrease in the oxidative stress biomarker by reducing protein carbonyl. The physiological mechanism elucidated by the results of this study involves an improve lipid profiles (cholesterol/HDL ratio and LDL/HDL ratio). This reduction in body fat mass (waist-hip ratio, abdominal fat, fat of both arms) mitigates lipotoxicity, reducing cellular apoptosis, leading to a concurrent reduction in inflammation within adipose tissue. This, in turn, diminishes the release of cytokines involved in the inflammatory process (IL-6) and curtails the release of substances linked to oxidative stress (protein carbonyl). Additionally, this decrease in lipid level contributes to a reduction white blood cell count (basophil counts), that typically observed in obese individuals, signifying a reduction in chronic low-grade systematic inflammation. Consequently, these changes of these biomarker should translate to a reduced risk of hyperlipidemia in individual with overweight and obesity.

1.1 Effect of 12-week Home-based HIIT on Immune Response, Inflammatory and Oxidative Stress Biomarkers

The popularity of high-intensity interval exercise, often termed intermittent or HIIT, is on the rise. HIIT training consists of repeated bouts of vigorous exercise (5 seconds to 8 minutes) performed at 80%–95% of estimated maximal heart rate, interspersed with periods of low-intensity activity or rest. Total session durations typically range from 20 to 60 minutes (Campbell & Rutherford, 2018; Roy, 2013).

According to this study, total exercise duration of the home-based HIIT was 32 minutes with 4 minute for each cycle of exercise periods and at 75% to 85% of rating of perceived breathlessness.

From the result of this study, the 12-week home-based HIIT program proved to be benefit in improving one type of innate immune cell know as eosinophil counts. However, there were on changes of total white blood cell, leucocyte, neutrophil, basophil counts after 12-week training. Notably, while previous studies have primarily examined the acute effects (0 to 24 hr) of HIIT on various blood cell counts, research on its chronic effects has been limited (Souza et al., 2021). According to previous studies of acute effect, a study by Wahl et al. (2020) reported either no change or a decrease in basophil and eosinophil counts after a HIIT protocol (Patrick Wahl et al., 2020). For instance, a prior study conducted by Kargotich et al. (1997) found no significant change in eosinophil counts following HIIT (Kargotich, Keast, Goodman, Crawford, & Morton, 1997). Regarding chronic studies, performing HIIT for 1to 24 weeks provide no change on leucocyte count (Souza et al., 2021). Therefore, this study is one of the long-term studies that confirm the effects of HIIT, which leads to changes in eosinophilic white blood cells.

In our 12-week home-based HIIT program, we did not observe any changes in inflammatory cytokines and oxidative stress biomarkers. Previous meta-analyses have highlighted the potential of HIIT to reduce inflammation markers in a range of populations, including healthy individuals, those who are overweight or obese (Gonzalo-Encabo, Maldonado, Valadés, Ferragut, & Pérez-López, 2021), and patients with cardiometabolic disorders (Martland, Mondelli et al. 2020, MATTIONI MATURANA, MARTUS et al. 2021). However, currently, data on the effects of HIIT are still very sparse. In contrast to a previous study where HIIT was conducted on electronically braked cycle ergometers for 14 minutes per day, 2 days per week, over a 12-week period at 90%-95% of maximum heart rate, resulting in a significant reduction in serum concentrations of CRP, high-sensitivity CRP, IL-6, and lipopolysaccharide-binding protein (Reljic, Dieterich, Herrmann, Neurath, & Zopf, 2022). Comparable to our result, we found significant changes in of the IL-6, MDA and PC measures, which may be due to the appropriated intensity during exercise phase.

1.2 Effect of 12-week Home-based HIIT on Lipid Profile and Glucose Level

A meta-analysis comparing the effects of HIIT and moderate-intensity continuous exercise (MICE) on blood lipid concentrations in overweight and obese young adults revealed that HIIT is more effective than MICE in reducing total cholesterol and LDL concentrations in this population. Enhancing LDL and TC levels in adulthood has the potential to reduce the risk of cardiovascular disease and chronic heart conditions in later life, as demonstrated by previous research (Mc, Mamikunian, & Thorp, 2023). Thus, our results indicate that the 12-week home-based HIIT program significantly reduced cholesteral by 13.89±16.16 mg/dL, resulting in reducing cholesteral/HDL ratio of 0.64±0.45 and an LDL/HDL ratio of 0.23±0.45. According to prior study that investigate HIIT and moderate-intensity interval training (MIIT) for 8 weeks on lipid profile in fourty one females with overweight/obesity found that there are significant reductions in the levels of triglyceride and total cholesterol level and increasing HDL (Ghodsi, Zolfaghari, & Fattahi, 2016). The mechanism that partially explains the effect of HIIT on reducing LDL involves the post-HIIT increase in the release of growth hormone, which is likely to enhance fat oxidation following the completion of HIIT exercises. This increased lipid oxidation is mediated by the release of growth hormone. (Bahr, Høstmark, Newsholme, Grønnerød, & Sejersted, 1991). So, HIIT interventions may have a role in enhancing long-term cardiovascular health.

The 12-week home-based HIIT program led to a significant improvement in HDL with an increase of 4.56±3.47 mg/dL (8.79%). However, a meta-analysis did not find a significant impact of HIIT on HDL concentrations (Mc et al., 2023). Previous studies have shown that HIIT induced minor positive changes in HDL, resulting in a small effect of approximately 3% increase, which may not be of clinically significant. In contrast, our study demonstrated 8.79% increase in HDL or three times greater than the prior study. These suggest that our home-based HIIT program may offer clinical benefits for individual with obesity.

1.3 Effect of Asparagus Root Supplementation on Liver Function, Lipid Profile and Glucose Level

20-hydroxyecdysone is a natural plant steroid known for its low mammalian toxicity. Extensive data from academic and pre-clinical studies indicate its potential for various beneficial pharmacological effects in mammals, including humans. However, there are only a limited number of research have been validated through clinical trials. 20E is one of the most frequently encountered phytoecdysteroid and often serves as the predominant phytoecdysteroid within plants. The species of plant that a good source of 20E include ginseng (*Panax ginseng*) spinach (*Spinacia oleracea L.*) (Todorova et al., 2021), and also asparagus (*A. officinalis*) (Laurence Dinan, Tamara Savchenko, & Pensri Whiting, 2001).

The Asparagaceae family, as noted by Brummitt in 1992, consists of a single genus. Asparagus, which includes approximately 100 species of herbs, shrubs, and vines distributed widely. Of these, *A. officinalis*, known as vegetable asparagus, holds significant commercial importance. The tender spears of *A. officinalis* represent a valuable crop in many regions across Europe, North America, and Asia (Brummitt, 1992). Additionally, the presence of 20E has been identified in the leaves, stems, and roots of asparagus (Baltaev, 2000).

From our results, consuming capsules containing asparagus root crude extract alone (Asparagus group) was shown to be safe for the liver, as indicated by the levels of AST and ALT enzymes. However, there was no change in cholesterol, triglyceride, LDL, HDL and fasting blood glucose level after the 12-week intervention. According to previouse study that study in the effects of β-ecdysone on serum lipids on the metabolic syndrome. The results showed that 20E has no significant effect on serum lipids (L. Dinan et al., 2021). Furthermore, a study conducted by Denben et al. in 2023 involving ten healthy males who underwent 12 weeks of resistance training alongside the use of 20E also demonstrated no adverse effects on AST, ALT, BUN, and creatinine levels (B. Denben, S. Sripinyowanich, R. Ruangthai, & J. Phoemsapthawee, 2023). Hence, the utilization of asparagus root extracts in overweight or obese individuals appears to be safe for liver and kidney function. Nonetheless, consuming asparagus root extract alone, without of a resistance exercise or a HIIT exercise, is unlikely to result in any significant alterations in various blood lipid profiles.

1.4 Effect of Asparagus Root Supplementation on Immune Response, Inflammation and Oxidative Stress

Previous studies have found that obese and overweight individuals, who exhibit chronic low-grade inflammation, show increased levels of monocyte chemotactic protein-1, interleukin-6, and plasminogen activator inhibitor-1 (PAI-1) in the blood, which are caused by stimulation through the TLR4-mediated signaling pathway (Wong et al., 2009). While the production of anti-inflammatory agents by 20E is reduced, TLR-4 is an essential mechanism that influences immune function, both in innate immunity and adaptive immunity. Exposure to 20E has the effect of reducing the mRNA levels involved in the TLR4-mediated signaling pathway, resulting in 20E having an anti-inflammatory effect (Lafont & Dinan, 2003). However, our results showed that the Asparagus group yielded negative outcomes: an increase in oxidative stress, as evidenced by the elevated MDA level, and a higher eosinophil count, with no change inflammation, in contrast to previous studies. Currently, we cannot provide a definitive reason for this observation. However, it is possible that our research did not account for all factors that could be associated with oxidative stress, such as dietary intake of foods rich in anti-oxidative substances like vegetables and fruits. Additionally, hormonal factors, including estrogen, adiponectin, and cortisol, were not considered. Therefore, in future studies, we recommend controlling for these related factors to gain a more comprehensive understanding of the results (Fernández-Sánchez et al., 2011; Marseglia et al., 2014).

2. The Meachnism linkage between Body Composition, Pulmonary Function and Cardiorespiratory Fitness of 12-week Home-based HIIT with Asparagus Root Supplementation

Based on the study's findings, the COM group exhibited a reduction in the percentage of arm fat mass as well as a decrease in abdominal fat mass. Consequently, there was a decrease in the waist-to-hip ratio, which, in turn, expanded lung capacity within the abdominal cavity. This expansion increases the intercostal spacing, thereby lengthening the expiratory muscles and enhancing their length-tension relationship. As a result, it was observed that the expiratory muscles had strengthened (MEP), leading to improved lung function (FEV_1/FVC, $FEV_1/FEV_{\%predicted}$), cause to

prolonged exercise duration and ultimately an enhanced capacity for VO_2peak in individual with overweight and obesity.

2.1 Effect of 12-week Home-based HIIT On Body Composition and Anthropometric Measures

Participants in the HIIT program did not exhibit significant changes in body weight, body mass index (BMI), muscle mass, fat-free mass, mineral content, or protein levels. This observation aligns with previous studies that have explored the impact of HIIT on weight in sedentary overweight or obese individuals, which have generally shown only minimal reductions in weight. Nevertheless, the findings from the previous studies we reviewed indicate that HIIT may have the potential to facilitate weight loss in this population. However, research conducted a minimum of 12 weeks, is warranted to provide a more conclusive understanding (Alahmadi, 2014). From our results, following 12-week HIIT interventions, only a trended reduction in waist circumference was observed among participants in the HIIT group. The reason why the waist circumference had not significantly changed might be attributed to the lower exercise intensity level in this study (75-85% HRmax) compared to previous studies (90-95% HRmax). According to a previous study by Astorino et al., a longer HIIT protocol (60 seconds at approximately 75 to 95% HRmax with 75 seconds of recovery) resulted in no significant change in body weight after 12 weeks of training (Astorino et al., 2013). In a longer intervention, Tjønna et al. reported that HIIT reduced total fat mass by 0.9 kg at 3 months and 2.4 kg at 12 months. A recent 6-week low-volume HIIT study (~90% HRmax) in overweight or obese women demonstrated significant improvements in body composition, with DEXA showing decreased abdominal and total body adiposity alongside increased leg lean mass. Conversely, two other recent HIIT studies found no significant changes in weight or body composition among sedentary, overweight, or obese participants (Tjønna et al., 2009). Two possible explanations for the lack of weight loss in exercise interventions are increased energy intake due to the stimulatory effect of exercise on appetite and decreased non-exercise activity thermogenesis (NEAT) to compensate for the increase in exercise-induced energy expenditure (King et al., 2007; Melanson et al., 2013). Thus, only minor differences of weight and body composition were observed in this study.

2.2 Effect of 12-week Home-based HIIT On Vital Sign and Pulmonary Function

Oxygen saturation (SpO_2) is a critical parameter for assessing and comprehending an individual's condition. The body tightly regulates oxygen levels because hypoxemia can have significant acute adverse effects on various organ systems. Numerous anatomical and physiological factors influence SpO_2, including pulmonary ventilation and perfusion, vascular circulation, oxyhemoglobin concentration, arterial blood for oxygen transport, and tissue perfusion (J. A. Collins, Rudenski, Gibson, Howard, & O'Driscoll, 2015; Kaufman, Kandle, Murray, & Dhamoon, 2023). Unexpectedly, it was discovered that oxygen exchange improved in our the HIIT group. The exact mechanism underlying the improvement in SpO_2 remains uncertain. However, given our study's results, which indicated an increase in maximum expiratory pressure (MEP) in the HIIT group, we propose a hypothesis based on MEP findings, suggesting that improved SpO_2 might be attributed to the enhanced strength of the expiratory muscles. This increased strength may facilitate more effective ventilation of the bronchus in lungs, thus, creates additional lung emtrying and space for next inhalation. Consequently, this improved breathing enables a greater influx of oxygen into alveoli, leading to an increase in the tissue oxygen saturation.

2.3 Effect of 12-week Home-based HIIT On Cariorespiratory Fitness

From our results, after the 12-week HIIT program, participants in the HIIT group exhibited enhanced endurance during the Bruce exercise stress test. This improvement is clearly reflected through an increased exercise test time of 72.33±82.15 seconds and a higher peak heart rate (HRpeak) of 191.00±9.57 beats per minute when compared to the control group. This reflects that the HIIT program can improve cardiorespiratory endurance in overweight and obese individuals. A systematic review was conducted, encompassing fifteen randomized controlled trials (RCTs) that included VO_2max as an outcome parameter. The findings indicate that HIIT exhibited significantly greater effectiveness in improving VO_2max when compared to traditional exercise (Mean Difference: 1.83, 95% Confidence Interval: 0.70-2.96) (Türk et al., 2017). Primary mechanisms underlying HIIT-Induced Cardiac Fitness improvement in obesity is HIIT mitigates cardiac metabolic dysfunction and

remodeling caused by obesity through several fundamental mechanisms, including enhancements in mitigating lipotoxicity, optimizing glucose metabolism, reducing inflammation, and alleviating endoplasmic reticulum (ER) stress (Bo et al., 2023).

2.4 Effect of Asparagus Root Supplementation on Body Composition

Ecdysteroids are widely promoted to athletes as dietary supplements, with claims of enhancing strength and muscle mass during resistance training and reducing fatigue (Isenmann et al., 2019). 20E has been demonstrated to increase protein synthesis in skeletal muscles (V. Syrov, 2000) and can induce muscle hypertrophy with a potency comparable to, or even greater than, that demonstrated by anabolic androgenic steroids, SARMs, or IGF-1 (Parr et al., 2015b). Natural dietary intake of ecdysteroids is typically low, usually less than 1 mg per day, whereas bodybuilders often consume doses as high as 1,000 mg per day (Parr et al., 2015b). However, the participants in Asparagus group did not experience significant changes in weight, BMI, muscle mass, fat-free mass, minerals, or protein levels. According to study of healthy males that 20E administrated with resistance training also found no change of body circumference, muscle strength (B. Denben et al., 2023). These lack of changes observed during the 12-week trial may be attributed to the relatively lower ecdysteroid levels, which might not have been elevated enough to result in noticeable changes when compared to the levels typically used by muscle athletes, such as 1,000 mg/day (Parr et al., 2015b) or 100 mg of 20E per day, as shown to affect muscle mass in previous studies (Isenmann et al., 2019).

2.5 Effect of Asparagus Root Supplementation on Pulmonary Function and Cardiorespiratory Fitness

This is the first study to examine the effects of 20E on pulmonary function in human. According to our findings, the consumption of 90 mg/day of 20E in isolation resulted in an enhancement of pulmonary function, as evidenced by an improvement in $FEV_1/FEV_{\%predicted}$. This improvement suggests a potential enhancement in bronchial ventilation, possibly through increased respiratory muscle strength or a reduction in airway constriction associated with chronic inflammation. Therefore, further research is needed to explain the related mechanism.

Most studied of cardiorespiratory fitness changed by 20E had been done in rats. For instance, animals administered ecdysteroids for one week exhibited

significantly longer swimming times (Azizov & Seĭfulla, 1998). These effects bear resemblance to those induced by anabolic steroids. Additionally, 20E has been shown to enhance muscle ATP content in vitamin D-deprived rats (Kholodova Iu, Tugaĭ, & Zimina, 1997). 20E indeed promotes muscle growth, provided that there is an adequate protein supply. These anabolic effects lead to increased physical performance even without training (Lafont & Dinan, 2003). Nonetheless, this study had initiated an investigation into the impact of 20E on cardiopulmonary fitness in humans. The findings indicate that the consumption of 20E alone did not result in any changes in cardiopulmonary fitness.

3. Limitattions of the Study

3.1 This study observed a trend of muscle mass increase in the arms and abdomen among participants in both the Asparagus groupr and the HIIT group. Consequently, future research should consider incorporating assessments of muscle size and skeletal angles, as well as measuring strength in the arm and leg muscles, to validate these changes.

3.2 This study did not investigate alterations in the autonomic nervous system and vascular function that could potentially occur after exercise. Such changes can often be observed through variations in partial oxygen saturation. Therefore, in future studies, it is recommended to incorporate measurements of changes in the autonomic nervous system, such as heart rate variability and blood pressure variability, as well as assessments of blood vessel function, including endothelial function.

3.3 The assessment of patients' dietary changes during the intervention period relied on self-reported food records. While these self-reported measures might be susceptible to certain biases, such as social desirability or lapses in memory.

4. Clinical Implication

Utilizing high-intensity interval training in conjunction with the consumption of asparagus root extract supplement is a safe and available option for individuals who are overweight or obese. This regimen can effectively support immune system, diminish inflammatory responses and oxidative stress, as well as lower blood lipid levels and reduce upper-body fat. Furthermore, it has the potential to enhance

respiratory muscle strength, augment lung capacity, and improve exercise endurance. This holistic approach might serve as a preventive against cardiovascular diseases, dyslipidemia and respiratory disorders. However, we are aware of some potential limitations of our study.

5. Benefits from this study

5.1 This study provides additional data on health benefits of asparagus root which increases value of this vegetable, at least in terms of supplementary product development.

5.2 This study provides additional data on health benefits of HIIT as exercise therapy for overweight and obese people.

6. Conclusion

Participating in high-intensity interval exercise with Tabata protrocol while consuming asparagus root extract for 12 weeks resulted in a decrease in eosinophil white blood cells, reduced inflammation in the body, decreased oxidative stress, decreased Cholesterol/HDL ratio, and a reduced LDL/HDL ratio. It also led to an increased blood sugar, a reduced waist-hip ratio, enhanced strength of the exhaling muscles, and increased lung capacity through forceful exhalation. Additionally, there were no changes in lung volume. It also enhances the exercise endurance and VO_2peak of overweight and obesity.

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APPENDICES

1. Ethical Approved

สำเนา

ที่ IRB3-038/2565

เอกสารรับรองผลการพิจารณาจริยธรรมการวิจัยในมนุษย์
มหาวิทยาลัยบูรพา

คณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยบูรพา ได้พิจารณาโครงการวิจัย

รหัสโครงการวิจัย : G-HS018/2565

โครงการวิจัยเรื่อง : ผลของการออกกำลังกายแบบหนักสลับเบาและการบริโภคสารสกัดจากโคนหน่อไม้ฝรั่งต่อตัวชี้วัดทางชีวภาพของสุขภาพและโรคทางระบบหัวใจและหลอดเลือด และสมรรถภาพของหัวใจและปอดในอาสาสมัครที่มีน้ำหนักเกินและอ้วน

หัวหน้าโครงการวิจัย : นางสาวทัศวิญา พัดเกาะ

หน่วยงานที่สังกัด : คณะสหเวชศาสตร์

อาจารย์ที่ปรึกษาโครงการหลัก (สารนิพนธ์/ งานนิพนธ์/ วิทยานิพนธ์/ ดุษฎีนิพนธ์) : รองศาสตราจารย์ ดร.ปิยะพงษ์ ประเสริฐศรี

หน่วยงานที่สังกัด : คณะสหเวชศาสตร์

วิธีพิจารณา : ☐ Exemption Determination ☐ Expedited Reviews ☑ Full Board

คณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยบูรพา ได้พิจารณาแล้วเห็นว่า โครงการวิจัยดังกล่าวเป็นไปตามหลักการของจริยธรรมการวิจัยในมนุษย์ โดยที่ผู้วิจัยเคารพสิทธิและศักดิ์ศรีในความเป็นมนุษย์ไม่มีการล่วงละเมิดสิทธิ สวัสดิภาพ และไม่ก่อให้เกิดภยันตรายแก่ตัวอย่างการวิจัยและผู้เข้าร่วมโครงการวิจัย

จึงเห็นสมควรให้ดำเนินการวิจัยในขอบข่ายของโครงการวิจัยที่เสนอได้ (ดูตามเอกสารตรวจสอบ)

1. แบบเสนอเพื่อขอรับการพิจารณาจริยธรรมการวิจัยในมนุษย์ ฉบับที่ 2 วันที่ 18 เดือน พฤษภาคม พ.ศ. 2565
2. เอกสารโครงการวิจัยฉบับภาษาไทย ฉบับที่ 1 วันที่ 21 เดือน เมษายน พ.ศ. 2565
3. เอกสารชี้แจงผู้เข้าร่วมโครงการวิจัย ฉบับที่ 2 วันที่ 18 เดือน พฤษภาคม พ.ศ. 2565
4. เอกสารแสดงความยินยอมของผู้เข้าร่วมโครงการวิจัย ฉบับที่ 1 วันที่ 21 เดือน เมษายน พ.ศ. 2565
5. เอกสารแสดงรายละเอียดเครื่องมือที่ใช้ในการวิจัย ฉบับที่ 2 วันที่ 18 เดือน พฤษภาคม พ.ศ. 2565
6. เอกสารอื่น ๆ (ถ้ามี)

6.1 คู่มือการออกกำลังกายแบบหนักสลับเบาที่บ้าน ฉบับที่ 1 วันที่ 21 เดือน เมษายน พ.ศ. 2565

6.2 ประกาศประชาสัมพันธ์เชิญชวนเข้าร่วมโครงการวิจัย ฉบับที่ 1 วันที่ 21 เดือน เมษายน พ.ศ. 2565

วันที่รับรอง : วันที่ 24 เดือน พฤษภาคม พ.ศ. 2565

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สำเนา

ลงนาม *นางสาววรมร แย้มประทุม*

(นางสาววรมร แย้มประทุม)

ประธานคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยบูรพา

ชุดที่ 3 (กลุ่มคลินิก/ วิทยาศาสตร์สุขภาพ/ วิทยาศาสตร์และเทคโนโลยี)

2. Research publication

Padkao, T., & Presertsri, P. (2023, June 19–23). High-intensity Interval Training Combined with Asparagus Root Supplement Can Improve Lipid Profiles, Waist-hip Circumference and Pulmonary Function in People with Overweight and Obesity (EP43). Paper presented at the Siriraj International Conference of Medicine and Public Health, Mahidol University, Bangkok, Thailand.

Padkao, T., & Prasertsri, P. (2025). The Impact of Modified Tabata Training on Segmental Fat Accumulation, Muscle Mass, Muscle Thickness, and Physical and Cardiorespiratory Fitness in Overweight and Obese Participants: A Randomized Control Trial. Sports (Basel, Switzerland), 13(4), 99. https://doi.org/10.3390/sports13040099

Padkao, T., & Prasertsri, P. (2025). Effects of High-Intensity Intermittent Training Combined with Asparagus officinalis Extract Supplementation on Cardiovascular and Pulmonary Function Parameters in Obese and Overweight Individuals: A Randomized Control Trial. Journal of Functional Morphology and Kinesiology, 10(2), 202. https://doi.org/10.3390/jfmk10020202

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