T.C.
YEDİTEPEUNIVERSITY
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INVESTIGATION OF OBESOGENIC EFFECTS OF ALDRIN, ENDOSULFAN AND LINDANE IN MALE RAT MODEL

MASTER THESIS

NADA ABDELHAMID MOHAMED BOUJANAH

İSTANBUL-2025

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This thesis has been deemed bythe jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated.....and numbered .....

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Nada AbdelHamid Mohamed Boujanah

DEDICATION

I dedicate this thesis to myhusband...

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SYMBOLS AND ABBREVIATIONS

AHR:	Aryl hydrocarbon/dioxin receptor
ALP:	Alkaline phosphatase
ALT:	Alanine transaminase
AR:	Androgen receptor
AST:	Aspartate transaminase
BMI:	Body mass index
DDE	P,p-dichlorodiphenyldichloroethylene
DHT:	Dihydrotestosterone
EDCs:	Endocrine disrupting chemicals
ER	Estrogen receptor
FNDC5:	Fibronectin type III domain-containing protein 5
NCDs:	Noncommunicable diseases
PCBs:	Polychlorinated biphenyls
PGC-1α:	PPAR-γ coactivator 1-alpha
POPs:	Persistent organochlorine pollutants
PPARs:	Peroxisome proliferator-activated receptors
RXR:	Retinoid X receptor
T2D:	Type 2 diabetes
TBT:	Tributyltin
WHO:	World Health Organization

ABSTRACT

Boujanah, N. (2025) Investigation of Obesogenic Effects of Aldrin, Endosulfan and Lindane in Male Rat Model, Yeditepe University, Institute of Health Sciences, Department of Physiology, MSc thesis, İstanbul.

Obesity has become an internationally prevalent public health issue. According to recent studies, certain environmental contaminants may have obesogenic consequences. Adipogenesis is influenced by the genes for uncoupling protein-1 (UCP1) and peroxisome proliferator activating receptor gamma (Pparγ). These Genes are significantly manifest in both brown and white adipose tissue (WAT and BAT). The purpose of this study was to examine the obesogenic effects of Lindane, Endosulfan, and Aldrin. The control, Lindane, Aldrin, and Endosulfan groups were the four randomly selected groups of thirty-two adult male Sprague-Dawley rats. The animals received oral gavages of organochlorine pesticides (OCPs; 1 mg/kg) dissolved in corn oil every other day for four weeks. The controls only received the vehicle. During the studies, the animals' body weights were measured. Following the animals' decapitation, BAT and WAT samples were collected to measure Pparγ and UCP1 levels. Serum samples were collected to measure levels of liver enzymes, levels of triglycerides and cholesterol serum. The Control Group maintained normal physiological and biochemical parameters, serving as a baseline for comparison. Results indicated that Lindane and Aldrin led to significant weight gain, particularly in the later stages of the study, suggesting compensatory metabolic responses. Endosulfan resulted in more subtle weight gain, Biochemical analysis revealed significant reductions in HDL and total cholesterol in the Endosulfan group, indicating disrupted lipid metabolism. Liver enzyme analysis showed hepatotoxicity, with Endosulfan causing the most pronounced liver dysfunction. Gene expression analysis in adipose tissues revealed reduced UCP3 expression in (WAT) in the Endosulfan group, indicating impaired thermogenesis, while Aldrin exhibited increased PPARG expression in (BAT), suggesting a shift toward lipid accumulation. Overall, these results imply that pesticide exposure could be a factor in obesity through both direct mechanisms, such as disrupted thermogenesis and lipid metabolism, and indirect mechanisms, such as liver dysfunction. Further research is necessary to understand the long-term effects of these pesticides on metabolic health

Keywords: Adipogenesis, Aldrin, Endosulfan, Lindane, Obesogen, liver enzymes.

ÖZET

Boujanah, N. (2025) Aldrin, Endosulfan ve Lindan'ın Erkek Sıçan Modelinde Obeziteye Neden Olan Etkilerinin Araştırılması, Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Fizyoloji Anabilim Dalı, Yüksek Lisans Tezi, İstanbul.

Obezite, uluslararası düzeyde yaygın bir halk sağlığı sorunu haline gelmiştir. Son yıllarda yapılan çalışmalara göre, bazı çevresel kirleticilerin obeziteye neden olan etkileri olabileceği öne sürülmüştür. Adipogenez, esas olarak ayrışma proteini-1 (UCP1) ve peroksizom proliferatörle aktive olan reseptör gama (Pparγ) genleri tarafından etkilenir. Bu genler, kahverengi ve beyaz yağ dokularında (BAT ve WAT) önemli derecede ifade edilmektedir. Bu çalışmanın amacı, Lindan, Endosulfan ve Aldrin'in obeziteye neden olan etkilerini incelemektir.Çalışmada otuz iki yetişkin erkek Sprague-Dawley sıçanı rastgele olarak dört gruba ayrılmıştır: kontrol, Lindan, Aldrin ve Endosulfan grupları. Hayvanlara, her iki günde bir, dört hafta boyunca mısır yağı içinde çözülmüş 1 mg/kg dozunda organoklorin pestisitler (OCP'ler) oral yolla verilmiştir. Kontrol grubuna yalnızca taşıyıcı verilmiştir. Çalışma süresince hayvanların vücut ağırlıkları ölçülmüş, deney sonunda BAT ve WAT örnekleri alınarak Pparγ ve UCP1 seviyeleri ölçülmüştür. Serum örneklerinde karaciğer enzimleri, serum kolesterol ve trigliserit seviyeleri analiz edilmiştir.Kontrol grubu, karşılaştırma için referans olarak normal fizyolojik ve biyokimyasal parametrelerini korumuştur. Sonuçlar, özellikle çalışmanın ilerleyen aşamalarında, Lindan ve Aldrin'in anlamlı kilo alımına yol açtığını ve bunun metabolik telafi mekanizmalarını düşündürdüğünü göstermiştir. Endosulfan daha hafif bir kilo artışıyla sonuçlanmıştır. Biyokimyasal analiz, Endosulfan grubunda HDL ve toplam kolesterolde anlamlı düşüşler olduğunu ve lipit metabolizmasının bozulduğunu ortaya koymuştur.Karaciğer enzim analizi, Endosulfan'ın hepatotoksik etkisini belirgin şekilde göstermiştir. Yağ dokularında yapılan gen ekspresyon analizi, Endosulfan grubunda (WAT) UCP3 ekspresyonunda azalma olduğunu ve bunun termogenezde bir bozulmaya işaret ettiğini ortaya koymuştur. Aldrin grubu (BAT) PPARG ekspresyonunu artırmış ve bunun lipit birikimine doğru bir kayma olduğunu düşündürmüştür. Genel olarak bu bulgular, pestisit maruziyetinin hem termogenez ve lipit metabolizmasının bozulması gibi doğrudan mekanizmalar hem de karaciğer fonksiyon bozukluğu gibi dolaylı mekanizmalar yoluyla obeziteye katkıda bulunabileceğini göstermektedir.

Anahtar Kelimeler: Adipogenez, Aldrin, Endosulfan, Lindan, Obezitenin nedeni, karaciğer enzimleri.

1. INTRODUCTIONand PURPOSE

Obesity is a serious health condition marked by the excessive buildup of body fat or its uneven distribution [1]. condition is a significant contributory factor for a number of chronic illnesses, including diabetes, cancer, and cardiovascular diseases (CVDs). Additionally, obesity has detrimental effects on overall health [2]. Globally, the rate of obesity has increased within the past three decades, rendering it a significant public health issue [3]. Excess energy intake compared to energy use is the primary catalyst for increased body weight that subsequently results in metabolic impairment [4]. Research indicates that individuals with obesity exhibit elevated levels of Physical inactivity and sedentary behavior, which are positively correlated with associated health risks [5]. The analysis of obesity trends reveals that leisure-time physical activity increased by 47–120% from 1988 to 2006. However, after adjusting for calorie and macronutrient intake, In comparison to 1988, the anticipated BMI in 2006 was still up to 2.3 kg/m² higher, This indicates that additional factors may be contributing to the rise in BMI levels [6]. energy use is the primary catalyst for increased body weight that subsequently results in metabolic impairment [4]. Recent research indicates that individuals with obesity exhibit elevated levels of sedentary behavior and physical inactivity, which are positively correlated with associated health risks [5]. analysis of obesity trends reveals that leisure-time physical activity increased by 47–120% from 1988 to 2006. However, after adjusting for calorie and macronutrient intake, the expected BMI in 2006 was still up to 2.3 kg/m² higher than in 1988. This indicates that additional factors may be contributing to the rise in BMI levels [6]. Obesogens have been implicated in several theories regarding the rise in the average BMI. These obesogens, a subclass of endocrine-disrupting chemicals (EDCs), change metabolism and promote lipid storage, which raises the risk of weight gain . These compounds can be found in insecticides, cleaning supplies, and materials used to package food and beverages [7]. Obsogens mimic natural hormones, interfering with regular physiological functions as well as leading to detrimental impacts on health health effects. It is essential to understand their impact [7]. These substances' capacity to imitate hormones depends on their shared properties, such as lipophilicity and low molecular weight, with those of natural hormones. An obesogen's capacity to function as a xenohormone is influenced by three crucial factors: the partition stable, half-life, and its molecular weight [7]. Endocrine-disrupting chemicals (EDCs) are a worldwide hazard to Health and the natural environment. They are described as externalsubstances

or mixture of substances that may obstruct any part of hormone activity. [8]. These chemicals are divided into two main categories. The first includes natural phytoestrogens, which are compounds found in fruits, grains, fungi, grasses, herbs, and legumes and are generally less potent than the body's endogenous estrogens. The second category comprises synthetic chemicals, specifically human-made organic compounds containing carbon, hydrogen, nitrogen, and chlorine. These substances can disrupt endocrine function and pose risks to human health [9]. Hazardous materials like insecticides and herbicides can expose both humans and animals to endocrine-disrupting chemicals (EDCs). Eating or drinking tainted food or water can result in further exposure. EDCs are released into the environment through a variety of processes, such as plastic combustion and manufacturing, Understanding the extent of these chemicals' use is essential to creating regulations that will lessen the adverse effects on the environment and public health [9]. Ingestion is the primary way that humans are exposed to EDCs, with inhalation and dermal absorption also playing a role [8]. Endocrine disruption mechanisms involve numerous endocrine- disrupting chemicals (EDCs) that can directly bind to nuclear receptors (NRs) due to their structural similarities with NR ligands. These EDCs can act either as antagonists, preventing the receptor from activating, or as agonists, promoting gene expression [10]. However, (EDCs) can significantly impact the function of various receptors in several ways. First, they can induce receptor degradation, which reduces the overall availability and activity of these receptors within the cell. Second, EDCs can activate signaling pathways such as the aryl hydrocarbon receptor (AhR) pathway. When activated, the AhR can sequester essential co-activators and the aryl hydrocarbon receptor nuclear translocator (ARNT) away from the nuclear receptors (NRs). This action disrupts normal signaling processes that rely on these co-activators, impairing the receptors' functions. Third, Aryl hydrocarbon receptors (AhR) can bind to EDCs, which bind to inhibitory XREs near nuclear response elements (NREs). This binding disrupts the function of NRs by blocking essential co-activators and impairing gene expression. [10]. Additionally, Enzymes that are activated by AhR not only play a role in xenobiotic metabolism but also contribute to the breakdown of substances like steroid hormones. Consequently, the activation of these enzymes can result in a decrease in the levels of endogenous hormones [10]. Research has shown that exposure to endocrine- disrupting chemicals can disrupt neuronal synapse formation, potentially affecting brain function and behavior [9]. Hereditary and environmental factors, including food quantity and

insufficient physical activity, are widely regarded as primary contributors to the metabolic alterations, Recent years have documented that endocrine-disrupting chemicals (EDCs) stimulate adipogenesis and contribute to weight gain. These endocrine- disrupting chemicals (EDCs) have consequently been identified as "obesogens" [8]. Endocrine disrupting chemicals (EDCs) and the term "endocrine disruptor" were the subject of a workshop led by Theo Colborn and colleagues at the start of the 1990s that resulted in a consensus declaration about the outcomes of EDCs on human and environmental health in the Wingspread Statement [8]. Endocrine disruptors were identified by the US Environmental Protection Agency (EPA) in 1996 as an external element that interferes with hormone activities. The synthesis, secretion, transport, binding, action, or elimination of the body's regular hormones—which are responsible for homeostasis, reproduction, development, and manners—are disturbed [8]. medications, Numerous natural and artificial pollutants, including as pesticides, dioxin, compounds that resemble dioxide, polychlorinated biphenyls, plasticizers, and medications, can cause endocrine disruption [8]. Numerous commonplace items, such as plastic bottles, metal food cans, food, toys, cosmetics, pesticides, deter- gents, and flame retardants, can contain endocrine disruptors. Research indicates that when organs and neural systems are developing throughout pregnancy and the initial postpartum phase, endocrine disruptors may be the most dangerous Endocrine disruption is regarded as a significant concern in both health and environmental contexts [8]. Various environmental contaminants, such as polychlorinated biphenyls (PCBs) and organochlorinated pesticides (OCPs), have been identified as having "endocrine disruptor" effects [8]. Persistent organic pollutants cause many human health problems and significant environmental contamination issues. These POPs cause widespread environmental contamination and are linked to many health issues in people. POPs cause congenital disabilities, neurotoxicity, hepatotoxicity, nephrotoxicity, immune system impairment and cancer [8]. Being subjected to these contaminants regularly can cause long-term effects on hormones, metabolic activity, adipose tissue, and ultimately weight. People who are exposed during pregnancy also run the risk of developing obesity in later life [8]. Several EDCs, particularly POPs, are lipophilic and have a history of bioaccumulating body fat. According to research, the more EDCs that are retained in fat, the higher the BMI. Thus, in addition to fat deposition, chronic exposure to POPs is associated with obesity and other illnesses [8]. Recent studies suggest that certain environmental contaminants may

promote obesity. Key factors in fat cell development include uncoupling protein-1 (UCP1) and peroxisome proliferator-activated receptor gamma (PPARγ) in brown andwhite adipose tissues. Additionally, irisin and UCP3 are involved in non-shivering thermogenesis [11]. Results from a study on 23 male adults Sprague-Dawley rats indicate that both DDT and DDE (EDCs) suppress white adipocytes, which reduces the browning of WAT and may cause male rats to become obese. Additionally, alteration in Pparγ and Ucp1 expression in WAT brought on by HCB, DDT, and DDE suggest that adipogenic activity is differently regulated. Furthermore, it appears that these three POPs have no effect on thermoregulation because there is no change in body temperature, weight, or muscle Ucp3 or irisin levels [11]. Recognizing and identifying these obesogens is crucial for global health reform, as obesity is a widespread concern and represents a billion-dollar industry glob

2. LITERATURE REVIEW

2.1. Obesity

2.1.1 Definition and Epidemiology

More than 70% of premature deaths globally are caused by non- communicable diseases (NCDs), which include diabetes mellitus, cancer, and cardiovascular disorders [12]. As a condition that raises the risk of (NCDs), obesity can result in early disability and mortality [12]. Depending on the severity of the condition and any associated diseases, a major risk factor for NCDs is linked to a reduced life expectancy of 5–20 years [12]. A BMI of 30 kg/m2 is considered obese, according to the WHO, obesity is defined as an excessive body fat buildup that could damage health [12]. The prevalence of obesity has risen significantly on a global scale over the past fifty years, now reaching pandemic levels. This increase in obesity rates has been observed across all age groups and genders, regardless of geographic location. [12,13] Approximately one-third of the world's population is thought to be obese or overweight, representing a substantial public health challenge that requires further investigation and intervention [13]. If current trends continue, 3.3 billion individuals worldwide—roughly 57.8% of the adult population—will be overweight or obese by 2030 [14].

2.1.2. Pathogenesis

Obesity typically results from the chronic energy imbalance between too many calories consumed (in our body, this energy originates from the primary important nutrients: carbs, protein, and fat) and too few calories burned [12]. Obesity, however, is a complex and multifaceted illness. Its etiology includes two individual factors such as genetics (during the fetal period), internal signals (between the brain and fatty tissue), and external factors [12,15]. Social determinants, including dietary customs and a sedentary lifestyle, contribute to the prevalence of obesity [12,15]. Three categories of significant genetic variables contribute to obesity: Polygenic obesity, syndromic obesity, and monogenic causes [16]. Monogenic obesity is an uncommon and severe form of early-onset obesity linked to endocrine abnormalities, while environmental factors have less impact, genetics has a major one. The main cause of this type of obesity is gene alterations in the leptin/melanocortin pathway, which controls food intake [17].

Syndromic obesity is a phrase used to describe extreme weight gain along with other phenotypes such as dysmorphic traits, mental difficulties, and developmental defects unique to a particular organ. There are currently over 100 disorders linked to obesity [17]. Polygenic obesity involves both hereditary and environmental variables that contribute to obesity, The combined action of several genes brings it on, the impact of which is enhanced in a setting that encourages gaining weight [16,18]. Over the past decade, many endocrine-disrupting chemicals have been identified as having obesogenic effects. As a result, these substances are referred to as “obesogens.” [8- 19-20].

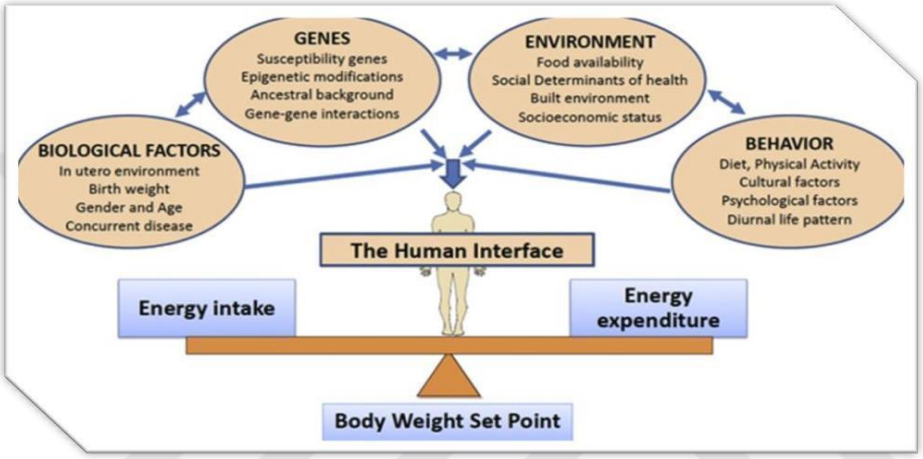

Figure 1. The complex pathophysiology of obesity. Obesity is a complex disease influenced by genetics, environment, biology, and behavior that promotes positive energy balance. Each individual's unique interaction of these factors determines their regulation of energy balance and sets an equilibrium body weight. (Adapted from Garvey WT, 2022) [21].

2.2. Endocrine Disrupting Chemicals and Obesogens

EDCs are a Worldwide concern for the health of people and the environment These incredibly varied chemical substances include pesticides such as chlorinated insecticides, lindane, imidazole, and triazole, pharmaceutical agents, dioxins, bisphenol A, polychlorinated biphenyls (PCB), persistent organic pollutants (POP), plastic compounds, plasticizers, solvents for industry and lubricants and their byproducts, and dioxins [22]. Endocrine disruption is indeed a serious concern for both public health and the environment. According to research, many environmental pollutants have been found as "endocrine disruptor" impacts, Forinstance, organochlorinated pesticides (OCPs) and polychlorinated biphenyls (PCBs) These pollutants are organic and

persistent (POPs) are responsible for causing environmental pollution on a global scale and have been known to pose numerous challenges for human health [8]. globally and are known to present a variety of health risks to people. It is crucial to understand that exposure to (EDCs) can happen in several ways, including by contact with contaminated food, water, soil, or air, or through occupational exposure. Both the ecosystem and human health may suffer greatly because of this exposure [23]. Obesity is a complicated disease with a variety of causes, disabilities, pathophysiology, and comorbidities. It satisfies the definition in medicine of a disease because it is a physiological malfunction of the human body that is influenced by environmental, genetic, and behavioral factors [24]. Recent studies have indicated that aging, food, exercise, and genetics may not be the only factors contributing to metabolic illnesses. The prevalence of weight gain, type 2 diabetes, and other disorders linked to the metabolic syndrome is also influenced by environmental elements [25]. Among these significant environmental influences, EDCs have recently come to light as dangerous substances that can disrupt hormones, particularly those involved in metabolism. Additionally, they are frequently exposed to a variety of consumer products, which can have detrimental impacts on both the environment and human health [26]. these EDCs are known as "obesogens" or "environmental obesogens,"[20-27-28]. It has been suggested that obesogens can promote the development of fat cells (adipogenesis) and lead to an accumulation of lipids in the body. Disruption of lipid homeostasis can occur through various mechanisms and may contribute to the development of metabolic disorders. There are several mechanisms through which thiscan occur, including 1) a rise in the account and size of adipocytes, 2) affecting the development of adipose tissue by altering its endocrine regulation, 3) altering hormones control of appetite, satisfaction and dietary preference,4) altering energy balance and basal metabolic rate to promote calorie storage,5) and altering insulin sensitivity across the body [19].

2.2.1. Persistent Organic Pollutants (POPs)

Long-lasting organic pollutants are long-term surroundings contaminants that can have a detrimental effect on human health [8]. These compounds are lipophilic, can bioaccumulate adipose tissue, and can contaminate the food chain. As a result, these substances may accumulate to excessive levels that could impair several bodily processes. Because POPs may travel great distances and be disseminated globally by air

and ocean currents, they can pose a hazardous threat to the entire planet in addition to local areas [29]. In 2001, the Stockholm Convention mandated the implementation of measures to limit the release of persistent organic pollutants (POPs) into the environment and to minimize their contamination of the food chain to the extent that it is technically practicable and economically viable [30,31]. POPs continue to be detected in environmental and human biological samples even after laws have been passed and implemented [29]. Twelve POPs were named the "dirty dozen" at the Stockholm Convention approximately 20 years ago, and they had serious negative impacts on both the environment and individuals [30,31]. In 2008 and 2014, a list of chemicals was created along with guidelines for their storage and removal [8]. In addition to chemicals used in industry and byproducts, the dirty dozen included PCBs, polychlorinated dibenzofurans, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, toxaphene, aldrin, chlordane, and dichlorodiphenyltrichloroethane (DDT) [30,31]. Persistent organic pollutants (POPs) have become a significant global concern. Extensive experimental and epidemiological studies have investigated their biological and toxic effects, patterns of human exposure, and overall risk assessment [8]. Some of these pollutants, including DDT, polychlorinated biphenyls (PCBs), chlorophenols, and chlorobenzenes, were deliberately manufactured for various commercial applications due to their pesticidal or technical advantages. Additionally, other highly toxic and persistent pollutants, such as polychlorinated dibenzo-p-dioxins and dibenzofurans, have been identified as unintentional byproducts of industrial activities, including chemical manufacturing, waste incineration, chlorine-based pulp and paper bleaching, and certain metallurgical processes [32]. over the last thirty years, analytical evidence has shown that the environment is contaminated worldwide. This is mostly the logical outcome of POPs' physical and molecular characteristics [32]. Reports indicate that these substances exhibit high resistance to both biological and chemical degradation. The long-term persistence of PCBs and other chlorinated contaminants, particularly those with high chlorine content, in soils, water, sediments, and living organisms has been well-documented [32,33]. Additionally, because POPs are nonpolar molecules, they can accumulate in adipose tissues, which increases their abundance at the upper trophic levels of the dietary chain [32]. As humans occupy the top of the food chain, high concentrations of these lipophilic and persistent chemicals are frequently detected in body tissues, including serum, adipose tissue, and breast milk [32]. It is estimated that over 90% of the organochlorine burden in the general population originates from dietary

intake. Furthermore, the level of pollutant exposure is directly related to the quantity and type of food consumed, including fish, animal fats, dairy products, cereals, and vegetables. Extensive research on persistent organic pollutants (POPs) has been conducted across various countries, with efforts underway to identify sources and potential contamination sites [34].A recent analysis suggests that POP exposure is closely associated with type 2 diabetes and may be a risk factor for the development of type 2 diabetes in and of itself, most likely in combination with other risk factors such as obesity [35]. However, long-term alteration of immunological, endocrine, and metabolic system processes is possible with exposure to any kind of POP. Because POPs are strongly associated with type 2 diabetes, metabolic syndrome, and cancer—all of which are closely related to obesity, they are therefore receiving more scientific and public health attention [36]. Even though most POPs were outlawed in the 1970s, people are nevertheless exposed to these substances by consuming meals high in fat because of their elevated lipophilicity and slower metabolic breakdown [37].

2.2.2. Organochlorine Pesticides (OCPs)

Insecticides, herbicides, fungicides, and rodenticides are all considered pesticides. They are primarily categorized based on their 1. chemical structure 2. application demands 3. The intended use or target organism [38]. According to their chemical structure, pesticides can be divided into eleven categories: Organochlorines (such as Lindane, Aldrin, Endosulfan, DDT), Organophosphates (such as Dimefox, Mipafox, Methyl Parathion,Ronnel),Carbamates, Pyrethroids, Phenyl amides, Phenoxyalkonates,Trazines, Benzoic acid, Phtalimides, Dipyrids and Others [38]. Most pesticide classes have the potential to negatively affect human health [39]. OCPs are the most hazardous EDCs due to their lipophilic nature and potential for bioaccumulation, even though other pesticide classes have the potential to have negative health impacts [8]. As indicated above, food consumption and chemicals absorption are the main ways that populations are exposed to pesticides. However, skin absorption and inhalation may be significant OCP exposure pathways [8]. Despite being phased out more than three decades ago, OCPs are still widely dispersed throughout the environment and garner a lot of scientific and regulatory interest due to their bioaccumulation, persistence, and several endocrine-disrupting risks to human health and ecosystems [40]. Certain xenohormones may have anti-estrogenic effects by interacting with AHR and starting the synthesis of cytochrome P450 enzymes that metabolize E2. and having structural parallels

with E2, or estradiol. Epidemiological studies conducted in several nations have discovered residues of the organochlorine pesticide (OCP) in human tissues [41, 42].

OCP levels present in human biological specimens, such as serum, fat tissue, and breast milk, have been demonstrated in numerous epidemiological investigations. This study has also investigated possible correlations with various human illnesses and conditions [8]. OCPs residues have even been found in samples of cord blood [43].

2.2.2.1. ALDRINE

The OCP pesticide Aldrin C12H8Cl6 was widely used until the 1990s, when it was outlawed in most nations. Aldrin belongs to the class of insecticides known as "classic organochlorines"[54]. Before the prohibition, it was extensively used as a pesticide for the treatment of seed and soil. Aldrin and related "cyclodiene" pesticides were identified as POPs [55], it is stable in situations with a pH between 4 and 8 and can be carried through the atmosphere by dust particles [56]. Aldrin has been reported to cause neurotoxicity, adversely affecting nerve cells and potentially resulting in symptoms such as dizziness, headaches, and in severe cases, seizures [57]. When aldrin is released into the environment, it can disperse and accumulate in the air, soil, and water, potentially leading to widespread contamination [58]. Due to the quick change from aldrin to dieldrin and the following delayed degradation of that aldrin, aldrin concentrations are found in plants and the surroundings around the initial exposure [59]. Animals that eat contaminated plants or feed on other animals living in the contaminated water may also contain these quantities. Their Adipose tissue may accumulate significant quantities of contaminants because of this biomagnification process. It is crucial to remember that the central nervous system is the principal site of aldrin and dieldrin's negative effects [58]. High doses of aldrin and dieldrin were found to have neurotoxic effects on rats in animal experiments. Furthermore, a number of investigations have demonstrated that the mouse liver is particularly susceptible to dieldrin-induced hepatocarcinogenicity [60]. It is important to note that there is limited research on the obesogenic effects of aldrin. This underscores the need for further exploration into the potential impact of these substances on human health [61].

2.2.2.2. Endosulfan

Endosulfan $C_9H_6Cl_6O_3S$ (.6,7,8,9,10,10-hexachloro-1,5,5a,6,9ahexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide) is a type of pesticides and acaricide that falls under the category of off-patent OCPs. It is currently in the process of being gradually discontinued on a global scale [62], it has a significant acute toxicity, potential for bioaccumulation, and disruptive impact on the endocrine system. Negotiated under the Stockholm Convention in April 2011, a comprehensive ban on its manufacture and use took effect in mid-2012, with specific exemptions granted for an additional five years [63]. The substance had been utilized in agricultural practices worldwide to manage insect pests such as whiteflies, aphids, leafhoppers, potato beetles and cabbage worms [64]. Endosulfan has been recognized by the Agency for the Registry of Toxic substances and Diseases and the EPA as a possible endocrine disruptor. Insects, animals, and humans are all acutely neurotoxic [65]. in the US population an epidemiological investigation mentioned that OCPs are significantly related to raised levels of triacylglycerol and increase fasting glucose levels [66]. Due to its high molecular weight and lipid solubility, endosulfan has the potential for bioaccumulation in adipose tissue [67].

2.2.2.3. Lindane

is an OCP, also known as HCH γ- isomer [44] used in agriculture as an insecticide also used as a treatment of head and body lice and scabies, in forms of lotion, cream, or shampoo. It is highly recalcitrant and persistent pesticides Although this kind of organochlorine pesticide has been officially stopped to use worldwide, however, it is still prescript in some developing areas in Asia, Africa and Latin America, it is a widespread contaminant in aquatic ecosystems [44,45]**.**Lindane is a toxic substance that may inhibit GABA neurotransmitter activity by engaging within the GABAA receptor-chloride Channel complex through the picrotoxin binding area. In humans, lindane may cause neurotoxicity, hepatoxicity, nephrotoxicity and cancer [46- 47-48]. Large doses of lindane can be fatal, and its most common acute side effects include headache, fainting, and convulsions [49]. The EPA (Environmental Protection Agency) has classified lindane as a probable human carcinogen (B2/C), whereas the International Agency for Recherche on Cancer (IARC) has classified it as carcinogenic to humans (Group 1) [50,51]. the Stockholm Convention lists Lindane in Annex A (elimination), indicating that there is a high probability that lindane will have a

substantial negative impact on humans as well as the environment [52]. Because lindane is lipophilic, it deposits in tissues that are high in lipids. The following tissues are affected by lindane buildup, which is dependent on exposure duration: Adipose tissues, kidney, heart, liver, lungs, brain, muscle, and blood are ranked in order [53]. It has endocrine disruptive qualities, but there are very few investigations into the obesogenic impacts of γ- HCH (Lindane).

2.3. Peroxisome Proliferator-Activated Receptors (PPARs)

Weight gain and, eventually, obesity have been associated with prolonged exposure to EDCs. Nuclear receptors that control lipid homeostasis and adipogenesis, including the retinoid X receptor (RXR) and the peroxisome proliferator-activated receptor, can be bound by triphenyltin chloride and tributyltin chloride [32], [68]. Obesogenic activity can occur at the cellular level because of disrupted endocrine actions that interfere with certain steroid receptors and peroxisome proliferator-activated receptors (PPARs) [8]. As nutrition sensors, PPARs translate signals that regulate cellular bioenergetics and regulate metabolism to stabilize systemic metabolism [69]. It comes in three varieties: PPARα, γ, and δ (sometimes called PPARβ). Additionally, they contain storage or pro-oxidative properties [70]. With the RXR, PPARs can form their own heterodimers. Target gene expression is changed by these heterodimers [7]. Consequently, heterodimers alter the rate at which free fatty acids, eicosanoids, and xenobiotics are metabolized by binding with PPAR sensitive sites and modulating with coactivator and corepressor proteins [70]. Since PPARα and PPARγ are thought to be pharmaceutical targets for obesity treatment and management, they are extremely significant cellular components. Because obesity rates are rising worldwide, it is critical to comprehend how the body's PPAR receptors control metabolism and energy homeostasis [70]. Thiazolidinedione medications have been used to treat insulin- related T2D by targeting PPARγ, which increases insulin sensitivity while also promoting adipogenesis [7]. In the 3T3-L1 cell line, tributyltin induces preadipocytes to grow into adipocytes, enhances obesity, and lowers metabolic processes in rats by boosting PPARγ [8]. According to reports, several EDCs may change adipogenesis by disrupting the activity of PPAR-γ. They control adipocyte differentiation, reproduction, and lipid inflow. Certain EDCs alter gene expression and bind to specific nuclear receptors, which encourages fat [8]. The PPARγ/RXR heterodimer may be activated by a variety of obesogens via distinct methods. To comprehend the underlying molecules

pathways, research on the obesogenic effects of EDCs is crucial. An understanding of how obesogens affect the PPARγ/RXR heterodimer could be helpful in removing obesogenic impacts [7].

2.4. Aryl Hydrocarbon/dioxin Receptor (AHR) Pathway and Adipogenesis

The aryl hydrocarbon/dioxin receptor (AHR), a related transcription factor, inhibits environmental pollutants. AHR has been shown to be important in a number of tissues and cells in recent decades [71 In rats, obesity and fatty liver disease have been shown to decrease when the AHR pathway is inhibited [72] It is well recognized that LDLs can trigger AHR signaling [72]. Fats are the source of LDLs, which are carried by the blood. Apolipoprotein B protein, 50–60 accessory proteins, and approximately 5,000 fat molecules make up the lipoprotein particle in LDLs. These molecules include triglycerides, phospholipids, and cholesterol [72]. Many labs have investigated the formation of adipogenesis extensively using 3T3-L1 cells as an in vitro system [73]. Once quiescent, confluent cells can proliferate further because to the related hormonal actions of insulin (IDM), the phosphodiesterase inhibitor isobutyl methylxanthine, and the glucocorticoid dexamethasone [73]. That is causing growth to stop irreversibly, and then the same genes are stimulated in adipocytes in vivo.m [73]. Serial increases in C/EBPβ, C/EBPα, and PPARγ promote the changes in gene expression, which include the transient appearance of c-myc and c-jun [73]. PPARγ-activating medications, like the thiazolidinedione BRL-49653, intensify the effects of hormonal mix IDM. These medications are necessary for MEF cells like 10T1/2 to stimulate adipogenesis [73]. In animals, 2,3,7,8- Tetrachlorodibenzo-p-dioxin can cause diabetes symptoms, including decreased glucose absorption in the adipose tissues, and reroute triglycerides from adipose tissue to the liver. It has been demonstrated that TCDD decreases the activity of several adipogenic genes [73]. AHR may modify PPAR-γ expression, which in turn may impact adipogenesis.The current study examined the obesogenic effects of long-term exposure to ALDRIN, ENDOSULFAN, and LINDANE in a male rat model by examining adipogenesis, UCP1 levels, and Pparγ in brown and white adipose tissues.

3. MATERIALS and METHODS

3.1. Animals

Thirty-one adult male Sprague-Dawley rats were utilized in this study. The animals had unrestricted access to water and were provided with standard rat chow. Housing conditions were maintained at the Yeditepe University Medical School Experimental Research Centre (YÜDETAM), where they were kept under a 12-hour light/dark cycle, a controlled temperature of 21±2°C, and a relative humidity of 50±10%. The rats were acclimatized to these conditions for a period of four weeks. All experimental procedures involving animals were approved by the Yeditepe University Ethics Committee for Animal Research.

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3.2. Experimental Groups and Administration of the Drugs

Aldrin, endosulfan, and lindane were procured from Sigma-Aldrich and dissolved in corn oil. The animals were randomly assigned to four groups (n = 8 per group). Each experimental group received 1 mg/kg of the respective organochlorine pesticides (OCPs) via oral gavage, administered every other day for a duration of four weeks. The control group received only corn oil through oral gavage. Body weight measurements were recorded weekly. At the end of the four-week exposure period, all animals were euthanized by decapitation. Blood samples were collected via cardiac puncture, and serum was separated and stored at -80ºC for subsequent analysis. Additionally, white adipose tissue (WAT) and brown adipose tissue (BAT) samples were harvested and preserved at -80ºC for quantitative real-time polymerase chain reaction (qRT-PCR) analysis.

3.3. RNA Isolation, cDNA Synthesis, and Gene Expression Analysis

To assess gene expression, white adipose tissue (WAT), brown adipose tissue (BAT), and skeletal muscle samples were thawed on ice and homogenized in TRI Reagent using the TRI Bullet Blender X24 (NextAdvance), following the manufacturer's guidelines. Total RNA was extracted using the DirectZol™ RNA MiniPrep Plus kit (Zymo Research, R2072) in accordance with the supplier's protocol. To eliminate genomic DNA contamination, a DNase treatment was performed as specified by the same manufacturer. RNA concentrations were measured, and equal amounts (50–100 ng) were used for complementary DNA (cDNA) synthesis via the iScript™ cDNA

Synthesis Kit (Bio-Rad, 1708891), which contained a mix of random primers and oligo(dT), strictly following the provided instructions.Specific primers targeting Pparγ, Irisin, Ucp1, and Ucp3, along with the reference gene β-Actin, were designed using Primer3web (version 4.1.0) [Primer3web, (https://primer3.ut.ee/)]. Final primer concentrations were standardized at 250 nM per reaction. The sequences for β-Actin (Oligomer Biotechnology, Turkey), Ucp1 (Sentebiolab, Turkey), Ucp3 (Oligomer Biotechnology, Turkey), Irisin (Oligomer Biotechnology, Turkey), and Pparγ (Sentebiolab, Turkey) are provided in Table 1. Quantitative real-time PCR (qRT-PCR) was carried out using SsoAdvanced™ Universal SYBR® Green Supermix on the CFX96 Touch Real-Time PCR Detection System (Bio-Rad, 1725270). Primer specificity was confirmed by analyzing melting curves to ensure single peaks and the absence of primer dimerization. The thermal cycling conditions, applied uniformly across all reactions, are detailed in Table 2. Relative gene expression levels were normalized to the control group and calculated using the 2^-ΔΔCT method.

3.4. Statistical Analysis

Statistical analyses were performed using SPSS version 29 (Statistical Package for the Social Sciences). Data are expressed as means ± standard deviation (SD). The Kolmogorov-Smirnov test was applied to evaluate the normality of data distribution. Outliers were identified and excluded using the ROUT method, with a significance threshold set at Q = 1%. Group comparisons were conducted using One-Way Analysis of Variance (ANOVA), followed by post-hoc analyses utilizing the Least Significant Difference (LSD) test to assess differences between study groups.

4. RESULTS

4.1. Body Weight

Over the course of the trial, the Control Group's weight increased steadily and consistently. In contrast, the Lindane Group showed a gradual increase, with a marked rise in the fourth week. The Aldrin Group revealed a significant increase in weight during the 4th Week, while the Endosulfan Group showed a slight increase across the observation period. These findings suggest varying patterns of weight change among the different treatment groups. (Figure 2).

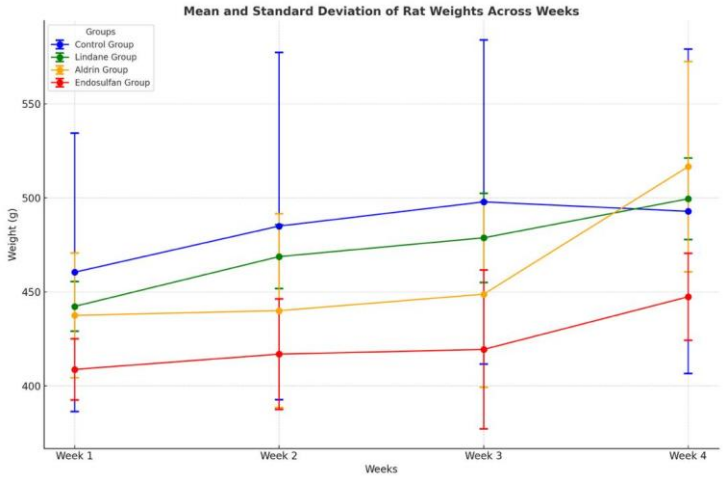

Figure 2. Bodyweight and measurements ofthe animals throughout the experimental period.

4.2. Serum Cholesterol and Triglyceride level

Statistical analysis using ANOVA revealed significant differences among groups for CHO2I ($F = 4.608$, $p = 0.010$) and HDLC4 ($F = 5.838$, $p = 0.003$), In contrast, no significant differences were observed for TRIGL ($p = 0.115$), VLDL ($p = 0.126$), or LDLH ($p = 0.099$), suggesting that these variables were less affected by the treatments. Notably, the Endosulfan Group exhibited the lowest mean values for most parameters (Table1)

Table1. Anova Test Results for Group Differences Serum lipid profile result

Variable	Group	Mean	Std. Deviation	F	p-value
CHO2I (mg/d)	Control Group	74.714	10.579	4.608	0.010**
	Lindane Group	76.375	5.999		
	Aldrin Group	74.750	5.418		
	Endosulfan Group	63.625	8.280		
TRIGL (mg/d)	Control Group	143.00	64.748	2.169	0.115
	Lindane Group	124.625	28.081		
	Aldrin Group	114.375	39.950		
	Endosulfan Group	90.625	20.805		
HDLC4 (mg/d)	Control Group	49.429	7.871	5.838	0.003**
	Lindane Group	49.625	5.630		
	Aldrin Group	47.625	4.534		
	Endosulfan Group	38.375	6.545		
VLDL (mg/dl)	Control Group	26.007	13.074	2.086	0.126
	Lindane Group	24.263	5.132		
	Aldrin Group	21.786	7.413		
	Endosulfan Group	17.719	4.118		
LDLH (mg/d)	Control Group	-3.286	11.715	2.310	0.099
	Lindane Group	2.000	5.345		
	Aldrin Group	4.250	7.797		
	Endosulfan Group	7.125	5.718		

** ($p < 0.01$) Highly significant, *** ($p < 0.001$), and *($p < 0.05$) statistically significant TRIGL (triglycerides), HDLC4 (high-density lipoprotein cholesterol), VLDL (very low-density lipoprotein), LDLH (low-density lipoprotein cholesterol), CH2OI (total cholesterol levels), and Std = standard deviation is all extremely crucial.

4.2.1 Comparative Analysis of CHO2I and HDLC4 Levels in Response to Lindane, Aldrin, and Endosulfan Exposure: A Statistical Evaluation of Metabolic Marker Variations

The statistical analysis identified significant differences in CHO_2I (mg/dL) and $HDLC_4$ (mg/dL) levels among the experimental groups in comparison to the control group. Notably, the Endosulfan Group demonstrated significantly elevated CHO_2I and $HDLC_4$ levels relative to the Control Group ($p = 0.010$ and $p = 0.002$, respectively), as well as in comparison to the Lindane Group ($p = 0.003$ and $p = 0.001$) and the Aldrin Group ($p = 0.008$ and $p = 0.006$). Conversely, no statistically significant differences were detected between the Control Group and either the Lindane or Aldrin Groups for these parameters ($p > 0.05$), suggesting that Lindane and Aldrin may exert minimal or negligible effects on CHO_2I and $HDLC_4$ levels under the given experimental conditions (Table 2).

Table 2. Post-Hoc Test Results for Differences Between Groups in Blood Lipid Analysis

Dependent Variable	Comparison	Mean Difference	p-value(Sig.)
CHO2I(mg/dL)	Control Group vs. Lindane Group+	-1.66071	0.681
	Control Group vs. Aldrin Group	-0.03571	0.993
	Control Group vs. Endosulfan Group	11.08929*	0.010**
	Lindane Group vs. Control Group	1.66071	0.681
	Lindane Group vs. Aldrin Group	1.62500	0.677
	Lindane Group vs. Endosulfan Group	12.75000*	0.003**
	Aldrin Group vs. Control Group	0.03571	0.993
	Aldrin Group vs. Lindane Group	-1.62500	0.677
	Aldrin Group vs. Endosulfan Group	11.12500*	0.008**
	Endosulfan Group vs. Control Group	-11.08929*	0.010**
	Endosulfan Group vs. Lindane Group	-12.75000*	0.003**
	Endosulfan Group vs. Aldrin Group	-11.12500*	0.008**

HDLC4 (mg/dL)	Control Group vs. Lindane Group	-0.19643	0.952
	Control Group vs. Aldrin Group	1.80357	0.579
	Control Group vs. Endosulfan Group	11.05357*	0.002**
	Lindane Group vs. Control Group	0.19643	0.952
	Lindane Group vs. Aldrin Group	2.00000	0.524
	Lindane Group vs. Endosulfan Group	11.25000*	0.001***
	Aldrin Group vs. Control Group	-1.80357	0.579
	Aldrin Group vs. Lindane Group	-2.00000	0.524
	Aldrin Group vs. Endosulfan Group	9.25000*	0.006**
	Endosulfan Group vs. Control Group	-11.05357*	0.002**
	Endosulfan Group vs. Lindane Group	-11.25000*	0.001***
	Endosulfan Group vs. Aldrin Group	-9.25000*	0.006**

** ($p < 0.01$) Highly significant, *** ($p < 0.001$), and *($p < 0.05$) statistically significant TRIGL (triglycerides), HDLC4 (high-density lipoprotein cholesterol), VLDL (very low-density lipoprotein), LDLH (low-density lipoprotein cholesterol), CH2OI (total cholesterol levels), and Std = standard deviation is all extremely crucial.

4.3. Liver enzyme results, ALT, AST, ALP

Endosulfan observed significantly increased the ALT and AST levels with reduced ALP levels ***(p<0.001). On the other hand, Lindane and Aldrin represent marked significantly reduced levels of ALP ***(p<0.001). Furthermore, the control group showed the greatest ALP levels in contrast to the various other groups, while the aldrin group had reduced levels of all enzymes compared to the other groups, P-value for liver enzymes test was statistically significant ***(<0.001) across all the studied substances (Table 3).

Table 3. Anova Test Results for Group Differences (I) Liver enzymes test result with Mean ± Std dev,

Group	ALT (U/L)	AST (U/L)	ALP (U/L)
Control	64.547 ± 11.518	187.598 ± 189.638	229.109 ± 88.162
Lindane	63.375 ± 8.400	124.000 ± 29.962	155.125 ± 28.155
Aldrin	57.625 ± 4.438	137.875 ± 70.972	180.750 ± 28.155
Endosulfan	73.281 ± 8.854	313.062 ± 147.352	168.966 ± 34.571

** (p < 0.01), * (p <0.05) statistically significant, ALT -(alanine aminotransferase), AST -(aspartate aminotransferase), and ALP (alkaline phosphates) Very important, *** (p < 0.001) Significantly important, Std = the standard

4.3.1. Pairwise Comparisonsof LiverEnzyme Levels (ALT, AST, ALP) Among Control, Lindane, Aldrin, and Endosulfan Treatment Groups

For ALT (U/L), there were no discernible variations between the Control and Lindane, Aldrin, or Endosulfan groups, but Endosulfan significantly differed from Lindane *(p = 0.024) and Aldrin ***(p < 0.001). For AST (U/L), the Control group showed no significant differences compared to Lindane or Aldrin but had significantly lower levels than Endosulfan ***(p = 0.001), with Endosulfan also significantly differing from Lindane and Aldrin (p < 0.001 for both). For ALP (U/L), the Control group had significantly higher levels than Lindane **(p = 0.007), Aldrin *(p = 0.046), and Endosulfan *(p = 0.025), though no significant differences were found among the treatment groups (Table 5).

Table 4. Post Hoc Analysis of Pairwise Group Comparisons in Liver Enzyme Levels (ALT, AST, ALP) Across Experimental Treatments

Dependent Variable	Comparison	Mean Difference	Standard Error (SE)	p-value (Sig.)	Significance
ALT (U/L)	Controlvs. Lindane	2.054	4.478	0.650	Not Significant
	Controlvs. Aldrin	7.804	4.478	0.093	Not Significant
	Controlvs. Endosulfan	-8.321	4.478	0.074	Not Significant
	Lindane vs. Aldrin	5.750	4.326	0.195	Not Significant
	Lindane vs. Endosulfan	-10.375	4.326	0.024*	**Significant**
	Aldrin vs. Endosulfan	-16.125	4.326	<0.001***	**Significant**
AST(U/L)	Controlvs. Lindane	22.857	54.325	0.677	Not Significant
	Controlvs. Aldrin	8.982	54.325	0.870	Not Significant
	Controlvs. Endosulfan	-198.768	54.325	0.001***	**Significant**
	Lindane vs. Aldrin	-13.875	52.483	0.794	Not Significant
	Lindane vs. Endosulfan	-221.625	52.483	<0.001***	**Significant**
	Aldrin vs. Endosulfan	-207.750	52.483	<0.001***	**Significant**

	Comparison	Mean Difference	Standard Error (SE)	p-value (Sig.)	Significance
ALP(U/L)	Control vs. Endosulfan	72.571	30.496	0.025*	**Significant**
	Lindane vs. Aldrin	-25.625	29.462	0.392	Not Significant
	Lindane vs. Endosulfan	-16.875	29.462	0.572	Not Significant
	Aldrin vs. Endosulfan	8.750	29.462	0.769	Not Significant
	Control vs. Lindane	89.446	30.496	0.007**	**Significant**
	Control vs. Aldrin	63.821	30.496	0.046*	**Significant**

** ($p < 0.01$), * ($p < 0.05$) statistically significant, ALT -(alanine aminotransferase), AST -(aspartate aminotransferase), and ALP (alkaline phosphates) Very important, *** ($p < 0.001$) Significantly important, Std = the standard

4.4. Pparγ , UCP1, UCP3 and FDNC5 levels in WAT and BAT

Statistical analysis using ANOVA revealed no significant differences in PPARG, UCP1, and FDNC5 expression between the groups ($p > 0.05$). Nevertheless, UCP3 demonstrated notable variation* ($p = 0.0379$), indicating differential expression across groups. These results suggest that the treatments may specifically influence UCP3. on the other hand, the Significant differences were observed brown adipose tissue. for PPARG *($p = 0.048$) and UCP1 **($p = 0.0011$), indicating that these compounds may modulate adipogenesis and thermogenic pathways. In contrast, no significant effects were detected for FDNC5 ($p = 0.0709$) or UCP3 ($p = 0.0636$). Notably, Aldrin exhibited unusually high mean values for PPARG and FDNC5(Table 6)

Table 5. ANOVA Analysis of Lindane, Aldrin, and Endosulfan Effects on PPARG, UCP1, FDNC5, and UCP3 in White and brown Adipose Tissues

Marker	Tissue Type	Group	Mean ± SD	F-Statistic	p-value	Result
PPARG	White	Control	1.01 ± 0.22	0.6124	0.6136	No significant differences
		Lindane	1.14 ± 0.28			
		Aldrin	1.05 ± 0.23			
		Endosulfan	0.95 ± 0.33			
	Brown	Control	1.43 ± 0.99	3.1145	0.0480*	Significant differences
		Lindane	0.89 ± 0.55			
		Aldrin	896.27 ± 1229.85			
		Endosulfan	1.22 ± 0.43			
UCP1	White	Control	1.12 ± 0.61	0.9762	0.4218	No significant differences
		Lindane	1.40 ± 0.79			
		Aldrin	1.61 ± 0.71			
		Endosulfan	1.06 ± 0.29			
	Brown	Control	1.07 ± 0.75	7.5690	0.0011**	Significant differences
		Lindane	1.46 ± 0.77			
		Aldrin	3.04 ± 0.57			
		Endosulfan	4.19 ± 2.43			
FDNC5	White	Control	1.53 ± 1.65	0.4327	0.7317	No significant differences
		Lindane	2.13 ± 1.86			
		Aldrin	1.55 ± 0.90			
		Endosulfan	1.29 ± 0.68			
	Brown	Control	1.20 ± 0.79	2.6765	0.0709	No significant differences
		Lindane	0.96 ± 0.43			
		Aldrin	6.45 ± 8.76			
		Endosulfan	0.50 ± 0.43			
UCP3	White	Control	1.22 ± 0.89	3.2907	0.0379*	Significant differences
		Lindane	1.40 ± 0.93			
		Aldrin	0.61 ± 0.29			
		Endosulfan	0.46 ± 0.17			
	Brown	Control	1.33 ± 0.95	2.8038	0.0636	No significant differences
		Lindane	0.48 ± 0.18			
		Aldrin	8.56 ± 11.49			
		Endosulfan	0.67 ± 0.63			

* ($p < 0.05$), FDNC5 (Fibronectin Type III Domain Containing 5), UCP1 (Uncoupling Protein 1), PPARG (peroxisome. Proliferator-Activated Receptor Gamma), and UCP3 (Uncoupling Protein 3) * ($p < 0.01$) is statistically significant. Significantly important, *** ($p < 0.001$) Significantly important, Std = the standard.

4.4.1 Comparison of Gene Expression Levels (PPARG, UCP1, FDNC5, UCP3) Across Treatment Groups (Lindane, Aldrin, Endosulfan) and Control Using LSD Test

The results show no variations in the mean expression levels . For PPARG, the mean differences ranged from -0.0643 to 0.1254, with p-values between 0.3751 and 0.7668. Similarly, for UCP1, mean differences varied from -0.0675 to 0.4816, with p-values ranging from 0.2239 to 0.8018. FDNC5 exhibited mean differences from - 0.2422 to 0.0193, with p-values between 0.7317 and 0.9793. UCP3 demonstrated mean differences from -0.7626 to 0.1754, with p-values ranging from 0.0652 to 0.7254. None of these comparisons achieved statistical significance ($p > 0.05$) (Table 7). In the analysis of BAT, PPARG also revealed no significant differences, with mean differences ranging from -0.5378 to 894.8398 and p- values between 0.1025 and 0.6409. However, UCP1 exhibited significant upregulation in the Aldrin group (mean difference: 1.9702, $p = 0.0002$) and the Endosulfan group (mean difference: 3.1199, $p = 0.0137$). Meanwhile, FDNC5 expression did not show significant variation across treatments, with p-values ranging from 0.0691 to 0.5045. Similarly, UCP3 expression did not indicate significant changes, with mean differences from -0.8518 to - 0.6569 and p-values ranging between 0.0566 and 0.1579. These findings underscore notable alterations in UCP1 expression in response to Aldrin and Endosulfan, while other genes remain unchanged (Table 7).

Table 6. LSD Test Results Comparing Gene Expression in White and Brown Adipose Tissue (WAT/BAT): Analysis of PPARG, UCP1, FDNC5, and UCP3 Levels in Lindane, Aldrin, and Endosulfan Treatment Groups Relative to Control

Group	Tissue	Marker	Mean Difference	p-value	Significant
Lindane	WAT	PPARG	0.1254	0.3751	No
		UCP1	0.2719	0.4879	No
		FDNC5	-0.0319	0.9657	No
		UCP3	0.1754	0.7254	No
	BAT	PPARG	-0.5378	0.2473	No
		UCP1	0.3963	0.3484	No
		FDNC5	-0.2419	0.5045	No
		UCP3	-0.8518	0.0566	No
Aldrin	WAT	PPARG	0.0366	0.7668	No

		UCP1	0.4816	0.2239	No
		FDNC5	0.0193	0.9793	No
		UCP3	-0.6112	0.1272	No
	BAT	PPARG	894.8398	0.1025	No
		UCP1	1.9702	0.0002	**Yes**
		FDNC5	5.2546	0.1643	No
		UCP3	-0.7473	0.0903	No
Endosulfan	WAT	PPARG	-0.0643	0.6757	No
		UCP1	-0.0675	0.8018	No
		FDNC5	-0.2422	0.7317	No
		UCP3	-0.7626	0.0652	No
	BAT	PPARG	-0.2028	0.6409	No
		UCP1	3.1199	0.0137	**Yes**
		FDNC5	-0.7012	0.0691	No
		UCP3	-0.6569	0.1579	No

* Statistically significant ($p < 0.05$), * very significant ($p < 0.01$), and *** extremely significant ($p < 0.001$

4.4.2. Comparative Analysis of Gene Expression in (WAT) and (BAT) Across Treatment Groups

No significant differences were observed for PPARG in any group. UCP1 expression was significantly lower in WAT compared to BAT for Aldrin ($p = 0.0035$) and Endosulfan ($p = 0.0141$). FDNC5 levels were significantly higher in WAT than BAT for Endosulfan ($p = 0.0380$). UCP3 showed a significant increase in WAT relative to BAT for Lindane ($p = 0.0407$) (Table 8.)

Table 7. LSD Test Results Comparing Gene Expression Profiles in White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT): Differential Effects of Control, Lindane, Aldrin, and Endosulfan on PPARG, UCP1, FDNC5, and UCP3 Levels

Gene	Group	Mean Difference (WAT - BAT)	p-value	Significant
PPARG	Control	-0.4108	0.3214	No
	Lindane	0.2524	0.3442	No
	Aldrin	-895.214	0.1024	No
	Endosulfan	-0.2723	0.2677	No
UCP1	Control	0.0585	0.8759	No
	Lindane	-0.0659	0.8773	No
	Aldrin	-1.4301	0.0035	Yes
	Endosulfan	-3.1289	0.0141	Yes
FNDC5	Control	0.334	0.6414	No
	Lindane	0.5441	0.2188	No
	Aldrin	-4.9012	0.1905	No
	Endosulfan	0.793	0.0380	Yes
UCP3	Control	-0.1105	0.8267	No
	Lindane	0.9167	0.0407	Yes
	Aldrin	0.0256	0.8872	No
	Endosulfan	-0.2161	0.4098	No

* Statistically significant ($p < 0.05$), * very significant ($p < 0.01$), and *** extremely significant ($p < 0.001$).

5. DISCUSSION and CONCLUSION

The study involved thirty-two adult male Sprague-Dawley rats, divided into four groups: Control, Lindane, Aldrin, and Endosulfan. Experimental groups received 1 mg/kg doses of their respective chemicals via oral gavage daily for four weeks, while controls received corn oil. Body weights were monitored, and at study end, brown and white adipose tissues were collected for gene expression analysis (Pparγ, UCP1, UCP3, FDNC5). Serum samples were analyzed for liver enzymes (ALT, AST, ALP), cholesterol, and triglycerides.

The analysis of body weight revealed clear differences in the effects of pesticide exposure across the groups. The Control Group exhibited a steady and consistent increase in weight throughout the study, reflecting normal physiological growth under the experimental conditions. In contrast, the Lindane Group showed a gradual weight gain with a marked increase in the fourth week. This pattern suggests that Lindane exposure may initially disrupt growth but may subsequently lead to compensatory physiological adaptations resulting in increased weight gain later in the study.

The Aldrin Group displayed a significant increase in weight during the fourth week, suggesting a more pronounced effect of Aldrin on growth, potentially linked to metabolic or hormonal changes during this phase.Meanwhile, the Endosulfan Group exhibited a slight but consistent weight increase, indicating a subtler impact on overall weight compared to the other groups, possibly due to toxic effects suppressing growth. These patterns suggest that each pesticide affects body weight through distinct pathways, possibly involving metabolic dysregulation or altered energy homeostasis. The biochemical analysis of serum cholesterol and triglycerides revealed significant group- specific variations. For CHO2I (total cholesterol), the Control Group exhibited the highest mean values, with statistically significant reductions observed in the Endosulfan Group ($p = 0.010$). This suggests that Endosulfan may impair cholesterol biosynthesis or increase its Meanwhile, The Lindane and Aldrin Groups displayed comparable amounts to the control group, Suggesting a negligible impact on total cholesterol levels in these groups.

For HDLC4 (high-density lipoprotein cholesterol), significant reductions were noted in the Endosulfan Group compared to all other groups ($p = 0.002$). This reduction points to a potential impairment in lipid transport and metabolism, as HDL plays a key role in cholesterol homeostasis and catabolism. Supporting this, a study reported that Endosulfan exposure disrupted lipid homeostasis in rats, leading to reduced total cholesterol and HDL levels due to oxidative stress-induced damage [76]. No significant differences were observed in the Lindane and Aldrin Groups compared to the control. For TRIGL (triglycerides), VLDL (very low-density lipoprotein), and LDLH (low-density lipoprotein), no significant differences were found among the groups. This finding suggests that the effects of pesticide exposure on lipid metabolism may be selective for total cholesterol and HDL, particularly in the Endosulfan Group.

Liver enzyme analysis revealed significant alterations in ALT, AST, and ALP levels, indicating pesticide-induced hepatotoxicity. The Control Group exhibited the highest ALP levels, reflecting normal biliary function, and ALT and AST levels within the normal range, indicating healthy liver function. In the Lindane Group, reduced ALP levels in contrast to the Control Group ($p < 0.001$) suggest impaired biliary function, while ALT and AST levels remained moderately elevated, indicating mild hepatocellular injury. Research on Lindane toxicity supports these findings, demonstrating significant to moderate increases in ALT and AST levels in a fish model, suggesting mild to moderate hepatotoxic effects [77,78]. The Aldrin Group showed similar trends, with significantly reduced ALP levels ($p < 0.001$) and ALT levels lower than AST, indicating mild liver stress. However, AST levels in the Aldrin Group did not significantly differ from ALP, suggesting less severe liver dysfunction compared to Endosulfan. Chronic exposure to Aldrin has been associated with histopathological liver changes, including hepatocyte hypertrophy and enzyme elevation, even at low doses [79]. The Endosulfan Group exhibited the most pronounced hepatotoxic effects, with significantly elevated ALT and AST levels ($p < 0.001$). ALP levels were moderately reduced, but AST levels were significantly higher than both ALT and ALP. These results highlight severe hepatocellular damage and mitochondrial dysfunction in the Endosulfan Group. A study examining Endosulfan exposure through oral and inhalation routes confirmed significant increases in liver enzymes and histopathological evidence of liver tissue damage, supporting the hepatotoxic potential observed in this study [80]

Subtle but significant patterns in WAT's response to Lindane, Aldrin, and Endosulfan were found in the expression of genes linked to adipogenesis and thermogenesis. PPARG, a master regulator of adipocyte differentiation and lipid storage, did not show significant differences in expression among the groups ($p > 0.05$). This indicates that none of the chemicals strongly influenced adipogenesis in WAT under experimental conditions. The lack of significant upregulation of PPARG suggests that the chemicals did not directly stimulate the formation of new adipocytes, but their obesogenic effects may instead be mediated through other pathways, such as lipid metabolism or thermogenesis. For thermogenic markers, UCP1 and FDNC5 also showed no significant changes in expression in WAT ($p > 0.05$). The stable expression of UCP1 indicates that none of the chemicals strongly influenced energy dissipation through uncoupling protein pathways in white adipose tissue. Similarly, the absence of significant changes in FDNC5, which encodes irisin (a myokine linked to the browning of WAT), suggests that these chemicals did not trigger browning processes in WAT.

In contrast, UCP3, a marker of thermogenesis and energy expenditure, exhibited significant differences ($p = 0.0379$) across the groups. The Endosulfan Group showed the greatest reduction in UCP3 expression compared to the Control Group, indicating impaired thermogenesis in WAT. Reduced UCP3 expression is associated with lower energy dissipation and increased lipid storage, which could contribute to the observed obesogenic effects of Endosulfan. The Lindane and Aldrin Groups did not show significant alterations in UCP3, suggesting that their impact on thermogenesis in WAT is limited.

Gene expression analysis in BAT highlighted distinct responses to the chemicals, particularly in thermogenesis and adipogenesis pathways. PPARG expression in BAT revealed notable variations between the groups ($p = 0.048$). The Aldrin Group exhibited unusually high PPARG expressions, which may indicate enhanced adipogenic activity in BAT. Elevated PPARG in BAT suggests a shift toward lipid accumulation rather than thermogenic activity, potentially impairing BAT's capacity to burn energy and contributing to the observed weight gain in the Aldrin Group. In contrast, PPARG expression in the Lindane and Endosulfan Groups was comparable to the Control Group, suggesting that these chemicals had minimal direct effects on adipogenesis in BAT.

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7. APPENDICES

7.1 CURRICULUM VITAE

Personal Informations

Name	NADA ABEDLHAMID MOHAMED	**Surname**	BOUJANAH

Degree	Department	The name of theInstitution GraduatedFrom	Graduation year
Doctorate			
Master	Physiology department	**Institute of health department**	2024-2025
University	Yeditepe university	**Institute of health department**	
Highschool	Sience	Libya-tripoli **-ALnejeela**	2010

Education

Languages	Grades (#)
English	good
Arabic	Mother languge

#All the grades must belistedifthere is morethan one (KPDS, ÜDS, TOEFL; EELTS vs),

WorkExperience (Sort from present to past)

Position	Institute	Duration (Year - Year)
Worked in dental clinic of Benghazi university , intern	Dentistry Benghazi	2019-2020

Computer Skills

Program	Level
Word	good
Power point	good

***Excellent, good, average or basic Scientific works**
The articles publishedinthe journals indexedbySCI, SSCI, AHCI

Articles publishedin other journals

Proceedings presentedininternational scientific meetings andpublished in proceedings book.

Journalsinthe proceedings book of the refereed conference / symposium

Others (Projects / Certificates / Rewards)

Post graduatescholar ship award fromthe Libyan ministry of higher education
Rank the first in senior high school among all students in my school