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The Physiological and Histological Effects of Orlistat on kidney function and the role of Cinnamon extract in improving for Male Rats with hyperlipidemia

A Thesis

Submitted to the Council of the College of Veterinary Medicine, University of Kerbala in Partial Fulfillment of the Requirements for the Master of Degree of Science in Veterinary Medicine / Physiology

By

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Supervised by

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بسم الله الرحمن الرحيم

وَأَنزَلَ مِنَ السَّمَاء مَاء فَأَخْرَجْنَا بِهِ أَزْوَاجًا مِّن

نَّبَاتٍ شَتَّى (53)

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I certify this thesis entitled (***The Physiological and Histological Effects of Orlistat on kidney function and the role of Cinnamon extract in improving for Male Rats with hyperlipidemia***) has been prepared by ***Benan Aad Abed*** under my supervision at the college of Veterinary Medicine, University of Kerbala in partial fulfillment of the requirements for the Degree of Master in the Sciences of Veterinary Medicine in Physiology, Biochemistry and Pharmacology.

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The recommendation of the Department

In the view of the above recommendation, I forward this thesis for scientific discussion by the examining committee

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I hereby declare that this dissertation is my original work except for equations and citations which have been fully acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at University of Kerbala or other institutions.

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Dedication

- To the creator of the soul, the pen, the atom, and the Breeze, and everything from nothingness (**God Almighty**).

- To those who have reached the prophetic message and performed honesty. and advised the nation. to the Prophet of mercy and the light of the worlds Muhammad (**may God bless him and his family and peace**).

- To the pure imams and the most position of the trust of God and the people of the house of prophethood (**peace be upon them**).

- To those who in my heart and the nearest me from myself, and the absence of eyes and the eye latent of insight to the rest of God the greatest. The owner of the age and time Muhammad Al -Mahdi (**God hurry his pussy**).

- To those who put in my soul the virtues morality of my first supporter in the march of my life career, Sindhi, my father, and my walkers, after God, "**My father**, May God have mercy on him".

- To Nebras of my days, and glow up of my life, to the one who declared her life in order to fulfill my ambitions, role model of my life (**my beloved mother**).

- To those who supported me with all love and get the trouble out of my way, paving the way for me, instill confidence and determination in me, my husband **Dr. Ahmed**, and to seeds of my heart and hope for tomorrow, my children (**Nardin and Amin**).

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Abstract

The current study examined the adverse effects of orlistat alone and in combination with cinnamon on changes in renal tissue in obese male rats. It also assessed the antioxidant properties and protective effects of the extract of cinnamon by examining its improved effects on the pathological changes in kidney tissue caused by the drug orlistat, as well as improvements in the state of oxidative stress, blood fat levels, and weight loss.

Forty adult male rats divided into two experiment :- First experience (induction obesity) the experimental animals divided into for Control group : 10 rats received only rats normal diet without fat , the High fat diet group : 30 rats received only fed with high-fat diet contain (Plate with soy fat) , After (six weeks) the weight gain , body weight , serum cholesterol , triglycerides and lipids were determined in the first and second main groups to ensure the induction.

Second experiment , after confirming the induction of obesity daily oral dosing with the Control group : 10 rats received only rats normal diet without fat, the High fat diet group: 30 rats after induction of obesity divided into the Group high fat diet with orlistat 10 rats (10 mg/kg/day) , the Group high fat diet with cinnamon 10 rats (100 mg/kg BW), the Group high fat diet with orlistat (10 mg/kg/day) and cinnamon (100 mg/kg BW) 10 rats.

Rats were given a chloroform anesthetic to make them unconscious, and then blood samples were taken from the heart to examine blood tests, liver enzymes oxidants and antioxidants, and dissected animals to get the kidney for a histopathological investigation , The mean value of weight gain and body weight were increase in a significant value in fat group comparatively to control group. while there were a significant decrement for weight gain and body weight in orlistat group and cinnamon group comparison with fat group.

Also a significant decrement for weight gain and body weight in group mix (orlistat and cinnamon) when comparative with orlistat group and cinnamon group. Addition that showed cholesterol **,** triglycerides **,** LDL-c and VLDL-c were increase

in a significant value while showed a significant decrease in HDL-c in fat group comparatively to control group. Also there were a significant decrease in cholesterol , Triglycerides , LDL-c and VLDL-c while showed a significant increase in HDL-c in orlistat group and cinnamon group as compared to fat group. while in group mix (orlistat and cinnamon) showed a significant decrease in cholesterol , Triglycerides , LDL-c and VLDL-c with a significant increase in HDL-c when comparative with orlistat group and cinnamon group.

The result also showed in examination of Urea , Creatinine , K^{+2} and Na were increase in a significant value while showed a significant decrease in Ca^{+2} in fat group comparatively to control group. Also there were a significant decrease in Urea , Creatinine , K^{+2} and Na with a significant increase in Ca^{+2} in orlistat group and cinnamon group as compared to fat group. While showed a significant decrease in Urea , Creatinine , K^{+2} and Na with a significant increase in Ca^{+2} in group mix (orlistat and cinnamon) when comparative with orlistat group and cinnamon group.

In this study showed Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) were increase in a significant value in fat group comparatively to control group. Also there were a significant decrease in Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in orlistat group and cinnamon group as compared to fat group. While showed a significant decrease in Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in group mix (orlistat and cinnamon) as compared to orlistat group and cinnamon group.

While in liver oxidant and antioxidant enzyme showed GSH were decrease in a significant value while there were a significant increment in MDA for fat group comparatively to control group. Also there were a significant decrement in GSH and MDA for orlistat group and cinnamon group when comparative with fat group. While showed a significant increment in GSH with a significant decrement in MDA in group mix orlistat and cinnamon group when comparative with orlistat group and cinnamon group.

Histological examination of kidney section of control group as showed the normal histological architecture of renal cortex with significant glomeruli and regular renal tubules , Also the histological examination of kidney section for a high fat diet group were staind with haematocylin and eosin , as showed the abnormal appearance of the renal cortex, severe infiltration of inflammatory cells into the interstitial space, substantial glomerular atrophy and tubular necrosis, and notable changes in the glomeruli, as evidenced by atrophy interstitial per glomerular inflammation.

Histopathological examination of kidney section for a high fat diet and Orlistat group showed mild histological improvements in cortical tissue , glomerulous atrophy , dilation of bowman capsule , interstitial inflammatory cells infiltration and significant tubular epithelium degeneration. Addition that in histological examination of kidney section for a high fat diet and Cinnamon group were staind with haematocylin and eosin , as showed significant histological improvements in renal cortical tissue , normal glomeruli , normal tubules , slight interstitial inflammatory cells infiltration and mild degeneration.

While in Histopathological examination of kidney section for a high fat diet and Cinnamon with orlistat group showed some Histopathological alterations in renal tissue , normal glomeruli with little atrophied , normal tubules ,slight interstitial inflammatory cells infiltration and marked congestion with slight degeneration and mild congestion. The study was concluded that hypolipidemic effect of cinnamon and reduced body weight

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List of Abbreviations

Abbreviations	Full word
AKI	acute kidney injury
ARF	acute renal failure
BMI	Body Mass Index
CAT	Catalase
CE	cinnamon extract

CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CYS	cystatin C
ECG	Electrocardiogram
ESRD	end-stage renal disease
FDA	United States Food and Drug Administration
GPx-1	Glutathione Peroxidase 1
GRAS	Generally Recognized As Safe
GSH	Reduced glutathione
H&E	haematocylin and eosin
H_2O_2	peroxide hydrogen
HDL-C	High Density Lipoprotein-cholesterol
HFD	high-fat diet
HO-1	Heme Oxygenase 1
IL	Interleukin
LDL-C	Low Density Lipoprotein-cholesterol
MDA	Malondialdehyde
MetS	Tradition Persian medicine
NADPH	nicotine amide diphosphate
NGAL	Neutrophil gelatinase-associated lipocalin
NO	nitric oxide
O^{-2}	superoxide ions

OH	hydroxyl radicals
ORL	Orlistat
ROS	reactive oxygen species
TC	Total Cholesterol
TG	Triglycerides
TNF	Tumor Necrosis Factor
TPM	matrix metallopeptidase-3
VLDL-C	Very Low Density Lipoprotein-cholesterol
WHO	World Health Organization

Chapter One: Introduction

1.Introduction

Based on an analysis of body mass index data, the World Health Organization (WHO) declared obesity to be a global epidemic hazard in 1997 (BMI) , Since then, the prevalence of obesity has alarmingly increased and is now a significant public health concern , In fact, obesity not only contributes to the development of chronic diseases such as stroke, osteoarthritis, sleep apnea, cancers, and inflammation-based pathologies, but also to metabolic disorders such as diabetes, hypertension, and cardiovascular diseases (**Mohajan and Mohajan ., 2023; Elmaleh *et al* ., 2023).**

As a primary disorder, obesity is characterized by a positive energy balance , Finding the underlying causes of this imbalance, which account for most cases diagnosed after secondary obesity-related causes are ruled out, is still difficult , Complex interactions between behavioral, genetic and environmental factors that are correlated with lifestyle choices and social and economic status lead to this chronic illness , Actually, populations that experience a long-term energy positive imbalance caused by a sedentary lifestyle, a low resting metabolic rate, or both are more likely to be obese **(Zou and Pitchumoni.,2023).**

Genes, metabolism, nutrition, physical activity, and the sociocultural environment are all contributing factors to obesity , that embodies the lifestyle of the twenty-first century , Finding plausible molecular targets that can be altered by outside influences, especially food and medications, may help people learn to regulate their appetite and prevent obesity , Nutritional genomics may be able to identify the precise nutrients that cause phenotypic changes that impact the likelihood of obesity and determine the most significant interactions **(Ghosh *et al* ., 2023).**

The main action of the pancreatic gastric lipase inhibitor **Orlistat** (ORL, tetrahydrolipstatin) is to reduce fat absorption, which in turn reduces calorie intake **(Hamza and Alsolami ., 2023)**. Foods containing orlistat selectively bind to gastrointestinal lipase by preventing the hydrolysis of ingested fat into glycero and

absorbable free fatty acids , Furthermore, Orlistat is a tetrahydrolipstatin that prevents the intestines from absorbing dietary fats by inhibiting the activity of the pancreatic and gastric lipase enzymes **(Rajan *et al* ., 2021)**. As a result, it is typically used as an anti-obesity drug to regulate and manage body weight in patients who are obese , In order to achieve this, Orlistat has shown promise in reducing obesity-related variables like BMI, lipid profile, white adipocyte size, and fecal fat excretion in animal replicas **(Othman *et al* ., 2021)**.

It has also been shown to be effective in reducing the consequences of obesity, such as metabolic syndrome and endothelial dysfunction in humans **(Abdel-Baky and Abdel-Rahman, 2021)**.Orlistat inactivates lipases by covalently adhering to the serine residues left on their active sites , Since triglycerides are not hydrolyzed when lipases are inactivated, free fatty acids are not absorbed , Orlistat primarily acts by causing a localized lipase hang-up in the stomach **(Jin *et al* ., 2021).** Orlistat can function without systemic absorption; it reduces the absorption of dietary fat by about 30% **(Braeckmans *et al* ., 2022).**

Nevertheless, despite the fact that orlistat has a very selective effect, numerous studies have noted some very serious adverse effects , The most typical gastrointestinal side effects of orlistat include dyspepsia, diarrhea, flatulence, and abdominal pain **(Adeyemi *et al* ., 2020).** It directly damages the intestinal villi as it is metabolized in the gastrointestinal tract , Moreover, deficiencies in fat-soluble vitamins (ADEK) are caused by malabsorption , It has been demonstrated that orlistat inhibits carboxylesterase-2, a key detoxification enzyme, increasing the risk of serious liver, pancreatic, and renal damage , Another target organ for a variety of anomalies resulting from this anti-obesity medication's side effects is the oral cavity **(Lee *et al* ., 2021; Uehira *et al* ., 2023).**

As a herbaceous plant, **Cinnamon** is a member of the Lauraceae family due to its physiological effects, cinnamon is one of the most widely used spices in the world,

both as a spice and condiment to flavor food and in medicinal mixtures , For centuries, various cultures across the world have utilized cinnamon as a culinary flavoring agent due to its organoleptic properties **(Abeysinghe *et al.*, 2020).**

It has been extensively researched due to its possible health-promoting qualities and has been used historically as a treatment for digestive and respiratory issues , These include qualities that are antilipemic, anticancer, antidiabetic, anti-inflammatory, and antimicrobial , Cinnamon has been shown to have anti-inflammatory qualities by inhibiting the expression of nuclear factors, which in turn reduces the production of proinflammatory cytokines like interleukin (IL) 6, C-reactive protein (CRP), and tumor necrosis factor (TNF) **(Ben Lagha *et al* ., 2021).**

Additionally, cinnamon encourages the activation of Nrf2, or nuclear factor erythroid 2-related factor 2, which increases a number of cytoprotective defenses and the production of antioxidant enzymes, including NAD(P)H dehydrogenase, glutathione peroxidase 1 (GPx-1), heme oxygenase 1 (HO-1), and catalase (CAT) **(Moreira *et al* ., 2023; Mafra *et al* ., 2023)**.

Aims of Study :-

This study was design to evaluated the hypolipidemic effects of cinnamon as compared with orlistat , by measure the following parameters:-

1) The weight gain and body weight% of animals (after 6 and 12 weeks of therapy).

2) The lipid profile in the blood (Serum total cholesterol (TC) , triglycerides (TG) , (HDL-c) High Density Lipoprotein-cholesterol , (LDL-c) Low Density Lipoprotein-cholesterol , (VLDL-c) Very Low Density Lipoprotein-cholesterol).

3) Changes in kidney functions and electrolytes levels in different groups (urea , creatinine , K++ , Na , Ca++ , Cystatin C , neutrophil gelatinase-associated lipocalin (NGAL).

4) Liver oxidant and antioxidant enzymes (reduced glutathione(GSH), and malondialdehyde (MDA).

5) Histopathological examination for Kidney.

Chapter Two : literature Review

2.1. Obesity

The illness known as obesity is complex and results from a combination of lifestyle, genetic, environmental, and nutritional variables , It is characterized by a positive energy balance, meaning that energy intake is greater than energy expenditure **(Abdulrahman *et al.*, 2020).** As a result of an imbalance between energy intake and expenditure, it is described as a medical disorder marked by the abnormal accumulation of fat in the body and hypertrophy (excessive growth) and hyperplasia (expansion) of adipose tissue , One of the main illness mechanisms in obesity-associated metabolic syndrome is increased oxidative stress brought on by fat buildup **(Koenen *et al.*, 2021).**

Numerous health issues, including cancer, type 2 diabetes, cardiovascular disease, and osteoarthritis, have been linked to obesity (**Furukawa *et al.*, 2017).** The World Health Organization estimates that there are over 1.9 billion overweight persons in the world and over 650 million of those people are obese (**Rodríguez-Pérez *et al.*, 2019).** Finding economically feasible ways to treat obesity becomes critical given the current health and financial costs associated with obesity , To target signaling pathways mediated by obesity, current strategies include exercise, weight loss, and the use of pharmaceuticals and other food intakes **(Abdulrahman *et al.*, 2020).**

In addition, several of the anti-obesity pharmaceuticals that are now on the market are costly, have serious adverse effects, may be abused, and shouldn't be used for an extended length of time (**Suleiman *et al.*, 2020; Chatterjee., 2023)**. Nowadays, obesity is a major worldwide health concern that affects both adults and children , In the US, the prevalence of obesity and overweight is close to 66% , 1.46 billion people worldwide are overweight as a result of the recent 20 years' global growth in obesity , Overall life expectancy may decline as a result of obesity , The metabolic syndrome is one of obesity's main effects (**Mohamed and Ashour, 2016).**

With or without diabetes, the presence of at least three of the following conditions central obesity, hypertriglyceridemia, low HDL cholesterol, increased fasting glucose, and hypertension—is referred to as the metabolic syndrome , Insulin resistance, which causes hyperglycemia and hyperinsulinemia and ultimately culminates in the development of diabetes, is a key component of the metabolic syndrome. Another characteristic of the is chronic inflammation metabolic syndrome, which causes intricate metabolic disorders when combined with insulin resistance (**Jiang *et al.*, 2023)**.

The obesity phenotype is not uniform rather, it is more likely to be a spectrum with different levels of metabolic illness **(Mutti *et al* ., 2023).** obesity that is unhealthy in terms of metabolism is frequently associated with the metabolic syndrome , Numerous, bidirectional, multi-layered, and complex relationships exist between obesity and chronic kidney disease (**Petruk ., 2020).** these relationships may be explained by common pathophysiological pathways (such as hyper-insulinemia, increased oxidative stress, and chronic inflammation), shared risk factor clusters, and associated diseases (such as insulin resistance, hypertension, and dyslipidemia**) (Lakkis and Weir.,2018).**

2.1.1. Classification of obesity

Obesity results from an excessive buildup of bodily fat, which has detrimental effects on a person's health , The factors used in the analysis of obesity include Body Mass Index (BMI) , has resulted in becoming an improved cardiovascular disease indicator , This displays the distribution of body fat in the central region and has been demonstrated to be a risk factor for health issues (**Suleiman *et al* ., 2020)**.

Adult patients are categorized based on their co-morbidity risk status using the clinical guidelines for the identification, evaluation, and treatment of obesity , The Classification of Diseases is used to identify co-morbidities that are chronic , Being overweight can result from eating more than one is active, which can promote fat

accumulation (exogenous), or it might result from endogenous metabolic or hormonal system failure (**Afolabi *et al* .,2020)**. Obesity by BMI can be further stratified into class I (30-34.9), class II (35-39.9), class III (≥40), class IV (≥50), and class V (≥60). Recommended cut points for overweight and obesity are lower in some Asian nations **(Lynn and Agrawal ., 2021). table(2-1).**

Classification	BMI Cut-Off Points (kg/m²)
Healthy Weight	18.5-24.99
Overweight (including obesity)	≥25.00
Obesity	≥30.00
Severe Obesity	≥40.00

Table (2-1): classification of Obesity (Lynn and Agrawal ., 2021)

2.1.2. Symptoms of obesity

The most obvious symptom is the increase in weight , therefore the symptoms that may be presented arise from this increase in weight that among others , may be difficult in sleeping , sleep apnea , daytime drowsiness , joint pains , excessive sweating , tolerance to heat , infectious in skin folds , fatigue , depression and feeling of shortness and breath (dyspnea)**(Baynes ., 2022).**

Additionally, there are signs of excessive obesity that include fatigue, decreased vital activity, difficulty sleeping, and back and joint pain , These symptoms also contribute to Type 2 diabetes, hypertension, elevated levels of triglycerides or cholesterol, heart-related disorders, gout, chronic kidney disease, and psychological issues (**Azzolino *et al* ., 2020)**.

2.1.3. Causes of obesity

The majority of the causes of obesity are believed to be explained at the individual level by a combination of high dietary energy consumption and low physical activity , Obesity can occasionally be caused by genetics, sickness, or mental health issues **(Elagizi *et al* ., 2020).** Conversely, rising obesity rates in society are

said to be brought on by automated production, widely accessible and appetizing food, and a greater reliance on automobiles , including lack of sleep, endocrine disruptors, reduced temperature variability, lower smoking rates because smoking suppresses appetite, higher use of weight-gaining medications (such as atypical antipsychotics)**(Gowan and Roller ., 2021).**

Proportionate increases in older and heavier ethnic groups, later pregnancy (which may increase a child's susceptibility to obesity), and epigenetic risk factors , handed down through generations, assortative mating increasing the concentration of obesity risk variables, and natural selection favoring higher BMI **(McFarlane .,2021).**

2.1.4. Diagnosis of obesity

Depended on Health history the physician may go over your past weight, attempts to lose weight, exercise routine, eating habits, problems you've had in the past, prescription drugs, stress levels, and other health-related matters , The physician could also go over the medical history of your family **(Kahan and Manson .,2019).** Also Initial diagnosis includes Temperature , blood pressure, heart rate, weight, and height **(Pureza *et al* ., 2021).**

With body Mass Index (BMI) and Taking a waist circumference measurement , Blood testing These might include liver function, thyroid, cholesterol, and other tests , A cardiac test like an electrocardiogram (ECG) can also be suggested by your physician (**AL-Mohannadi *et al* ., 2022)**.

2.1.5. Effects of obesity on health

An individual's risk of developing osteoarthritis, depression, Alzheimer's disease, cardiovascular disease, and some types of cancer is increased when they are obese **(Mohajan and Mohajan ., 2023).** The estimated reduction in life expectancy due to obesity ranges from 2 to 20 years, depending on the severity of the condition and the

existence of coexisting conditions **(Blüher ., 2019).** According to a RAK hospital study, obese individuals have a higher chance of developing long COVID 19 **(Rhodes *et al* ., 2021).**

Obesity is the single biggest risk factor for severe COVID-19 illness, according to data from the CDC **(Ajufo *et al* ., 2019).** Apart from its mechanical impact on the body, obesity is linked to an increased prevalence of several diseases **(Shaik Mohamed Sayed *et al* .,2023)** :-

2.1.5.1. Coronary heart disease

Obesity raises the risk of heart failure, an irregular heartbeat, angina or chest pain, and sudden cardiac death, Ventricular dysrhythmias are common even in the absence of heart failure due to obesity-related increases in electrical changes, The annual risk of sudden cardiac death was more than 40 times higher in the obese population than in the non-obese group **(Lopez-Jimenez *et al* ., 2022).**

2.1.5.2. High blood pressure

Studies on the endocrinology of adipose tissue have linked obesity to hypertension, this is likely because adipose tissue secretes immunomodulatory and bioactive chemicals, Epidemiological studies have shown that obesity accounts for 65–75% of the risk of hypertension. (**Avery *et al* ., 2021)**.

2.1.5.3. Diabetes mellitus

The most prevalent main type of diabetes, noninsulin-dependent diabetes mellitus, and impaired glucose tolerance have been linked to obesity, according to accumulating studies , Adipose tissue in obese people releases large amounts of hormones, pro-inflammatory cytokines, glycerol, and non-esterified fatty acids **(Alzamil ., 2020).** They are connected to the emergence of insulin resistance, which

results in compensatory hyperinsulinemia, which suppresses insulin receptors and overstimulates pancreatic cells **(Penhaligan *et al* ., 2023).**

2.1.5.4. Neurological disorders

Obesity and overweight can have a range of psychological effects, from poor self-esteem to severe clinical depression , In fact, those who are obese have three to four times greater incidence of anxiety and despair **(Moradi *et al* ., 2021).** Alzheimer's disease risk is greatly increased by obesity , High amounts of amyloid, the protein that builds up in the Alzheimer's brain and destroys nerve cells to cause cognitive and behavioral issues, are strongly correlated with BMI **(Chu *et al* ., 2019).**

2.1.5.5. Lung diseases

Chronic respiratory conditions, such as asthma, hypoventilation syndrome, and sleep apnea, are linked to obesity , Therefore, it is common for symptom improvement to follow weight reduction **(Young and Benjamin ., 2023).** Obesity has been widely reported to be associated with the disease progression of coronavirus disease 2019 (COVID-19) **(Chu *et al* ., 2020; Sattar *et al* ., 2020; Stefan *et al* ., 2021).**

Furthermore, the delayed and decreased ability to produce interferons promotes increased viral RNA replication, raising the potential for novel viral strains , Additionally, the unfavorable hormonal environment associated with obesity patients results in deficiencies in B and T cell responses as well as innate immunity **(Chu *et al* ., 2020).**

As a result, new research suggests a link between obesity and the seriousness of infectious respiratory illnesses , revealed that the body mass index (BMI) of non-survivors of COVID-19 patients was higher than that of survivors , An inverse relationship between obesity and mortality among critically ill patients, including those with ARDS **(Skinner *et al.*, 2018; Stefan *et al* ., 2021)**.

2.1.5.6. Cancer

Although the exact relationship between nutrition, obesity, and cancer is unknown, there may be some causative evidence given the growing global trend in both obesity and cancer , Excess adipose tissue synthesis of estrogen, inflammation brought on by adipocyte-secreted adipocytokines, and infiltrating macrophages or similar stromal cells have all been proposed as potential causes of these obesity-related malignancies (**Feng *et al* ., 2022)**.

2.1.5.7. Dislipidemia

Is most frequently caused by obesity , Increased availability of non-esterified fatty acids from lipid overflow in obesity, hyperinsulinemia, and/or insulin resistance leads to larger total glycemic storage in non-adipose tissues such as the liver, pancreas, and muscle , Lipotoxicity is the term used to describe problems caused by fatty acids **(Kansra *et al* ., 2021).**

Therefore, a little rise in total cholesterol and a noticeable decrease in high-density lipoprotein (HDL) cholesterol are frequently observed in conjunction with higher TG levels , Furthermore, hepatic lipase partly metabolizes low-density lipoproteins (LDL) high in TG, converting them into tiny LDL, which has a higher atherogenic potential **(Alizadeh *et al* ., 2020).**

2.1.5.8. Kidney disease

Kidney disease is one of the most prevalent comorbid illnesses linked to obesity , at least 72% of patients with end-stage renal disease (ESRD) also have hypertension, both of which are significantly influenced by obesity , Despite the fact that obesity poses a separate risk for ESRD (**Hall *et al.*, 2019).**

Chronic kidney disease is mostly caused by diabetes and hypertension , Recent epidemiological research has demonstrated that obesity-related kidney disease (CKD)

is a growing epidemic, with rising obesity prevalence coinciding with rising CKD rates. As a result, obesity is now recognized as a separate risk factor for chronic kidney disease (CKD) (**McPherson *et al.*, 2019)**. A significant challenge in researching the connection between obesity and kidney damage is the fact that metabolic and cardiovascular conditions, such as dyslipidemia, hypertension, and hyperglycemia, which can be brought on by obesity, or the combination of these conditions known as the metabolic syndrome (MetS), also play a role in the onset and course of kidney disease , Many studies have documented the links between hyperglycemia and hypertension and renal dysfunction in obese people (**Yang *et al.*, 2020)**.

It has been demonstrated that obesity has an independent impact on the course of preexisting renal disorders, such as IgA nephropathy, unilateral renal agenesis patients, and patients following a unilateral nephrectomy , These findings imply that obesity both causes and maybe even contributes to CKD , Patients may exhibit nephrotic syndrome clinically (**Radajewska *et al.*, 2023)**.

2.1.6. Mechanisms Action of Obesity

There are negative effects of increased adipocytes on the brain, heart, liver, kidneys, pancreas, muscles, and joints , Adipokine production starts the production of proinflammatory cytokines, which reduces immunity , The heart experiences an accumulation of fat on the myocardial as a result of increasing adiposity , This mechanism leads to dyslipidemia by increasing the hydrolysis of triglycerides to generate free fatty acids , Consequently, coronary heart disease develops , Reproductive systems are also affected because fat buildup in the organs results in the generation of reactive oxygen species, which lowers fertility, sexual behavior, and performance (**Garduño *et al* ., 2019; Tam *et al* ., 2019)**.

Similar to this, an increase in adipocytes causes mechanical stress on the muscles, joints, and kidneys, which in turn causes renal compression and joint

mechanical load, respectively. This finally results in osteoarthritis and kidney failure , The brain is impacted by increased insulin resistance because it increases neuronal insulin, which in turn causes leptin to function and produce neuronal inflammation, which in turn causes hippocampus neurodegeneration and memory impairment **(Kühnen *et al* ., 2019 , figure (2-1).**

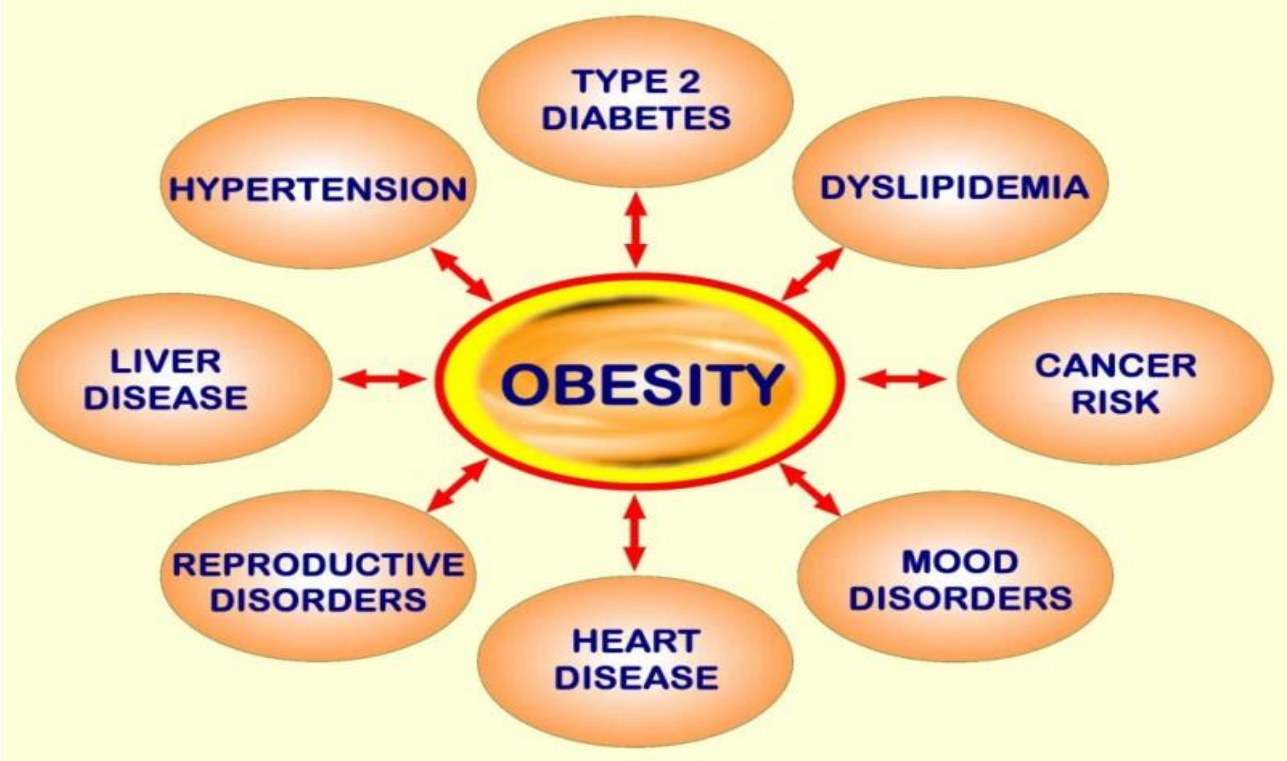

Figure (2-1):- Overweight and Obesity (Kyrou *et al* ., 2015).

2.1.7. Pathophysiological of obesity

The disease whose risk is increased by obesity can be classified into one of two pathophysiological groups , The first set of impairments is caused by the growing bulk of fat itself , These include osteoarthritis, sleep apnea, the stigma attached to being overweight, and the behavioral responses it causes , The second category includes risks associated with metabolic changes brought on by an excess of fat , These include heart disease, diabetes, gallbladder disease, hypertension, and certain cancers associated with obesity **(Busebee *et al* ., 2023).**

Adipose tissue may be thought of as an endocrine organ, and fat cells as a particular kind of endocrine cell ,The pathologic lesion in obesity is this organ's

hypertrophy and/or hyperplasia. Several more secretory peptides were discovered in the fat cell subsequent to the detection of adipsin or complement D , The most significant factor is unquestionably leptin, which upholds the status of fat as an endocrine organ and the adipocyte as an endocrine cell **(Lam *et al* ., 2023).**

However, from a pathophysiological standpoint, the release of free fatty acids could be the most significant , The distribution of fat affects how the body reacts to the hormones released by fat cells , Many variables influence the amount of fat that accumulates in visceral fat cells , The distribution of body fat is largely determined by the androgens and estrogen secreted by the gonads and adrenal glands, as well as by the peripheral conversion of 4-androstenedione to estrogen in fat cells , Adolescence is when the fat distribution of males, or androids, and females, or gynoids, develops **(Ahmed and Konje ., 2023).**

Gender plays a role in the growing adult deposition of visceral fat, although age-related fat accumulation is also influenced by cortisol, GH suppression, and altered testosterone levels , Obesity and hyperinsulinemia are linked to increased insulin resistance, which is exacerbated by increased visceral fat , Insulin resistance and hyperinsulinemia increase the likelihood of the comorbidities listed below **(Ahmed *et al* ., 2023).** Internal mediators of eating and appetite include ghrelin and leptin , The stomach secretes ghrelin, which influences the short-term appetitive control reflex, which tells the body to eat when it is empty and to stop when it is stretched , White adipose tissue produces leptin, which signals the body's stores of fat storage and regulates long-term appetitive controls, meaning eating more when reserves of fat are low and less when reserves of fat are high , By reducing food intake and increasing energy expenditure, it is essential for maintaining body weight and energy balance **(Barton .,2024)**.

There is a tiny percentage of obese people who are leptin deficient for whom leptin therapy may be beneficial , The majority of obese people are believed to be

resistant to leptin and have been discovered to have elevated leptin levels , The lack of evidence demonstrating leptin's ability to effectively decrease hunger in the majority of obese individuals is believed to be partially explained by this resistance , Despite being generated peripherally, leptin and ghrelin regulate hunger by acting on the central nervous system **,** Therefore, overeating results from a lack of leptin signaling, which can be caused by leptin resistance or deficiency , This may also be the cause of some hereditary and acquired types of obesity **(Izquierdo *et al* ., 2019) figure (2-2).**

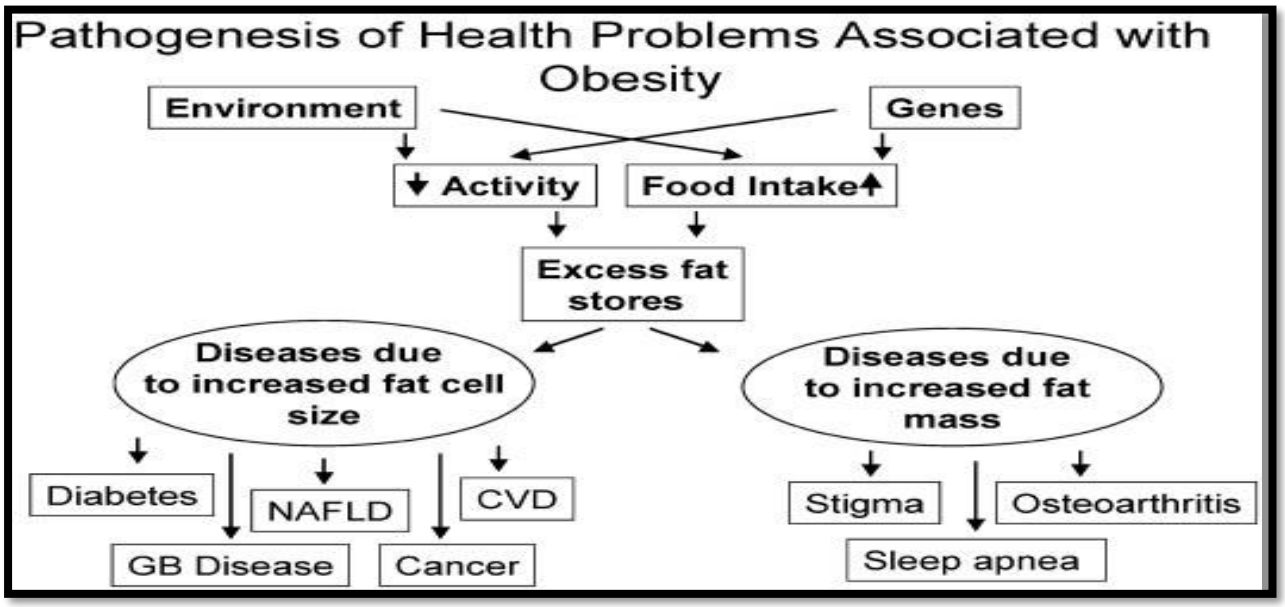

Figure (2-2):-The pathology of obesity produces the myriad of health related problems.These health related problems can be attributed to either the increased mass of fat or the increased release of peptides from enlarged fat cells. CVD,Cardiovacular disease; GB,gallbladder (Ahmed and Konje ., 2023).

2.2. Orlistat

Orlistat (Xenical) is a strong pancreatic/intestinal lipase inhibitor, it promotes the loss of fat in the feces , The effect is dose dependent, but at doses greater than 400–600 mg/day, it reaches a plateau , Orlistat does not appear to alter the pharmacokinetic characteristics of digoxin, phenytoin, warfarin, oral contraceptives, alcohol, frusemide, captopril, nifedipine, or atenolol; less than 1% of an oral dose is absorbed, according to pharmacodynamic studies **(Pilitsi *et al* ., 2019 ; Tak and Lee.,2021 ; Katimbwa *et al* ., 2022).**

weight-loss medication orlistat, also known as tetrahydrolipstin , Saturated derivative of lipstatin, a naturally occurring substance extracted from Streptomyces toxytricini, is what it is. It has been demonstrated to be a highly selective inhibitor of the lipases, which are the digestive enzymes of food that the stomach and pancreas primarily produce , Orlistat has the ability to bind to the lipase enzyme in the digestive tract, preventing the hydrolysis of triglycerides into free fatty acids. These acids are absorbed by the cells, and the undigested triglycerides are subsequently expelled through feces (**Aydin and Onbasi .,2021).**

Orlistat's inhibition of lipases will therefore result in a decrease in caloric intake , Orlistat is currently used to treat type 2 diabetes and cardiovascular diseases that are associated with obesity , Other clinical uses for orlistat include the treatment of Chylous ascites, primarily linked to cirrhosis **(Khedr *et al* ., 2020).** Inhibiting gastric and pancreatic lipases is how orlistat works, Dietary fat contains triglycerides (TG) that cannot be converted to fatty acids , About 30% of dietary fat is inhibited from being absorbed by orlistat , This lowers the amount of fat absorbed, and the undigested fat is subsequently expelled in the stool **(Qi ., 2018 ; Abou-El-Naga *et al* ., 2019; Kassab *et al* ., 2020).**

Orlistat is now utilized in clinical settings to treat cardiovascular disease and type 2 diabetes associated with obesity , In animal models, orlistat has shown promise in reducing obesity-related symptoms like metabolic syndrome and endothelial dysfunction as well as obesity-related parameters like BMI, lipid profiles, white adipocyte size, and fecal fat excretion **(Gomaa *et al*., 2019; Handing *et al*., 2022).**

Through induction of cell cycle arrest and apoptosis in preclinical models, orlistat has been shown in numerous studies to exhibit anti-tumorigenic activities against various types of solid and hematological malignancies, including prostate, leukemia, breast, ovarian, colon, gastric, melanoma, and oral cancers, with a minor inhibitory effect on normal cells **(Schcolnik-Cabrera *et al* .,2018)Figure (2-3).**

Figure (2-3): Orlistat (Schcolnik-Cabrera *et al* .,2018).

2.2.1. Mechanism action of Orlistat

Orlistat binds covalently to the serine residue found in the pancreatic and stomach lipases' active sites , Orlistat reduces the absorption of free fatty acids and monoglycerides by partially inhibiting the hydrolysis of triglycerides when given with foods high in fat , The way that orlistat works is by blocking the intestine's natural triglyceride-breaking enzymes, pancreatic and gastric lipases **(Kitadokoro *et al* ., 2020).**

Triglycerides from the diet are not hydrolyzed into absorbable free fatty acids when lipase activity is inhibited instead, they are eliminated undigested , After an oral dose, the main effect of orlistat is local lipase inhibition within the GI tract only trace amounts are absorbed systemically, The feces are the main method of elimination, Furthermore, it was discovered that orlistat inhibits the thioesterase domain of fatty acid synthase (FAS), an enzyme that is necessary for the growth of cancer cells but not healthy cells(**Rajan *et al*., 2021; Hou *et al* ., 2022)**.

Digestion of fat in food, Triglycerides are dissolved into monoglycerides and absorbable free fatty acids by them , Lipases are rendered inactive by orlistat through its covalent attachment to their serine residues. , Free fatty acids cannot be absorbed when lipases are inactivated because triglycerides cannot be hydrolyzed, The principal mode of action of orlistat is local lipase inhibition in the stomach (**Da Silva *et al* ., 2020; Hall *et al* ., 2021; Bansal and Al Khalili., 2022).**

2.2.2. contraindications of Orlistat

Examples of orlistat contraindications include indications against the following conditions: Intolerance to orlistat or any of its ingredients long-term malabsorption , Nostalgia , Bulimia and anorexia , Pregnancy , severe kidney damage in patients suffering from bulimia nervosa or anorexia, use with caution **(Bansal and Al Khalil ., 2022).**

2.2.3. Side effect of orlistat

Despite the fact that orlistat has a very selective impact, several studies have noted some very significant adverse effects, The most typical gastrointestinal side effects of orlistat are dyspepsia, diarrhea, flatulence, and stomach discomfort , It directly damages the intestinal villi when it is digested in the gastrointestinal system **(Tiryakioğlu *et al* ., 2023).** Moreover, deficiencies in fat-soluble vitamins (ADEK) are caused by malabsorption , Evidence suggests that orlistat inhibits the key detoxifying enzyme carboxylesterase-2, which puts patients at risk for serious liver, pancreas, and kidney damage. Another target organ for a variety of anomalies resulting from this anti-obesity medication's adverse effects is the mouth cavity **(Shaik and Pachava .,2017).**

Fecal incontinence, frequent or urgent bowel movements, and steatorrhea oily, loose stools with excessive flatus caused by unabsorbed fats reaching the large intestine are the main gastrointestinal side effects of the medication , the

manufacturer suggests that consumers adopt a low-fat, reduced-calorie diet **(Montoro *et al* ., 2021).**

Flatulence and oily stools can be managed by limiting the amount of fat in the diet to about 15 grams per meal , encouraging the patient to link eating fat with negative side effects , When starting therapy, side effects are at their worst and may become less frequent over time additionally, it has been proposed that the reduction in side effects may eventually be linked to sustained adherence to a low-fat diet (**May *et al* ., 2020)**.

2.2.4. Effect of orlistat on renal function

Orlistat can increase the risk of acute kidney injury; this occurs because the unabsorbed fat binds with calcium in the intestinal lumen resulting in excessive oxalate, which is absorbed and deposited in the kidney leading to oxalate nephropathy and increased risk of renal stones **(Bethesda ., 2020).** Oxalate nephropathy or kidney stones can result from taking orlistat , Orlistat-induced oxalate nephropathy frequently presents with no symptoms and develops gradually , After stopping orlistat, kidney function may not fully recover, which could lead to chronic kidney disease **(Tiryakioğlu *et al* ., 2023).**

2.3. Cinnamon

Many cultures all over the world have used cinnamon as a popular spice. The plant belongs to the Lauraceae family of laurel ,The four most commonly used species in this family are Cinnamomum burmanni, Cinnamomum aromaticum, Cinnamomum zeylanicum, and Cinnamomum loureirii, The inner bark of trees belonging to the genus Cinnamomum is used to make cinnamon **(Hajimonfarednejad *et al.*, 2019)**.

With numerous pharmacological properties, such as anti-inflammatory, antioxidant, anti-proliferative, antibacterial, antifungal, antiviral, antidote, anti-

hyperglycemia and anti-hyperlipidemic, antihypertensive, and anti-atherosclerotic effects, Also it is a priceless and powerful medicinal herb (**Singh *et al.*, 2021)**.

Cinnamon can be an excellent diuretic because it's a potent opener , The thick materials within the kidneys are softer and heated by It soothes and cleanses the kidneys Because cinnamon is so thin, it can also pass through organ obstructions such as the liver, spleen, and gallbladder , According to TPM (Tradition Persian medicine), cinnamon strengthens the stomach and liver for digestion, attenuates and cuts phlegm, cleanses the stomach of waste products, and warms the stomach and liver for the purpose of breaking down thick foods (**Alizadeh *et al.*, 2020)**. Improving the gastrointestinal tract's function is crucial and helpful in the treatment of patients with pneumonia and respiratory failure in the intensive care unit, in addition to monitoring respiratory and other complications (**Yakhchali *et al.*, 2021)**.

Numerous studies have been done on the possible health benefits of this spice for people , Cinnamon has anticancer properties that are mediated by a number of different molecular pathways (**Dutta and Chakraborty., 2018). Figure (2-4)**.

Figure (2-4): cinnamon (Dutta and Chakraborty., 2018).

2.3.1. History

Because of the presence of cinnamon, foreign invaders have historically been drawn to Sri Lanka (formerly known as Ceylon), The Portuguese invaded Sri Lanka at the start of the 16th century primarily to gain access to cinnamon, a product that Arab traders traded throughout the world up until the tenth or fifteenth century, taking great care to conceal the product's true origins (**De Cillia .,2021)**.

The Portuguese developed a very prosperous business of exporting cinnamon to Europe in the 16th and 17th centuries , After the Dutch took control of the island in the middle of the 17th century, they began the systematic cultivation of cinnamon on plantations, This was brought about when the king of Sri Lanka made it difficult to gather cinnamon from the forests **(Hancock ., 2021).**

Cinnamon exports to Europe continued after the British East India Company took control of Sri Lanka in 1796, with the company serving as the primary exporter ,The export of Ceylon cinnamon was drastically reduced as a result of the Dutch imposing high export duties; cheaper Cassia cinnamon took its place. Sri Lanka is still a major global supplier of Ceylon cinnamon to consumers around the glob **(Suriyagoda *et al.*, 2021).** It was also utilized in the embalming procedure in ancient Egypt , The bioactive compounds in cinnamon have been used in the perfume industry, to treat a variety of illnesses , and as a repellent for mosquitoes (**Baker and Grant., 2018).**

2.3.2. phytochemical or active contain of cinnamon

The type of plant of the tree, and the maturity stage all affect the concentration of cinnamon compounds , The essential qualities of the cinnamon extract may be impacted by these variables. Cinnamomum cassia (L.) J. Presl, for instance, has more coumarin (**Yakhchali *et al* ., 2021)**. Moreover, the components' composition changes based on the tree's section, The mature tree has the highest yield value of cinnamon

trans-aldehyde, and the upper and middle segments of the bark are more useful for extracting cinnamon oil (**Cha *et al.*, 2019)**.

However, the methods of separation, the solvents used, and every other aspect of the extraction and separation proccess including time, temperature, and pressure—all affect how effective the compounds are in the extracted cinnamon oil , One significant element influencing the oil's composition is extraction process optimization , The different techniques are applied to extract the constituents from cinnamon (**Adarsh *et al.*, 2020).** The composition of cinnamon is 52% carbohydrates, 33% fibers, 3.5% protein, and 4% fat,. Moreover, this spice contains 7.0 mg/g of iron, 20.1 mg/g of manganese, 85.5 mg/g of magnesium, 83.8 mg/g of calcium, 42.4 mg/g of phosphorus, and 134.7 mg/g of potassium (**Jiang ., 2019)**.

Trans-cinnamaldehyde, cinnamyl acetate, and eugenol essential oils; a variety of bioactive resinous compounds, such as cinnamaldehyde, cinnamic acid, and cinnamate; water-soluble polyphenols, such as procyanidin, quercetin, kaempferol, and epicatechin; and polyphenolic polymers are the main ingredients in cinnamon (**Alshahrani *et al* ., 2021; Hussein *et al.*, 2022; Moreira *et al.*, 2023).**

2.3.3 Food Uses of cinnamon

The process of encapsulating cinnamon oil into various food materials, including polysaccharides and gelatin, Tween 80, β-cyclodextrin, maltodextrin, vitamin D, chi-tosan, polylactic acid, polyvinyl alcohol, polypropylene films, mesoporous silica, and sodium alginate, has been widely used to enhance the oil , These substances can be added to food products or utilized as protective coatings to fend off infections and lengthen their shelf life **(Vasconcelos *et al.*, 2018).**

The escalation of drug-resistant microorganisms has made food-borne microbial infections a significant health concern , Compounds found in natural antimicrobials like essential oils have the ability to combat a wide range of micro and

macroorganisms found in food products **(Lee *et al* ., 2020).** The antimicrobial qualities of cinnamon are attributed to eugenol and cinnamaldehyde, while the antibacterial effects of coumarin, cinnamyl acetate, and benzaldehyde are negligible or absent, Cinnamaldehyde and cinnamic acid have the potential to cause harm to cell membranes, modify lipid profiles, and impede the activities of enzymes, reproduction, and the formation of biofilms in a variety of microorganisms **(Cadena *et al.*, 2018; Park *et al* ., 2018)**.

By cooking with cinnamon oil, By adding cinnamon oil to food products, coating or immersing them in a cinnamon oil solution, or utilizing it as a component of packaging materials, these antimicrobial properties were achieved. Additionally, cinnamon oil shows synergistic effects in the control of both "Gram-positive" and "Gram-negative" bacteria when combined with other plant-derived oils, such as thyme oil, Depending on the product's quality requirements, different procedures are followed when applying cinnamon oil to food commodities to enhance their postharvest quality **(Mutlu-Ingok *et al.*, 2020)**.

The "United States Food and Drug Administration" (FDA) has classified cinnamon oil as a "Generally Recognized As Safe" (GRAS) product , The results of the previously mentioned study and the US FDA's GRAS designation have expanded the potential applications of cinnamon in the food industry, including extending the shelf life of perishablees after harvest **(Tavares *et al* ., 2022).** Cinnamon's antioxidant activity In food products and animal feed, antioxidants can be used to delay the development of undesirable traits , such as unpleasant smells, tastes, and hazardous substances brought on by the oxidation of lipids (**Kumar *et al* ., 2023).**

Cinnamon's oleoresins have demonstrated inhibition of lipid oxidation activity, Antioxidants have the ability to shield human cells from the damaging effects of free transition metal ions and reactive oxygen species, which can harm the structural and functional components of cells and result in a variety of health issues **(Ashfaq *et al* .,**

2021). Plant-based natural antioxidants have gained more attention recently due to the detrimental health effects of many synthetic antioxidants that are frequently used in the food industry **(Suriyagoda *et al.*,2021)**.

2.3.4. Characteristic of Cinnamon

For centuries, people have utilized cinnamon as a spice and flavoring in cooking due to its aroma , Throughout the world, cinnamon is a popular ingredient in drinks, baked goods, sauces, and seasonings , The sweet taste of cinnamon is attributed to the presence of cinnamaldehyde, and the synergistic effect of the sweet aroma of cinnamon and the sweet taste of sugar intensifies the sweet sensation when cinnamon is combined with sweet food (**Meghani ., 2018)**.

Trimethylamine is the compound that gives cinnamon bark its deodorizing and masking qualities Because cinnamon oil contains phenolic compounds, food commodities treated with cinnamon have longer shelf lives (postharvest lives) Still, Cinnamon oil's applications are limited because phenolic compounds (**Suriyagoda., 2021).** have been observed to degrade, absorb unpleasant smells, and undergo color changes, Furthermore, researchers have found that cinnamon oil can combine to form complexes, or enrichments, with a wide range of food ingredients while retaining its biochemical characteristics, allowing for a wider range of food products to use it (**Kumar *et al* ., 2023).**

Cinnamon mimics the actions of insulin, including the activation of insulin receptor kinase by physiologically active substances, the upregulation of glucose absorption, the autophosphorylation of the insulin receptor, and the activation of glycogen synthase , It has been suggested that by altering the activity of glycogen synthesis **(Culas *et al* ., 2023).** Cinnamon increases the storage of glycogen , According to a study, the extract from cinnamon peels would raise glucose intake and improve insulin sensitivity , It has been discovered that the water-soluble parts of

cinnamon increase the efficiency of the insulin signaling pathway (**Kizilaslan and Erdem ,. 2019).**

2.3.5. Effects of cinnamon on health

Numerous healthy compounds, including antioxidants, can be found in cinnamon and might assist you in lowering inflammation, preventing heart disease, and controlling blood sugar, For millennia, cinnamon has been valued for its therapeutic characteristics (**Mishra and Srivastava ., 2022).** Modern science has begun to validate many of the possible health benefits linked to cinnamon in recent years , These ten health advantages of cinnamon are backed by scientific studies , has strong therapeutic qualities, Packed with protective agents, possibly anti-inflammatory qualities might shield against cardiovascular diseasemight increase insulin sensitivity, reduces the levels of blood sugar, might be advantageous for neurodegenerative illnesses, Cinnamon may offer cancer prevention. may shield against fungus and bacteria infections, possibly antiviral qualities **(Błaszczyk *et al* ., 2021).**

2.3.5.1. Effect of cinnamon on renal function

The cinnamon possesses potent kidney-protective qualities, particularly in relation to aminoglycosides (**Zeima and EL-Gawish ., 2021).** Aminoglycosides can only be used in therapy under specific circumstances , In similar circumstances to aminoglycoside renal toxicity, cinnamon may have protective effects on the kidneys , Cinnamon appears to have two unique benefits **first**, it appears to protect renal tubular cells from harmful substances, **second,** it appears to have blood glucose-regulating properties, Since nephropathy is one of the most significant side effects of diabetes mellitus, taking antioxidant supplements, particularly safe herbal remedies, is a helpful adjunctive treatment **(Raeeszadeh *et al* ., 2022).**

In fact, damage to the glomeruli and tubulointerstitium also causes diabetes kidney disease, Therefore, cinnamon may have complementary Therefore, cinnamon may work in concert with other nutrients to promote protection in people with diabetes **(Shiels *et al* ., 2021; Mafra *et al* ., 2021)**. The salutogenic effects of cinnamon in chronic kidney disease (CKD) are commonly attributed to two common pathways , the inactivation of the ERK/JNK/p38 MAPK pathway, which decreases renal interstitial fibroblast proliferation and hypertrophy, and the stimulation of the Nrf2 pathway, which attenuates renal damage and preserves renal function , Cinnamon has also been demonstrated to affect the production of NO and PGE2, inhibit lipid peroxidation, and nitrite-induced nitration (**Stenvinkel.,2019)**.

2.3.5.2. Toxicity

Contrary to popular belief, herbal medicines can have side effects and are not always safe According to data at Consuming rate has been connected to several health benefits, Conversely, overuse or long-term use for medicinal purposes can result in adverse effects such as gastrointestinal issues and self-limiting allergic reactions, which should be closely monitored (**Hajimonfarednejad *et al*., 2019)**. Even though every extract tested in vitro demonstrated potential antioxidant activity, animals displayed acute dose-dependent toxicity (**Yun *et al*., 2018).**

The majority of studies did not pinpoint the specific species of cinnamon that was causing these side effects, according to the authors of a systematic review of the negative effects of cinnamon , Studies on herbal medicines should be standardized to include the precise identification, dosage, and length of treatment in light of the fact that different species of cinnamon contain additional components, such as coumarin (**Hajimonfarednejad et al .,2019).** Also its important to consider the quantity of coumarin present in various kinds of cinnamon and any associated symptoms, like nausea, vomiting and diarrhea (**Moreira *et al*., 2023).**

Chapter Three : Materials and Methods

3. Materials and Methods

3.1. Materials

3.1.1. Instruments and Equipment for the Laboratory

Laboratory equipment's and apparatuses used in this study are listed in Table (3-1).

NO	Equipment & Instrument	Company	Country
1.	Anatomical set(Scissors, Forceps, Scalpel)	Chemo lab	China
2.	Balance	Shimadu company	Japan
3.	Beakers	Chemo lab	India
4.	Binocular Light Microscope	Olympus	Japan
5.	Centrifuge	Hettich Roto fix11	Japan
6.	Digital camera	Toup Cam	China
7.	Digital camera	Sonyo	Japan
8.	Eppendorf tube	Biolabse	England
9.	Filter paper	Chemo lab	India
10.	Freezer	Newal	Turkish
11.	Glassware different sizes and shapes	Duran	Germany
12.	Incubator	BINDER	Germany
13.	Jell tube	AFMA-Dispo	Japan
14.	Latex gloves	Great glove	Malaysia
15.	Light microscope	Leica	China
16.	Micropipette 100-1000 µl	CYAN	Germany
17.	Plan tube	A F M A- Dispo	Japan

18.	Sensitive analytical balance	Sartorius	Germany
19.	Serum tube	BioPro	China
20.	Slides and Cover Slides	Marienfeld	Germany
21.	Spectrophotometer	Labomed	UK
22.	Sterile syringes	PROTON	Malaysia

3.1.2. Chemicals

Chemicals used in this study and their suppliers are listed in table (3-2).

NO.	Chemicals	Company	Country
1.	Chloroform	Noorbrok	England
2.	Cinnamon	Local	Iraq
3.	Cystatin C Kit	Bioassay assay brand	China
4.	Ethanol 70%	Merck	Germany
5.	Formalin 10 %	TEDIA Company	USA
6.	Glutathione (GSH)	Bioassay assay brand	China
7.	Leishman stain	Macsen	India
8.	Malondialdehyde (MDA)	Elabscience	USA
9.	(NGAL) kit	Bioassay Technology Laboratory	China
10.	Orlistat	Hikma	Jordan
11.	Urea kit	Bioassay Technology Laboratory	China
12.	Creatinine kit	Bioassay Technology Laboratory	China
13.	Na , Ca , K kit	Bioassay Technology Laboratory	China
14.	Sliding Microtome	-	-

3.2. Methods

3.2.1. Preparation of Orlistat

Drug: orlistat (Xenical ®, Jordan). A commercially available formulation of 120 mg/ cap were purchased from a local private pharmacy. It was dissolved in normal saline and administered at 10mg/kg body weight.

Figure (3-1): Orlistat

3.2.2. Preparation of Cinnamon extract

Using a ceramic porcelain pestle and mortar, cinnamon bark was ground into small grains with an average particle size of 3 mm Next, a 500 ml Soxhlet extractor was filled with cinnamon particles, Two hours were dedicated to the extraction process using 250 milliliters of water, After that the dark brown solution was put into a rotating evaporator, The solution was worked on at 50 °C until it had risen to 10% of its starting volume, A Christ Alpha 2-4 LDplus freeze dryer was used to evaporate the remaining solvent for 48 hours at −60 °C and 5 mbar, Finally, the obtained extract was kept at −10 °C before its incorporation into nanofibers and add 100 gm to 2000 ml of water , Following a two-minute boil, Before filtering, the infusion was allowed to cool to room temperature **(Mohammed *et al* ., 2020: Yulianto *et al* ., 2021, figure (3-2) , Ahmadi *et al* ., 2021).**

Figure (3-2): cinnamon.

3.2.3. Taxonomy of cinnamon

Kingdom : Plantae

Division : Tracheophyta

Class : Magnoliids

Order : Laurales

Family : *Lauraceae*

Genus : *Cinnamomum*

Species : Cinnamomum verum (**Dr. Abu Dhar Al-Athari ., 2024**)

3.2.4. Animals Experimental:-

Forty male albino rats weighting (200-220 g) were used in the current study. Taken from the College of Veterinary Medicine , Tikrit University – Iraq , and their ages are between (12-15) weeks , animals were placed in good condition in special plastic cages. They are provided with appropriate conditions and ventilation. the light system was 12 hours. per day with a relative humidity of 50 ± 5%. They were kept for 2 weeks to adjust to standard experimental conditions. The experiment begins October 1th and ends December 30th. The temperature was maintained At (21-25)°C

using a room thermostat, the room air was changed continuously Using vacuum ventilation, feed the animals a pellet of fresh food ration.

3.3. The Experimental Design

Forty adult male rats divided into two experiment:-

First group (induction obesity) for six weeks to induce obesity , as indicated below **(Fig 3-3):**

1) Control group : For six weeks, 10 rats were fed a regular diet devoid of fat on a daily basis.

2) High fat diet group : 30 rats received fed with high-fat diet contain **(Plate with soy fat)** (**Oliveira ., 2020).**

After this period **(six weeks**) weight gain , body weight , serum cholesterol , triglycerides and lipids were determined in the first and second main groups to ensure the induction.

Second group for six weeks , The treatment period lasted from **week 6 to week 12** after confirming the induction of obesity daily oral dosing with the fallowing groups **(Fig 3-3):**

1) Control group : 10 rats received only rats normal diet without fat as a **daily dose for six weeks.**

2) Group high fat diet with orlistat 10 rats **(10 mg/kg/day) (Zakaria *et al* ., 2021).**

3) Group high fat diet with cinnamon 10 rats **(100 mg/kg BW) (Li *et al* ., 2022).**

4) Group high fat diet with orlistat (10 mg/kg/day) and cinnamon (100 mg/kg BW) 10 rats**.**

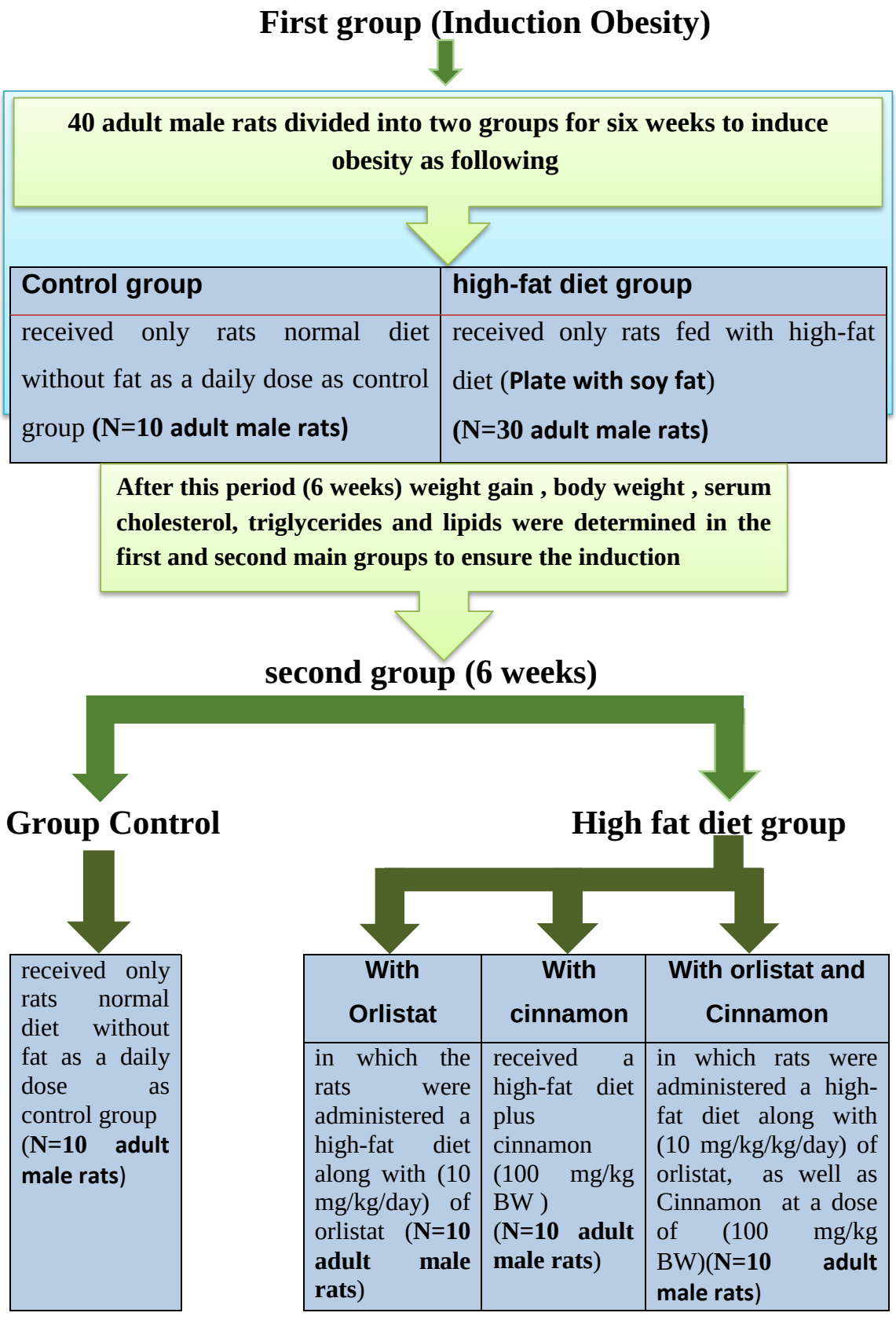

Figure (3-3): Experimental design

3.4. The Parameters:

The study will extend for a period of 12 weeks divided into two experiments, where the first experiment continues for 6 weeks , after which the second experiment begins and continues for 6 weeks for the purpose of measuring the following parameters:

Parameter 1	Parameter 2	Parameter 3	Parameter 4	Parameter 5
The **weight gain and body weight** % of animals (after 6 and 12 weeks of therapy).	The **lipid profile** in the blood Serum total cholesterol (**TC**) , triglycerides (**TG**), High Density Lipoprotein-cholesterol **(HDL-c)** , Low Density Lipoprotein-cholesterol **(LDL-c)**, Very Low Density Lipoprotein-cholesterol **(VLDL-c)**	Changes in **kidney functions** and electrolytes levels in different groups (**urea , creatinine , K++ ,Na , Ca++**) **Cystatin C** , neutrophil gelatinase-associated lipocalin (**NGAL**)	**Oxidative stress** biomarkers reduced glutathione (**GSH**) , and malondialdehyde (**MDA**)	**Histopathological** examination for Kidney

Table (3-3): Parameters

3.5. Ethical approve

Under the reference number UOK.VET.PH.2023.080, this research was carried out in the anatomical laboratory of the College of Veterinary Medicine at the University of Kerbala - Iraq

3.6. Blood Sample and Hematological study

Blood sample were collected via cardiac puncture from each male rat, placed in serum tube and left for 30 minutes, then to be centrifuged (3000 rpm for 10 minutes) and kept frozen at -20 °C to obtain the serum which then was transferred to the Eppendorf tubes. All these tubes were stored at (-4c) until analyze for biochemical Evaluation, also blood was put in EDTA tube and immediately transfer of samples for examination with Hematological test **(Nasir., 2018).**

3.7. Weight gain and Body weight% of animals

Following the **(first experience six weeks)** the weight was determined with a sensitive scale , Each group's weekly mean body weight gain was determined by keeping track of weight increases at the start and end of each week, using the following formula:-

Mean weekly weight gain=body weight at the end of the week **-** body weight at the beginning of the week **(Mamun *et al* ., 2024).**

3.8. Lipid Profile

3.8.1. Serum Total Cholesterol (TC) Concentration (mg/dl)

Total Cholesterol (TC) was detected by using Enzymatic method described by **(Ganiyat *et al* ., 2023).**

Principle:

Cholesterol is measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol , One of the reaction byproducts, H_2O_2 is measured quantitatively in a peroxidase catalyzed reaction that produces a color , Absorbance is measured at 500 nm , The

color intensity is proportional to cholesterol concentration , **as shown in Appendices I.**

3.8.2. Serum Triglyceride (TG) Concentration (mg/dl)

Total Serum Triglyceride was detected by useing Fossati and Prencipe method associated with Trinder reaction by (**Lu *et al* ., 2020) :-**

Principle:

Triglycerides are measured enzymatically in serum or plasma using a series of coupled reactions in which triglycerides are hydrolyzed to produce glycerol , Glycerol is then oxidized using glycerol oxidase, and H2O2, one of the reaction products, is measured as described above for cholesterol , Absorbance is measured at 500 nm , **as shown in Appendices II.**

3.8.3. Serum High Density lipoprotein-cholesterol (HDL-C) Concentration (mg/dl)

Serum High Density lipoprotein concentration was measured enzymatically by utilizing high density lipoprotein (HDL-C) kit according to **(Santos and Lavie., 2021)**.

Principle:

Accelerator selective detergent methodology. Direct method, without specimen pre-treatment. During the first phase, LDL, VLDL particles and Chylomicrons generate free Cholesterol, which through an enzymatic reaction, produce Hydrogen peroxide. The generated peroxide is consumed by a peroxidase reaction with DSBmT yielding a colourless product. During the second phase, specific detergent solubilizes HDL-Cholesterol. In conjunction with CO and CE action, POD + 4-AAP develop a

colored reaction which is proportional to HDL-Cholesterol concentration. The absorbance is measured at 600 nm , **as shown in Appendices III.**

3.8.4. Serum Low Density lipoprotein-cholesterol (LDL-C) Concentration (mg/dl)

Serum low density lipoprotein-cholesterol concentration was measured depending on **(Duran *et al* ., 2020)**:-

Principle

Direct method using selective detergents without specimen pre-treatment. During the first phase, only non-LDL lipoproteins are solubilised by detergent 1. Such generated Cholesterol, subjected to Cholesterol oxidase (CO) and Cholesterol esterase (CE) actions, produces a colourless compound. During the second phase, detergent 2 solubilises LDL-Cholesterol. The chromogenic coupler allows for colour formation that is proportional to the concentration of LDL-Cholesterol. The absorbance is measured at 546 nm (520-580) , **as shown in Appendices IV.**

3.8.5. Serum Very Low-density lipoprotein-cholesterol (VLDL-C) Concentration (mg/dl)

Serum Very low density lipoprotein-cholesterol concentration was measured depending on **(Ikezaki *et al* ., 2021).**

Principle

Direct method using selective detergents without specimen pre-treatment. During the first phase, only VLDL-C are solubilised by detergent 1. Such generated Cholesterol, subjected to Cholesterol oxidase (CO) and Cholesterol esterase (CE) actions, produces a colourless compound. During the second phase, detergent 2 solubilises VLDL-Cholesterol. The chromogenic coupler allows for colour formation

that is proportional to the concentration of VLDL-Cholesterol. The absorbance is measured at 546 nm (520-580) **, as shown in Appendices V.**

3.9. Kidney Functions and Electrolytes levels

3.9.1. Estimation of Urea

Principle

The sample was generated by the coupled reactions contained urea which lead to form complex which is colored that can be measured by spectrophotometry using a kit provided by BioSystems **(Besseling *et al* ., 2021) , as shown in Appendices VI.**

3.9.2. Estimation of Serum Creatinine

Estimation of Creatinine was done calorimetrically by Jaffe's method by use a kit provided **(Besseling *et al* ., 2021) , as shown in Appendices VII**.

Principle

Creatinine reacts with picric acid in an alkaline solution to form a reddish colored complex. The reaction is commonly known as the Jaffe reaction and the red colored product as the Janovski complex. The assay is based on the reaction of creatinine with sodium picrate as described by Jaffe. Creatinine reacts with alkaline picrate forming a red complex. The time interval was chosen for measurements avoids interferences from other serum constituents. The intensity of the color formed is proportional to the creatinine concentration in the sample.

3.9.3. Serum Cystatin C level

Serum cystatin C level is ELISA kit was used to estimate the renal function according to **(Chen *et al* ., 2022).**

Principle

The test principle applied in this kit is Sandwich enzyme immunoassay. The microtiter plate provided in this kit has been pre-coated with an antibody specific to Cystatin C(Cys-C). Standards or samples are added to the appropriate microtiter plate wells then with a biotin-conjugated antibody specific to Cystatin C(Cys-C). Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After TMB substrate solution is added, only those wells that contain Cystatin C(Cys-C), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450nm ± 10nm. The concentration of Cystatin C(Cys-C) in the samples is then determined by comparing the OD of the samples to the standard curve , as described in **Appendices VIII.**

3.9.4. Serum Neutrophil gelatinase-associated lipocalin (NGAL)

Serum Neutrophil gelatinase–associated lipocalin (NGAL) level is ELISA kit was used to estimate predict the future appearance of kidney injury according to **(Jahaj *et al* ., 2021).**

Principle

The test principle applied in this kit is Sandwich enzyme immunoassay. The microtiter plate provided in this kit has been pre-coated with an antibody specific to Neutrophil Gelatinase Associated Lipocalin(NGAL). Standards or samples are added to the appropriate microtiter plate wells then with a biotin-conjugated antibody specific to Neutrophil Gelatinase Associated Lipocalin(NGAL). Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After TMB substrate solution is added, only those wells that contain Neutrophil Gelatinase Associated Lipocalin(NGAL), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change

is measured spectrophotometrically at a wavelength of 450nm ± 10nm. The concentration of Neutrophil Gelatinase Associated Lipocalin(NGAL) in the samples is then determined by comparing the OD of the samples to the standard curve , as described in **Appendices IX.**

3.9.5. Serum Sodium level (mmol/L)

Serum sodium enzymatic method kits was used to estimate the levels of sodium according to **(Akbaribazm *et al* ., 2021).**

Principle

The LX system utilizes indirect (or diluted) I.S.E. methodology to determine the concentration of sodium in biological fluids. The LX determines sodium ion concentration by measuring electrolyte activity in solution. When the sample/buffer mixture contacts the electrode, sodium ions undergo an ion exchange in the hydrated outer layer of the glass electrode. As the ion exchange takes place, a change in voltage (potential) is developed at the face of the electrode. The potential follows the Nernst equation and allows the calculation of sodium concentration in a solution, **as shown in Appendices X.**

3.9.6. Serum Potassium level (mmol/L)

The enzymatic method kits was used to measure the serum potassium levels according to **(Akbaribazm *et al* ., 2021).**

Principle

Serum potassium is measured by the use of a flame photometer or ion-selective electrode. The procedure is rapid, simple, and reproducible. In interpreting serum potassium, it should be kept in mind that because the intracellular potassium concentration is approximately fortyfold greater than the extracellular concentration, any maneuver that would result in the release of a small amount of intracellular

potassium will erroneously raise serum potassium. These include: (1) tight tourniquet; (2) vigorous exercise of the extremity during blood drawing; (3) hemolysis due to vigorous shaking of the test tube; (4) thrombocytosis (platelet count greater than 600,000); and (5) leukocytosis (WBC greater than 200,000). In the last two situations, the longer the blood stands, the greater the rise in serum potassium will be **, as described in Appendices XI.**

3.9.7. Serum calcium level (mg/dL)

The clorimetric method was used to determine the levels of serum calcium (mg/dL) according to **(Akbaribazm *et al* ., 2021). by**

Principle

The measurement of serum calcium is fraught with possible errors , Several means of contamination might lead to false elevations of serum calcium concentration. In this method calcium reacts with 5-nitro-5'methyl-BAPTA (NM-BAPTA) under alkaline conditions to form a complex. This complex then reacts with EDTA to form a colored product whose intensity is directly proportional to the concentration of calcium in the specimen. It is measured photometrically at 340 nm **, as described in Appendices XII.**

3.10. Liver Oxidant and Antioxidant Enzymes

3.10.1. Determination of Serum Malondialdehyde Level (MDA) Concentration (µ mol/L)

Malondialdehyhe was estimated by Thiobarbituric acid (TBA) assay method on spectrophotometer **(Firdausa *et al* ., 2022).**

Principle:

This method quantifies lipid peroxides by measuring aldehyde breakdown products of lipid peroxidation. A basic principle of the method is the reaction of one molecule of malondialdehyde and two molecules of thiobarbituric acid to form a red MDA-TBA complex which can be measure at 535 nm , **as described in Appendices XIII.**

3.10.2. Serum reduced glutathione concentration (GSH)

The assay involves carefully optimized enzymatic recycling method using glutathione reductase and Ellman's reagent according to **(Abdelrazek *et al* ., 2022).**

Principle:

Catalase activity was assessed by incubating the enzymes ample in 1.0 ml substrate (65 mmol/ml hydrogen peroxide in 60 mmol/l sodium–potassium phosphatebuffer, pH7.4)at37 °C for three minutes. There action was stopped with ammonium molybdate. Absorbance of the yellow complex of molybdate and hydrogen peroxide is measured at374nm against the blank **,** as described in **Appendices XIV.**

3.11. Histopathological study

The kidney of each animal were prepared for histological study according to **(Mostafa *et al* ., 2022).**

Principle:

with aid of the light microscope as the following steps:

1) Fixation :- The specimen fixated in the formalin 10 % for 24 – 48 hours.

2) Washing and dehydration :- After fixation the specimens washed with water to remove the fixative in order to avoid the interaction between the fixative and staining materials used later. By dehydration the water had been completely extracted from

fragments by bathing them successively in a graded series of of ethanol and water (70 %, 80 %, 90 %, and 100 % ethanol)

3) Clearing :- Bathing the dehydrated fragments in solvent (xylene) for 30–60 minutes, this step was repeated 3 times. As the tissues clearing, they generally became transparent.

4) Infiltration and Embedding :- Once the tissue fragments were impregnated with the solvent, they were placed in melted paraffin in an oven, typically at 52℃. The heat causes the solvent to evaporate and the space within the tissues becomes filled with paraffin.

5) Sectioning :- After holds from the oven, the specimen let at room temperature to be solid and removed from their containers in order to sectioning they were put in the rotary microtome and were sliced by the microtome, a steel blade into sections 5 micrometers thick. The sections were floated on water bath (50–55oC), then transferred into glass slides coated with Mayers albumin as adhesive substance and left to dry.

6) Staining :- The histological sections of the studied organs were stained with Hematoxylin - Eosin stain , as described in **Appendices XV.**

3.12. Statistical analysis

Statistical analysis of data was performed using SAS (Statistical Analysis System - Version 9.1). One-way ANOVA and Least significant differences (LSD) post hoc test were performed to assess significant differences among means. $P < 0.05$ is considered statistically significant **(SAS, 2010).**

Chapter Four : Results and Discussion

4. Results and Discussion

4.1. Hematological Study

4.1.1. Effect of high fat diet , orlistat and cinnamon extract on body weight in Male rats

The mean value of weight gain and body weight were increase in a significant value (P<0.05) in fat group comparatively to control group.

while there were a significant (P>0.05) decrement for weight gain and body weight in orlistat group and cinnamon group comparison with fat group.

Also a significant (P<0.05) decrement for weight gain and body weight in group mix (orlistat and cinnamon) when comparative with orlistat group and cinnamon group.

Table 4-1: Effect of High fat diet , Orlistat and Cinnamon extract on Weight gain and Body weight in Male rats

Groups	Body weight (g)		Weight gain (g)
	Initial weight (g)	Final weight (g)	
Control	200.82±7.88a	340.58±13.23a	139.76±0.59a
Fat	253.50±11.23e	411.95±13.86b	158.45±1.01b
Orlistat	240.18±10.98d	371.56±12.76c	131.38±0.95c
Cinnamon	228.30±11.54c	329.89±14.12d	101.59±1.12d
Mix orlistat & cinnamon	216.39±12.06b	301.12±14.02e	84.73±1.43e

Data represented as mean ± SD different letters significant differences at P-value (P<0.05)

In this study, the HFD group's feed intake increased significantly during the experiment compared to the control group's , body weight significantly increased during the HFD free diet as opposed to the control diet , It was discovered that an HFD significantly increased body weight in comparison to rats fed a normal diet, the rats fed an HFD had higher body weights and weight gain **(Shang *et al* ., 2021 ; Suleiman *et al* ., 2020 ; Iftikhar *et al* .,2022).**

The groups treated with water cinnamon extract experienced a reduction in body weight due to increased thermogenesis and the observed decrease in weight at the end of the experiment which was attributed to the thermogenic effect , Additionally, cinnamon was used to prepare the thermogenesis which was significantly lower in rat adipose groups compared to fat groups because it worked synergistically with catechins to enhance thermogenesis (**Alhodieb ., 2024).**

In comparison to the control rats, HFD feeding resulted in a decrease in feed intake, which raised final body weight and weight gain , The HFD-fed rats treated with cinnamon extract had a lower final body weight and visceral fat percentage than the control rats, despite the fact that the treatment reduced body weight, fat, and weight gain in the HFD-fed rats **(Shang *et al* ., 2021).**

This is accompanied by modifications in the metabolism of fat and glucose in the diet , Cinnamon is helpful because of its antioxidant properties and responsiveness. Cinnamon extracts are known to function both in vitro and in vivo , The detrimental effects of variations in the HFD/HFD signal were mitigated by the use of cinnamon , The supplementation of cinnamon extract had improved body weight, visceral fat, and carbohydrate metabolism, including glucose and lipid profiles, antioxidant enzymes, and lipid peroxidation, in HFD-fed rats (**Yigit *et al* ., 2024)**.

The administration of orlistat increased the metabolic rate in the treated groups, increased the release of catecholamines and increased fat oxidation through lipolysis in fat cells, The highest group showed an anti-obesity action in rats at fat groups with the administration of orlistat recording a decrease in body weight gain , On the other hand the combination of orlistat and cinnamon can reduce non-significant differences in body weight gain percentage in obese rats (**Chen and Rao ., 2022)**.

4.2. The Lipid Profile

4.2.1. Effect of high fat diet , orlistat and cinnamon extract on Lipid Profile in Male rats

The mean value of cholesterol , Triglycerides , LDL-c and VLDL-c were increase in a significant value (P<0.05) while showed a significant (P<0.05) decrease in HDL-c in fat group comparatively to control group.

Also there were a significant (P<0.05) decrease in cholesterol , Triglycerides , LDL-c and VLDL-c while showed a significant (P<0.05) increase in HDL-c in orlistat groups and cinnamon groups as compared to fat group.

while in group mix (orlistat and cinnamon) showed a significant (P<0.05) decrease in cholesterol , Triglycerides , LDL-c and VLDL-c with a significant (P<0.05) increase in HDL-c when comparative with orlistat group and cinnamon group.

Table 4-2: Effect of High fat diet , Orlistat and Cinnamon extract on Lipid Profile in Male rats

Lipid Profile test					
Groups	**Cholesterol (TC) mg/dl**	**Triglycerides (TG) mg/dl**	**HDL-c mg/dl**	**LDL-c mg/dl**	**VLDL-c mg/dl**
Control	60.09±0.92a	110.80±1.63a	33.91±1.28a	44.21±0.93a	51.3±1.28a
Fat	85.11±0.51b	168.20±0.61b	19.06±0.51b	74.43±1.01b	78.28±1.43b
Orlistat & Fat	66.81±0.86c	149.48±1.32c	24.02±0.86c	60.59±0.92c	67.91±0.92c
Cinnamon & Fat	74.83±1.14d	116.79±0.81cd	29.38±0.92ad	51.07±0.83d	59.37±0.66d
Mix & Fat	59.99±1.07e	104.12±0.86e	32.78±0.92e	40.94±0.61e	44.48±0.30e

Data represented as mean ± SD different letters significant differences at P-value (P<0.05)

In the current study, feeding HFD resulted in a substantial alteration in the lipid profile and the induction of hyperlipidemia When compared to the control group **(Katoch *et al* ., 2024).** A high-fat diet (HFD) raises blood levels of cholesterol, triglycerides, low-density lipoprotein (LDL), and very low density lipoprotein-cholesterol (VLDL-c), with the exception of lower levels of high-density lipoprotein (HDL-c) in group fats **(Feingold ., 2024).**

Globally, obesity is now a serious health concern , Furthermore, endocrine, metabolic, and cardiovascular disorders are significantly increased by obesity , Therefore, using synthetic medications or functional foods that have safe properties would be very beneficial in the management of obesity **(Khedr *et al* ., 2020).** Numerous traditional herbal plants were widely used to control or lower blood lipid levels through lipid management , however, when using Natural plants like cinnamon have therapeutic benefits and almost certainly no negative side effects (**Mohammed and Abdel Fattah ., 2018).**

Its numerous benefits include being high in calcium, iron, manganese, and fiber, as well as having antibacterial and antioxidant properties that Furthermore, rats given cinnamon extract (CE) exhibited decreased levels of low density lipoprotein cholesterol (LDL), triglycerides (TG), and total cholesterol (TC) when compared to the fat group, and Very Low Density Lipoprotein-Cholesterol (VLDL-c) with the exception of elevated High Density Lipoprotein-Cholesterol (HDL-c) however When compared to the fat group **(Nagaty ., 2019).**

The lipid profile following HFD feeding was improved by the administration of cinnamon extract , The extract of cinnamon has a Strong lipolytic activity of cinnamon extract lowers free fatty acid levels in kidney subjects and prevents hypercholesterolemia and hypertriglyceridemia , Additionally the presence of cinnamon extract lowers cholesterol in rats given a high-fat diet by preventing the liver's 5-hydroxy-3-methylglutaryl-coenzyme A reductase from doing its job **(Khaafi *et al* ., 2024).**

Both groups in the current study lose weight after receiving treatment with either orlistat or cinnamon , When comparing the orlistat and cinnamon-treated groups to the pretreatment, it was significantly lower in both **(Saglam and Sekerler ., 2024).**

The administration of a mixture of orlistat and cinnamon to hyperlipidemic rats resulted in a significant reduction in total cholesterol, triglycerides, and VLDL+LDL, with the exception of an elevated level of HDL-c, or high density lipoprotein cholesterol **(Vijayakumar *et al* ., 2023)**.

The outcomes of the experiment demonstrated a noteworthy impact of cinnamon treatment on rats , Rats given cinnamon extract orally experienced a marked reduction in their lipid level **(Idoko *et al* ., 2023).** Feeding a high-fat diet causes hyperlipidemia and obesity, which have an impact on overall health , The risk associated with hyperlipidemia is the possibility of cellular damage brought on by changes in cellular function, which can result in a variety of pathological conditions **(Costa-Beber *et al* ., 2023).**

One of the most researched methods for assessing the possible effectiveness of weight-management medications is the anti-lipase effect , The bacteria Streptomyces toxytricini is the source of orlistat, which is intended to control obesity by decreasing the digestion of fats by forming a covalent bond with the serine residue of the lipase enzyme , The outcomes show how orlistat therapy reduced the level of lipase concentration , Hence , suggesting that orlistat has the potential to impact the metabolism of fat **(Ahmed *et al* ., 2024).**

Cinnamon is also the most well-known strong natural botanical inhibitor of pancreatic lipase , The findings of the study suggest that cinnamon inhibits the lipase enzyme because it contains flavonoids and phenolic acids, both of which have an inhibitory effect on the release of pancreatic lipase , additionally demonstrates that taking cinnamon seriously lowers body weight (**Albzoor ., 2019).**

However, the chylomicron formation and subsequent cholesterol synthesis in animal intestinal cells depend on the lipase enzyme , When compared to the control group, the treatment of both groups in the current study with orlistat and cinnamon resulted in significant changes in the lipid parameters, including a significant decline in triglycerides, total cholesterol, LDL cholesterol, and VLDL cholesterol , that have provided strong evidence that the antihyperlipidemic effect of orlistat may be caused by the drug's strong inhibitory action on pancreatic lipase, which slows down the breakdown of fat and prevents the body from absorbing fat **(Miah *et al* ., 2022).**

4.3. Kidney functions and electrolytes levels

4.3.1. Effect of High fat diet , Orlistat and Cinnamon extract on Urea , Creatinine , K^{+2} , Na , Ca^{+2} Levels in Male rats

The mean value of Urea , Creatinine , K^{+2} and Na were increase in a significant value ($P<0.05$) while showed a significant ($P<0.05$) decrease in Ca^{+2} in fat group comparatively to control group.

Also there were a significant ($P<0.05$) decrease in Urea , Creatinine , K^{+2} and Na with a significant ($P<0.05$) increase in Ca^{+2} in orlistat group and cinnamon group as compared to fat group.

While showed a significant ($P<0.05$) decrease in Urea , Creatinine , K^{+2} and Na with a significant ($P<0.05$) increase in Ca^{+2} in group mix (orlistat and cinnamon) when comparative with orlistat group and cinnamon group.

Table 4-3: Effect of High fat diet , Orlistat and Cinnamon extract on Urea , Creatinine , K^{+2} , Na , Ca^{+2} Levels in Male rats

Changes in kidney functions and electrolytes levels test					
Groups	**Urea mg/dl**	**Creatinine mg/dl**	**K++ mmol/L**	**Na mmol/L**	**Ca++ mg/dl**
Control	29.41±0.89a	0.57±0.01a	4.29±0.05a	133.2±0.58a	2.11±0.10a
Fat	71.65±1.11b	1.75±0.02b	7.82±0.11b	155.8±1.20b	0.99±0.06b
Orlistat & Fat	45.75±0.84c	1.34±0.01c	5.36±0.16c	134.6±0.86c	1.20±0.13c
Cinnamon & Fat	30.35±1.62d	0.31±0.01d	3.52±0.10d	123.1±0.50d	1.62±0.10d
Mix & Fat	25.69±1.34ed	0.19±0.01e	2.01±0.15ea	110.4±0.90e	1.93±0.05e

Data represented as mean ± SD different letters significant differences at P-value (P<0.05)

Long-term high-fat diet consumption causes obesity, which in turn damages the kidneys , Both oxidative and mitochondrial dysfunction are the causes of these damages , This is consistent with the higher levels of urea, Creatinine , K^{+2} and Na while low level in Ca^{+2} that we observed in the group that was fed a high-fat diet compare with control group **(Prem and Kurian ., 2021).**

According to the results, the group that was fed a high-fat diet had significantly higher levels of urea, creatinine, K^{+2}, Na and low level of Ca^{+2} This is because the group's excess fat caused significant damage , Studies have also shown that having too much fat on one's body speeds up the onset and progression of kidney disease because high cholesterol causes renal ischemia, tubule atrophy, and fibrosis of the kidney's interstitial tissues , Because excess iron is toxic and can cause tissue damage, it increases oxidation, which in turn increases the production of free radicals (ROS) such superoxide ions (O2-), hydroxyl radicals (OH), monooxygenase, and peroxide hydrogen (H_2O_2) **(Erejuwa *et al* ., 2021).**

These molecules all contribute to tissue damage , which all results in lipid peroxidation, which in turn causes oxidative stress and the destruction of kidney nephrons, raising the blood serum concentrations of urea, creatinine, K++, and Na **(Ranasinghe *et al* ., 2023).** Numerous hormones closely regulate electrolytes through the kidney, which is principally in charge of maintaining an equilibrium between electrolytes and removing them when needed , Since urea is the primary nitrogenous substance formed from metabolic waste that is formed and excreted through the urine, any damage to the kidney or its microtubules will result in an imbalance of bodily fluids and their components and decreased excretion of urea **(Chazot *et al* ., 2022).**

The kidney defect will cause it to aggregate and accumulate in the blood, raising its levels. In other words, the rise in urea is indicative of a malfunction in the kidney's filtration function , A rise in the proportion of body fat and absence of Obesity (being overweight) is caused by a higher body fat percentage, inactivity, and lack of movement , Increased levels of urea and creatinine also disrupt hormone regulation and metabolism through a variety of mechanisms , Additionally, an imbalance in the endocrine glands' functions, such as a high blood hormone concentration or an increase in the adrenaline gland's effectiveness, can both lead to an increase in the concentrations of urea and creatinine **(Stanciu *et al* ., 2020).**

Serum creatinine can be used as a single parameter in the diagnosis of acute renal disorder, also known as addition test urea, k++, Na, and Ca++ that as acute kidney injury (AKI) , Serum creatinine can also represent not only a kidney injury but also a normal response of the kidney to extracellular volume depletion or a decrease in renal blood flow , It was discovered that a rise in serum creatinine signifies the presence of acute kidney damage because high fat diet food **(Ranasinghe *et al* ., 2023).**

The findings of the analysis demonstrated that creatinine, urea, K++, Na, and Ca++ levels can be lowered by the cinnamon extract at all doses , Cinnamon extract can reduce other test results and serum creatinine levels , Following administration of a cinnamon extract, the rat's creatinine serum levels and other tests showed a decrease , The active ingredients in cinnamon, such as its polyphenols, act as antioxidants and anti-inflammatory to lower serum creatinine levels , The mechanism responsible for mitigating oxidative stress resulting from various oxidative reactions within the kidney **(Lusiana *et al* ., 2021).**

Cinnamaldehyde and cinnamic acid are two of the main bioactive ingredients in cinnamon Because of these compounds' anti-inflammatory and antioxidant qualities, numerous pharmacological benefits have been reported , Cinnamon also contains a high concentration of flavonoids, which are known to have kidney-protective properties , Due to its ability to scavenge free radicals by giving them a hydrogen atom, cinnamon and its other purportedly bioactive components have the potential to be bioactive **(Gilani and Najafpour ., 2022).**

The pharmacological benefits of cinnamon are attributed to its predominant allinn , allicin and ajoenes, which are organosulfur compounds , A recent study on male rats fed a high-fat diet showed that cinnamon inhibited oxidative damage and inflammation , Additionally, cinnamon contains a significant amount of flavonoids, such as quercetin , It has been shown to be beneficial in preventing a variety of illnesses, such as oxidative stresss **(Delgado *et al* ., 2021).**

There have also been reports that using different forms of cinnamon can help manage or even prevent a number of metabolic diseases, such as atherosclerosis and organ damage , Consuming a high-fat diet has a number of negative effects, one of which is its cause and effect link with metabolic syndrome, a group of risk factors for heart-related illnesses including diabetes, hypertension and organ damage (**Hariri and Ghiasvand ., 2016).**

The risk of kidney impairment, particularly hyperoxaluria or kidney stones, is increased by orlistat. Vitamin E, D, and A are among the fat-soluble vitamins whose absorption may be impacted by the treatment , It is well known that orlistat increases metabolism, which enhances kidney function and aids in weight loss , It was discovered that giving rats a diet high in fat increased both their body weight and blood lipid levels , When compared to the control group and the group that consumed a high-fat diet, the animals' weight significantly decreased as a result of orlistat administration **(Al-Safo and AlDulaimi ., 2022).**

This demonstrated how orlistat, which covalently binds to fat, improves metabolism and aids in weight loss by influencing the absorption of fat. the pancreatic lipase active site and creates a stable complex , The enzyme's conformation changes as a result of this combination, giving lipase a structure resembling a cap , The enzyme becomes inactive due to modifications made to its active site , Fats are excreted in feces because inactive lipase cannot convert them into fatty acids and monoglycerides **(Hasan *et al* ., 2024).**

Supplementing with the combination of orlistat and cinnamon has the potential to prevent or treat metabolic syndrome by lowering the urea , This is due to the fact that hyperuricemia induces hormones, growth factors, and cytokines, which are some of the main causes of hypertension and cardiovascular diseases **(Moreira et al ., 2023).**

4.3.2. Effect of High fat diet , Orlistat and Cinnamon extract on Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in Male Rats

The mean value of Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) were increase in a significant value (P<0.05) in fat group comparatively to control group.

Also there were a significant (P<0.05) decrease in Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in orlistat group and cinnamon group as compared to fat group.

While showed a significant (P<0.05) decrease in Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in group mix (orlistat and cinnamon) as compared to orlistat group and cinnamon group.

Table 4-4: Effect of High fat diet , Orlistat and Cinnamon extract on Serum Cystatin C and Neutrophil gelatinase - associated lipocalin (NGAL) in Male Rats

Changes in kidney Functions Test		
Groups	**Serum Cystatin C mg/l**	**Neutrophil gelatinase - associated lipocalin (NGAL) µg/L**
Control	0.55±0.01a	0.69±0.01a
Fat	2.71±0.03b	1.59±0.02b
Orlistat & Fat	0.37±0.02c	1.21±0.01c
Cinnamon& Fat	0.20±0.01d	1.11±0.01d
Mix & Fat	0.11±0.008e	0.58±0.01e

Data represented as mean ± SD different letters significant differences at P-value (P<0.05)

When compared to the fats group, this dietary change significantly reduced the amount of cystatin C, Neutrophil gelatinase-associated lipocalin, in the group mix (orlistat and cinnamon) **(Moreira *et al* ., 2023)**. It has been demonstrated that taking orlistat and cinnamon extract together with a high-fat diet greatly lowers Cyst S and NGAL and increases GFR; however, their ability to predict end-stage kidney disease or the decline in renal function is limited , As a result, Cyst-C has been suggested as a fresh, trustworthy marker of lowering GFR , Moreover, NGAL has been found to be

an inflammatory biomarker and an independent predictor orenal damage recently **(Gutiérrez-Cuevas *et al* ., 2024).**

Based on information from high-fat diets Serum CYS is a more accurate indicator of severe renal damage, according to data from high-fat diet experiments; in the fat group, CYS levels significantly increased, indicating the severity of renal injury , On the other hand, in CYS, the renal damage was evident , Furthermore, it is well recognized that a variety of non-renal factors, such as the consumption of protein, dehydration, gastrointestinal bleeding, infections, and steroid use, have a substantial influence on that , CYS is therefore a trustworthy marker of ARF (acute renal failure) in rats **(Xie *et al* ., 2017).**

A comprehensive understanding of the underlying pathophysiology of the condition has been made possible by animal models of high-fat diet-taking rats that demonstrated effects on the kidney when examined with cinnamon extract and orlistat , Moreover, the rise in CYS is significantly different in rat models , Additionally , the operation method has a major effect on the CYS levels , But CYS also has certain advantages For instance , the body consistently produces CYS regardless of diet or physical composition , Its biochemical composition also allows it to be freely filtered in the renal glomerulus before being fully catabolized by the proximal tubules and exiting the bloodstream , The advantages of employing CYS in the earlier and more sensitive detection of acute renal injury have been shown in a number of randomized studies **(Khedr *et al* ., 2020).**

In this study, the rats administered a combination of orlistat and cinnamon extract had much lower levels of CYS , Furthermore, the slight differences in CYS values observed in the study may have been caused by plants that were given special treatment , high-fat diet in the liver and kidneys, among other organs , Free radicals and other metabolites produced by obesity harm cells through lipid peroxidation and other mechanisms , These free radicals have the potential to cause organ failure on several levels **(Shaik Mohamed Sayed *et al* ., 2023).**

We investigated the efficacy of cinnamon extract and orlistat in reducing kidney damage by means of histological analysis, monitoring of oxidative stress and inflammatory markers, and kidney damage resulting from a high-fat diet , Therefore, the ability of plant extracts to scavenge radicals is measured by measuring a drop in the cystatin C test , The main source of cinnamon strong antioxidant properties was the presence of terpenoid compounds like cinnamon aldehyde , Furthermore , this may also have something to do with the polyphenolic compounds present in CE , Additionally , the polyphenolic compounds in CE may also be engaged in the antioxidant process **(Hoi ., 2021).**

The phenolic group's capacity to take an electron and create relatively stable phenoxyl radicals can stop the chain oxidation reaction , We examined the oxidative stress biomarkers , When the antioxidant balance is tipped in favor of the prooxidants , oxidative stress results , For the purpose of researching the oxidative damage that polyunsaturated fatty acids in cellular membranes cause , lipid peroxidation is a helpful marker , One of the most promising new indicators of renal epithelial injury is neutrophil gelatinase associated lipocalin (NGAL) , a protein generated by damaged nephron epithelia (**Romejko *et al* ., 2023)**.

Which can be used to measure kidney function , NGAL is released into the blood and urine after being specifically induced in the damaged nephron , Clinical research shows that NGAL is a marker that responds less to adaptive hemodynamic responses and more to tissue stress and nephron injury than creatinine does **(Singer *et al* ., 2013).** The primary indicators of acute kidney injury are NGAL , It has been observed that NGAL, a member of the lipocalin superfamily, rises in response to renal tubular damage, hypertension, and inflammation that result from taken high fat diet , The function of NGAL has been clearly defined in a number of clinical contexts, including contrast-induced nephropathy, kidney transplantation, and septic shock **(Chen *et al* ., 2023).**

As the NGAL's sensitivity in predicting acute kidney damage, Additionally, it has been shown that an intrarenal inflammatory influx increases the expression of

NGAL in the renal tissue , In this study, administering orlistat and cinnamon also decreased NGAL expressions in the renal tissue. , However, in other groups, significantly higher these elevated renal NGAL expressions, possibly due to its anti-inflammatory properties **(Jorge *et al* ., 2022).**

Furthermore , NGAL were considerably lower in the group that received both (orlistat and cinnamon) , The study's findings indicate the importance of NGAL as a biomarker for the early detection of acute kidney injury (AKI) that result from high fat diet in a variety of clinical contexts by closely tracking the NGAL trend **(Atere *et al* ., 2021).**

4.4. Liver Oxidant and Antioxidant Enzymes

4.4.1. Effect of High fat diet , Orlistat and Cinnamon extract on reduced glutathione(GSH) and malondialdehyde (MDA) in Male Rats

The mean value of GSH were decrease in a significant value (P<0.05) while there were a significant (P>0.05) increment in MDA for fat group comparatively to control group.

Also there were a significant (P<0.05) decrement in GSH and MDA for orlistat group and cinnamon group when comparative with fat group.

While showed a significant (P>0.05) increment in GSH with a significant (P<0.05) decrement in MDA in group mix orlistat and cinnamon group when comparative with orlistat group and cinnamon group.

Table 4-5: Effect of High fat diet , Orlistat and Cinnamon extract on reduced glutathione (GSH) and malondialdehyde (MDA) in Male Rats

Liver oxidant & antioxidant enzymes test		
Groups	**GSH nmol/mg**	**MDA mmol/l**
Control	45.1±0.008a	12.99±0.01a
Fat	25.9±0.00b	28.62±0.02b
Orlistat & Fat	20.2±0.009c	17.25±0.007c
Cinnamon& Fat	15.5±0.01d	14.89±0.01d
Mix & Fat	38.7±0.009e	11.31±0.01e

Data represented as mean ± SD different letters significant differences at P-value (P<0.05)

Long-term high-fat diet consumption causes higher serum MDA concentrations, and lower GSH activity when compare to control group , the group given a high-fat diet had higher MDA levels , This is because oxidative stress raises free radical production, which intensifies lipid oxidation reactions in cell membranes and causes partial damage and elasticity loss through lipid peroxidation , If the unsaturated fatty acids in cellular membranes are thought to be the most susceptible to free radical interactions due to their double bonding, then this results in an increase in MDA , Furthermore, the continuous production of free radicals causes lipid peroxidation to continue, and the absence of antioxidants from either internal or external sources causes oxidative damage **(Arisha *et al* ., 2020).**

Damage that is visible to the various body tissues, The reason for the significant drop in GSH levels in the rats fed high-fat food was that they were consuming more antioxidants to counteract the production of excess free radicals in cases of hypercholesterolemia and triglycerides and produce free radicals as well , This decline is caused by a reduction in the raw materials needed to make it, such as nicotine amide diphosphate (NADPH), which is produced by the pentaphosphate sugar pathway and acts as a catalyst to activate glutathione reductase, which converts inactive forms of GSH back into active ones **(Haidari *et al* ., 2020).**

Its low concentration could possibly be the result of its higher rate of consumption in the cells of the body because it is one of the most significant non-enzymatic antioxidants and functions to eliminate oxidative stress, which causes free radicals and their byproducts, particularly ROS, as well as the oxidation of glutathione due to its antioxidant activity and subsequent conversion to the binary oxidized form Because glutathione plays a part in restoring the efficacy of some antioxidants, like vitamin C, in cases of oxidative stress, GSSG, which is toxic and promotes the production of new classes of free radicals, also consumes relatively large amounts of glutathione , Other variables that may impact glutathione levels include age, growth stage, nutritional status, hormonal balance, and the degree to which the cell is producing glutathione **(Morgan *et al* ., 2014).**

Additionally, oxidative stress and the production of reactive oxygen species brought on by the high concentration of triglyceride led to an increase in MDA and a decrease in GSH in rats with hyperlipidemia relative to the control group , This inhibition of the triglyceride lipase enzyme, which is responsible for breaking down triglycerides, increased fat metabolism and its concentrations in blood serum and liver extract **(Idoko *et al* ., 2023).**

Antioxidant systems react to this by becoming more active oxidative damage. As time passes, these systems become less sensitive and under stress, which causes organs to be destroyed , This shows that oxidative phosphorylation in the mitochondria results in the formation of an excessive amount of reactive oxygen species (ROS) from various sources , This leads to oxidative damage to the cell and a decrease in the activity of the antioxidant mechanism in the blood and several other cellular systems, including the vascular wall cells as well as those found in the blood , In addition to the inactivation and nitrification of protein by active oxygen species, a decrease in GSH is accompanied by an increase in nitric oxide (NO) in the event of free radical formation and increased oxidation, which results in the rapid consumption of defense systems **(Ahmed *et al* ., 2017).**

Addition to the main bioactive components of cinnamon , that decreased activities of the liver enzymes in the groups fed supplemented diet shows that the supplementation could protect the liver against liver-damaging effects of high-fat diet and improved excretory function of the kidney that marker for peroxidation **(Idoko *et al* ., 2023).**

These substances' anti-inflammatory and antioxidant properties have been shown to provide a number of pharmacological advantages , attributes ,Moreover, cinnamon has a high content of flavonoids, which have been shown to have hepatoprotective properties , Due to its ability to scavenge free radicals by giving them a hydrogen atom, cinnamon and its other purportedly bioactive components have the potential to be bioactive **(Mohammed and Ahmed ., 2024).**

Cinnamon has been shown recently to reduce inflammation and oxidative damage in male rats fed a high-fat diet , The main organo compounds in cinnamon, including ajoenes, allicin, and allinn, are what give it its medicinal properties , Additionally, cinnamon contains a significant amount of flavonoids like quercetin , It has been shown to be useful in preventing a variety of illnesses, such as oxidative stress and cancer , Also, it had been stated that using different forms of cinnamon extract could control and/or prevent a number of metabolic disorders, such as atherosclerosis and organ damage **(Li *et al* ., 2022).**

The group that received orlistat and cinnamon extract had higher levels of GSH compare to fat group because it contains antioxidant-containing compounds like betaine Because of its high electronic donor property, betaine has the potential to be an antioxidant **(Huang *et al* ., 2021).**

In our current study, HFD-fed rats showed a significant decrease in GSH and a significant increase in MDA in their kidneys compared to FAT rats , The groups that received orlistat showed comparable results , The dose of orlistat had a direct impact on oxidative stress , This has to do with oxidative stress brought on by an unbalanced production of reactive oxygen species (ROS) and decreased levels of antioxidant activity , which results in lipid, protein, and DNA oxidative damage in cells and organs , Though lower blood lipid levels are associated with weight loss, hyperoxaluria is thought to be the cause of these orlistat-related pathological renal consequences , The small intestine produces a soapy substance when fats are not absorbed, and when combined, produces oxalate when it reacts with calcium , Oxalate then enters the bloodstream and accumulates in the kidneys, leading to health issues **(Al-Safo and AlDulaimi ., 2022).**

Orlistat has been shown to have an impact on kidney function, raising the risk of acute renal injury, kidney stone disease, and oxidative nephropathy , Orlistat resulted in increased blood uric acid levels and the formation of renal urate crystals, which in turn cause chronic tubular interstitial nephropathy and acute tubular necrosis , It also caused the formation of blood vessels, a focal necrotic area with infiltration

of inflammatory cells, and congestion of some renal tubules with degeneration due to nephritis **(Liu *et al* ., 2024).**

4.5. Histopathological study

4.5.1. Effect of High Fat Diet , Orlistat and Cinnamon Extract on Kidney

Following the animals had undergone anesthesia, the kidney was removed and following fixation , sections of the kidney were obtained and fixed with formalin (10%) , Following processing in an alcohol and paraffin, the blocking of the samples was divided into sections and the samples were then stained with (H&E) histological examination of kidney section of control group were staind with haematocylin and eosin , as showed the normal histological architecture of renal cortex with significant glomeruli (black arrow) and regular renal tubules (red arrow) , as seen in the figure (4-1) **(Demiraslan *et al* ., 2024 , Al-Safo and AlDulaimi ., 2022).**

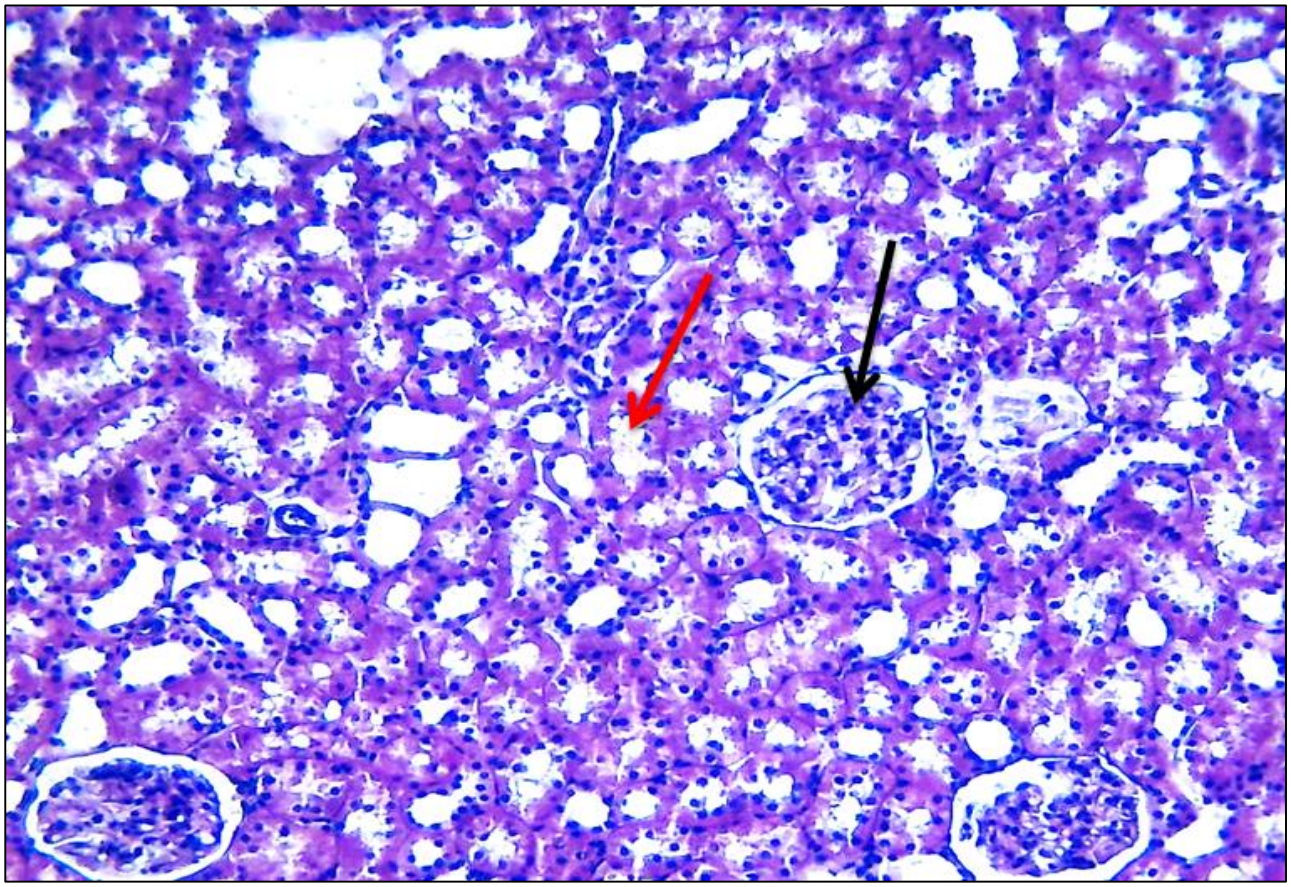

Figure (4-1) Photomicrograph of rats kidney tissue section from control group , showed the normal histological architecture of renal cortex with significant glomeruli (black arrow) and regular renal tubules (red arrow).(H and E, 10X)

Histological examination of kidney section for a high fat diet group were staind with haematocylin and eosin , as showed the abnormal appearance of the renal cortex, severe infiltration of inflammatory cells into the interstitial space, substantial glomerular atrophy and tubular necrosis, and notable changes in the glomeruli, as evidenced by atrophy interstitial per glomerular inflammation as seen in the figure (4-2)(4-3) (**Ramadan *et al* ., 2016).**

A high-fat diet are summed up and observed perivascular and per glomerular edema infiltrated with multiple inflammatory cells, along with dilated blood vessels **(Othman *et al* ., 2022).** There had been evidence of glomerular capillary and large blood vessel dilatation Similar findings were reported for histologically detected glomerular atrophy, necrosis, and oedema in addition to tubular deformations , The renal enlargement observed in HFD-fed rats could potentially be attributed to oedema resulting from infiltrations of mononuclear cells within the tubules , It makes perfect sense that dilatation could cause the kidney's volume to increase **(Yang *et al* ., 2024).**

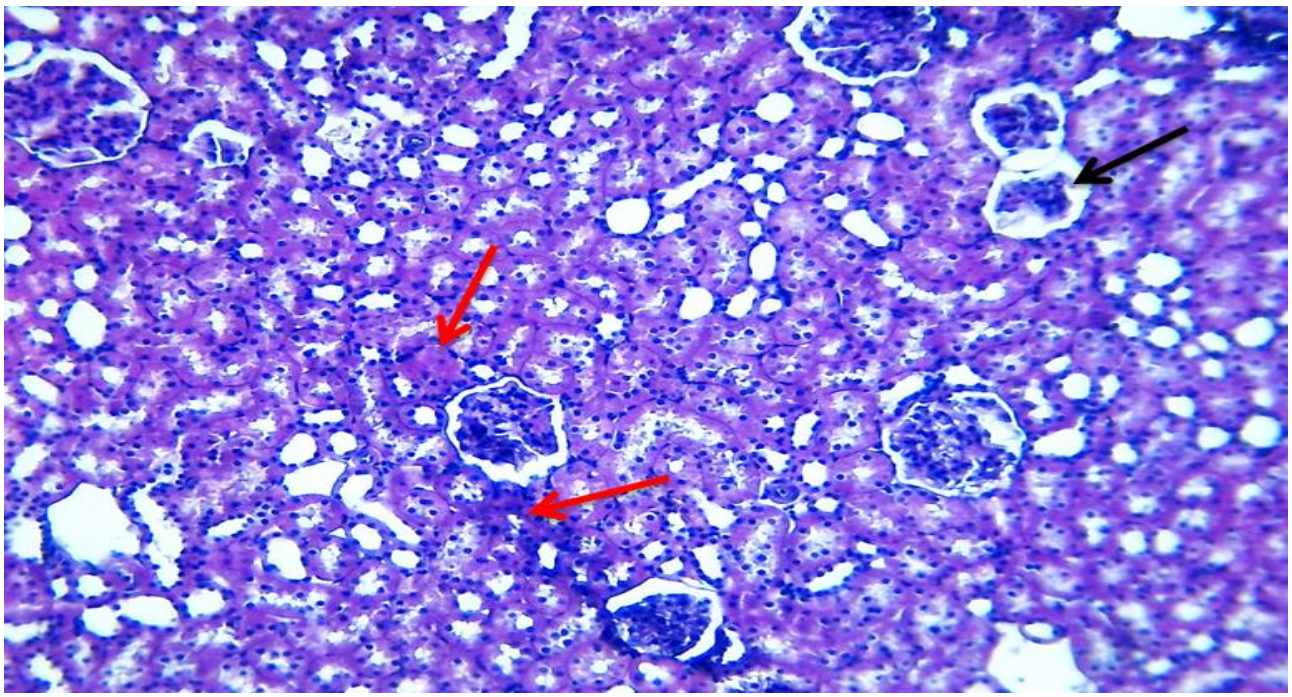

Figure (4-2) Photomicrograph of rats kidney tissue section from a high fat diet group , showing the abnormal appearance of renal cortex , significant glomerular atrophy (black arrow) and areas of tubular necrosis (red arrow).(H and E, 10X)

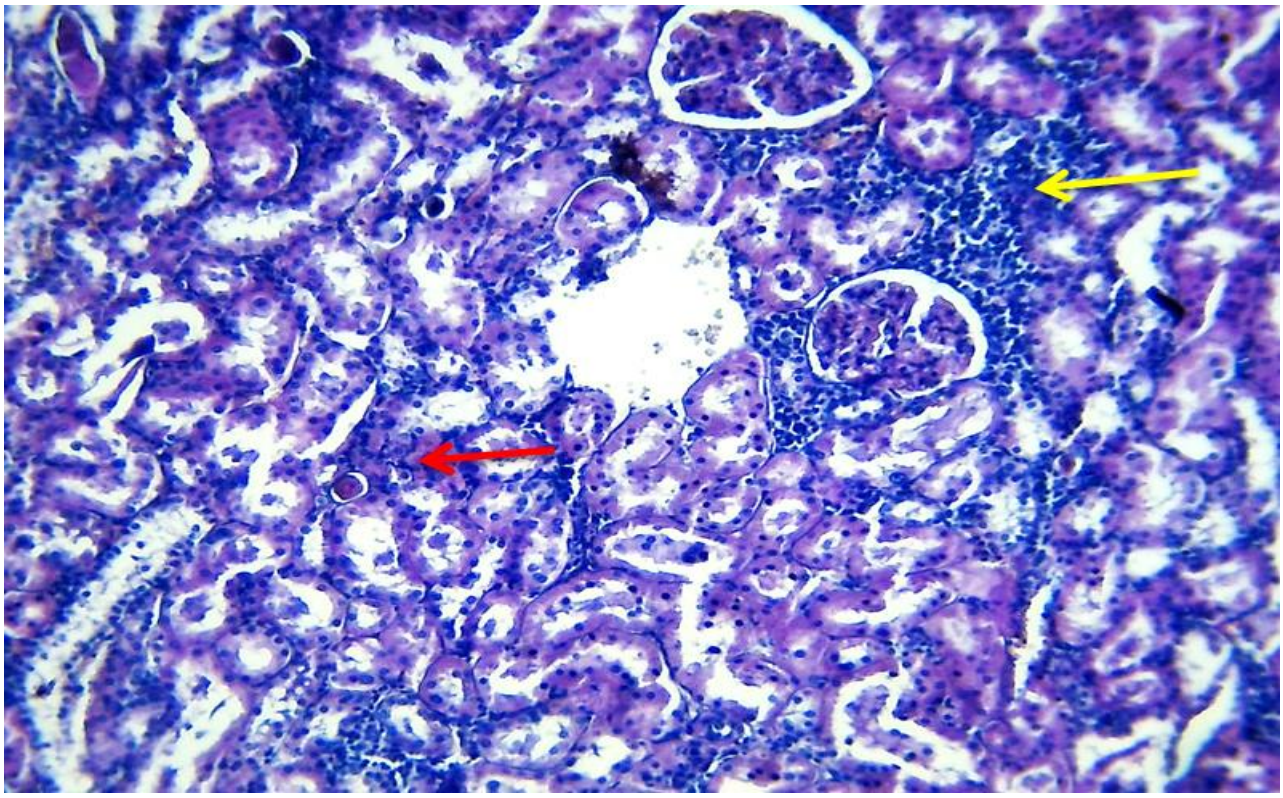

Figure (4-3) Photomicrograph of rats kidney tissue section from a high fat diet group , showing the abnormal morphological appearance of renal cortex , remarkable ,sever interstitial inflammatory cells infiltration (yellow arrow) and areas of tubular necrosis (red arrow).(H and E, 10X)

Histological examination of kidney section for a high fat diet and Orlistat group were staind with haematocylin and eosin , as showed mild histological improvements in cortical tissue , glomerulous atrophy , dilation of bowman capsule , interstitial inflammatory cells infiltration and significant tubular epithelium degeneration as seen in figure (4-4) **(Jin *et al* ., 2023).**

The administration of Orlistat to HFD rat results in various histological alterations in the kidney tissue, as demonstrated by the light microscopy observations conducted thus far **(Eleazu *et al* ., 2022).** These modifications include: **(a)** a hypermetric glomerular tuft linked to enlargement in the renal tubule lining epithelium and **(b)** a vacuolar glomerular tuft with enlarged endothelial cells lining the Bowman's capsule **(Sabik *et al* ., 2022).**

The administration of orlistat caused certain renal tubules to degenerate and there was a focal necrotic area with inflammatory cell infiltration and congested blood vessels **(Bays *et al* ., 2022).** HFD raises serum uric acid levels, which sets off

renal urate crystal formation and results in histological alterations , Urinary oxalate levels were found to be multiplied by orlistat, particularly in rats given diets high in fat or enriched with oxalate **(Amin *et al* ., 2014 , Al Obaidi and Rzoqi.,2023).**

Our histological analysis of kidney tissue showed that orlistat damages the kidneys by expanding Bowman's capsule and causing glomerular atrophy and tubule disruption in certain kidney tubules , It is believed that hyperoxaluria is the root cause of these pathological renal effects associated with orlistat , When fats are not absorbed in the small intestine leading to health issues **(Al-Safo and AlDulaimi ., 2022).** Furthermore, the effects of orlistat on kidney function showed that the drug may raise the risk of acute renal injury, kidney stone disease, and oxidative nephropathy , A focused necrotic area with inflammatory cell infiltration as a result of taking orlistat **(Verma *et al* ., 2023).**

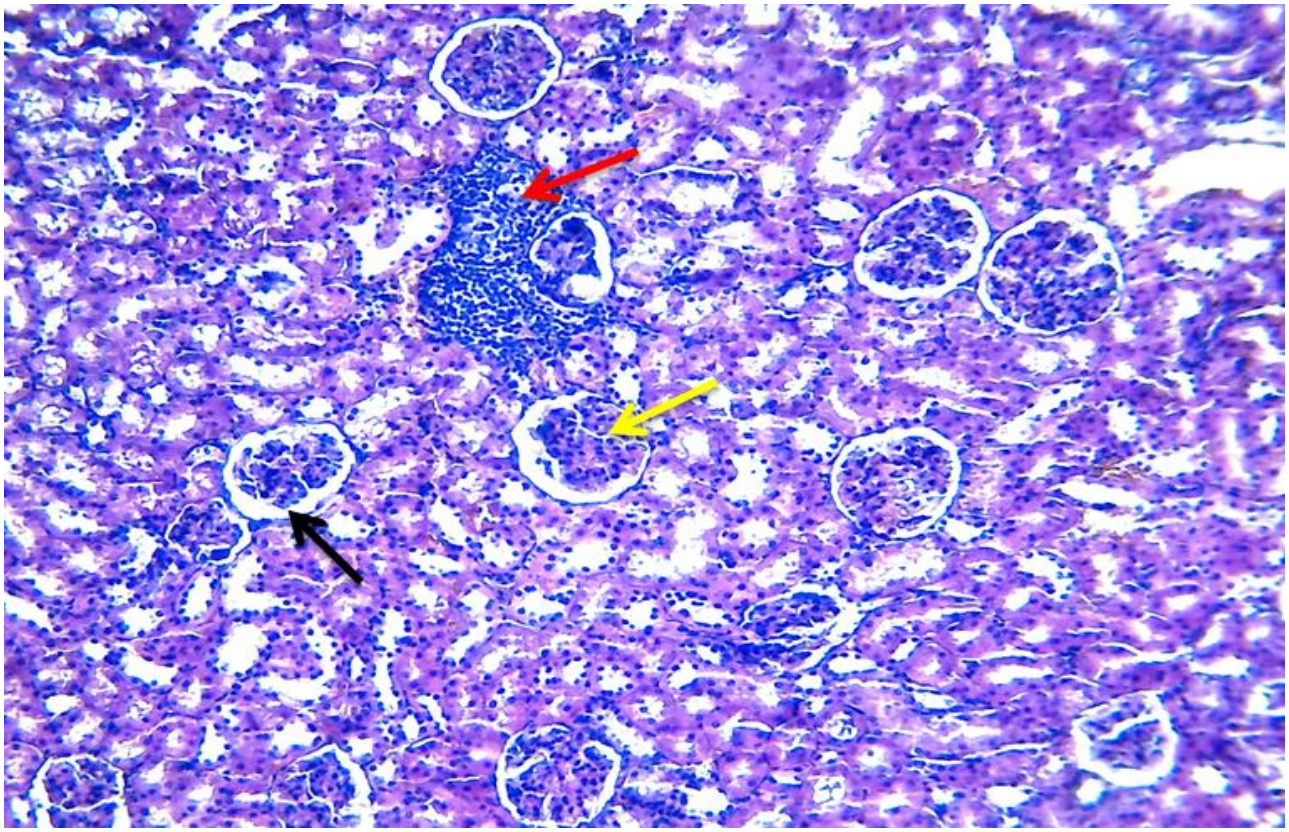

Figure (4-4) Photomicrograph of rats kidney tissue section from a high fat diet and Orlistat group , showing mild histological improvements in cortical tissue , glomerulous atrophy (yellow arrow) , dilation of bowman capsule(black arrow) , interstitial inflammatory cells infiltration (red arrow).(H and E, 10X)

Histological examination of kidney section for a high fat diet and Cinnamon group were staind with haematocylin and eosin , as showed significant histological

improvements in renal cortical tissue , normal glomeruli , normal tubules , slight interstitial inflammatory cells infiltration and mild degeneration as seen in figure (4-5) **(Sobhey *et al* ., 2023).**

Effects of long-term HFD on kidney levels that cinnamon's ability to shield against the toxicity of HFD , Strong antioxidants called flavonoids and phenolic compounds are found in high concentrations in cinnamon , Numerous studies have looked into cinnamon's antioxidant capacity against various agents' HFD **(Tekeli *et al* ., 2021).**

In this study, rats given cinnamon in addition to HFD consistently displayed notable findings clearly point to a beneficial improvement in renal function , Cinnamon may have a protective effect on the kidneys from HFD-induced oxidative damage by boosting antioxidant defense system activity, scavenging reactive oxygen species, and preventing lipid peroxidation because cinnamon has a high concentration of flavonoids and phenolic compounds, which function as potent antioxidants in addition **(Aslam *et al* ., 2023 , Khalisyaseen and Mohammed ., 2021).**

Histological of kidney showed normal glomeruli and tubules , Normal kidney morphology was also observed as they reported that cinnamon protects the kidney by reducing glomerular expansion and decreasing the tubular dilations (**Idoko *et al* ., 2023).**

Our histological examination revealed that the convoluted tubule close to the kidney was the most damaged area; however, the damage was significantly reduced when cinnamon was taken, and as a result of the effect, these components were not lost in the urine **(Ghonim *et al* ., 2017).**

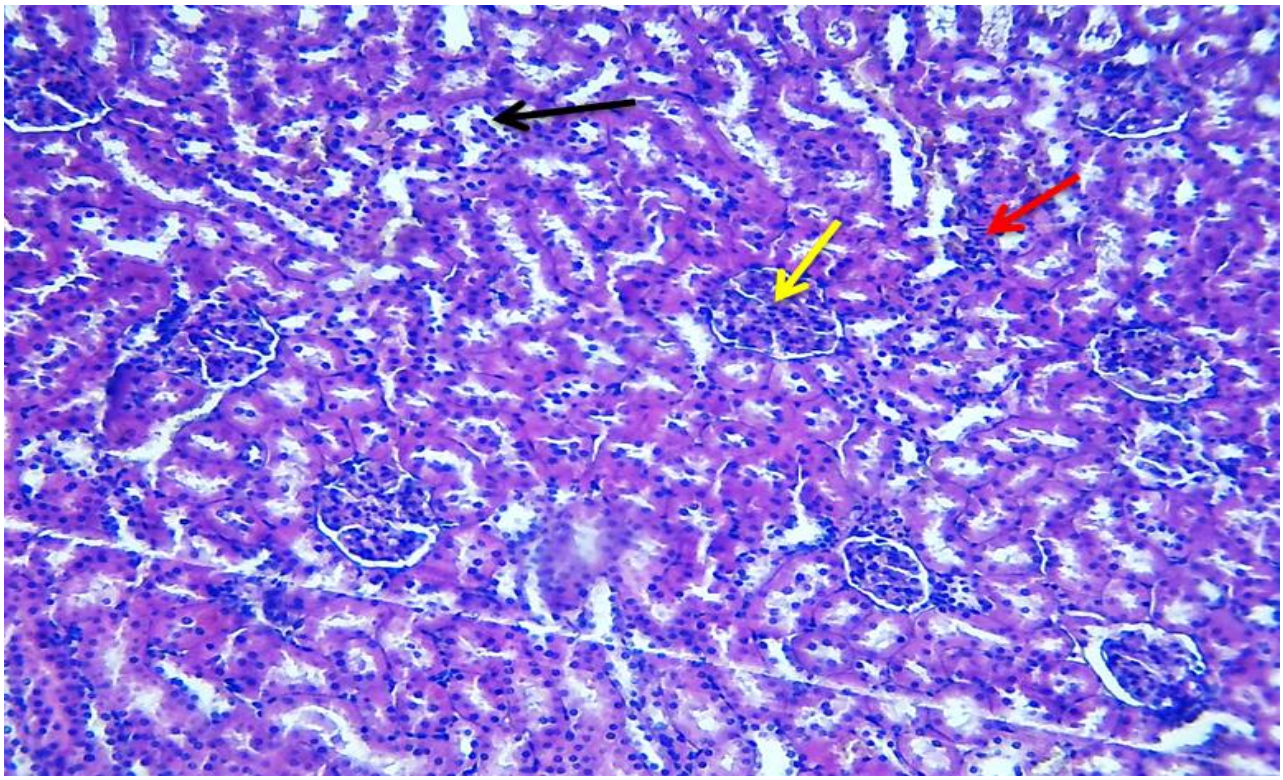

Figure (4-5) Photomicrograph of rats kidney tissue section from a high fat diet and Cinnamon group , showing significant histological improvements in renal cortical tissue , normal glomerli (yellow arrow) , normal tubules (black arrow) ,slight interstitial inflammatory cells infiltration (red arrow).(H and E, 10X)

Histological examination of kidney section for a high fat diet and Cinnamon with orlistat group were staind with haematocylin and eosin , as showed some histological alterations in renal tissue , normal glomeruli with little atrophied , normal tubules ,slight interstitial inflammatory cells infiltration and marked congestion with slight degeneration and mild congestion as seen in figure (4-6) **(Hamden ., 2022).**

Rat's pathological anatomical alterations in the kidneys were investigated in a combination group fed a high-fat diet along with rats given cinnamon with orlistat , Our analyses revealed that the combination therapy significantly altered the kidney's structural characteristics, which were classified as the elimination of significant cellular damage and necrosis, the absence of inflammatory cell infiltration, and the absence of tubular dilatation with cellular that same size and look **(Alshahrani *et al* ., 2021).**

Nonetheless, a combination of orlistat and cinnamon prevented cellular damage in rats fed a high-fat diet , In addition to these cellular modifications and kidney protection in the combination groups, histological observations further confirmed that taking the combination of cinnamon and orlistat with a high-fat diet showed non-cellular changes such as improved tubular damage and reduced renal necrosis , Nonetheless, the recent study demonstrates that consuming a high-fat diet along with the combination of cinnamon and orlistat improves cellular morphology because of their potent antioxidant activity, which also helps to strengthen and lessen kidney damage **(Hussain *et al* ., 2023).**

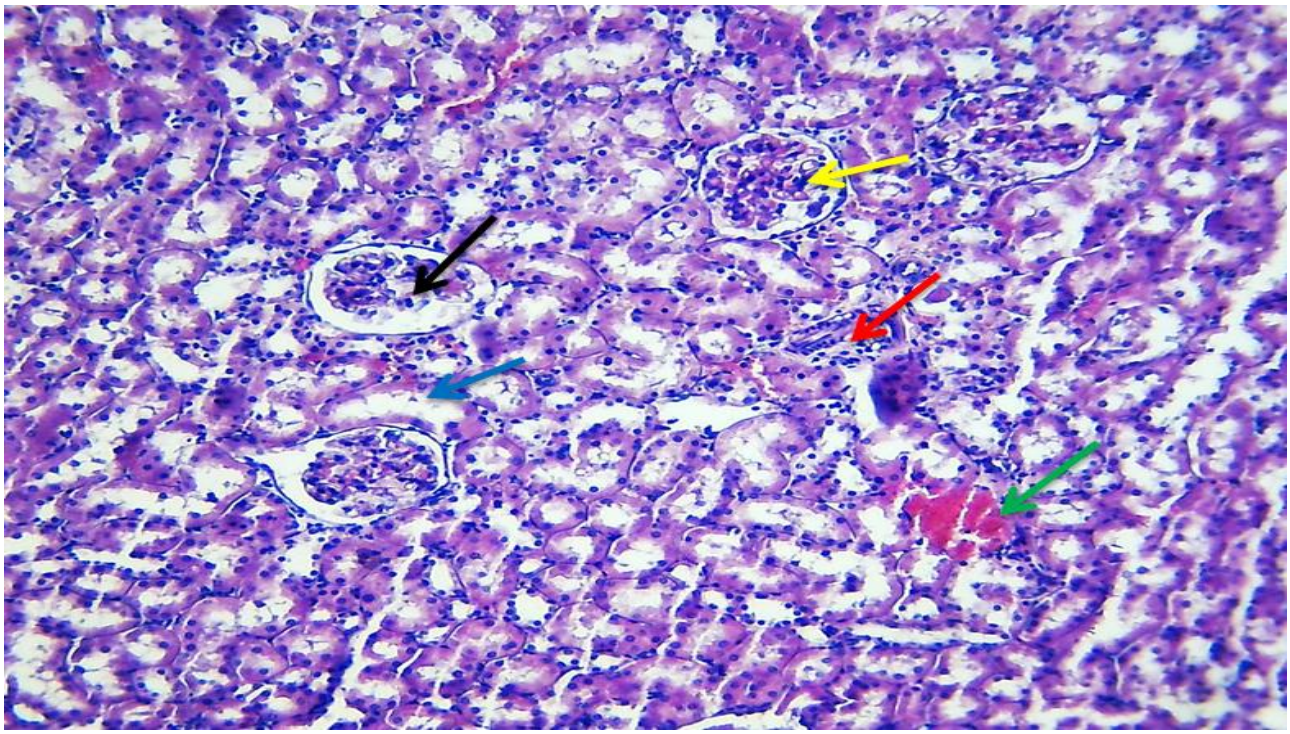

Figure (4-6) Photomicrograph of rats kidney tissue section from a high fat diet and Cinnamon with orlistat group , showing some histological alterations in renal tissue , normal glomeruli (yellow arrow)with little atrophied (black arrow) , normal tubules (blue arrow) ,slight interstitial inflammatory cells infiltration (red arrow) and marked congestion (green arrow).(H and E, 10X)

Chapter Five : Conclusions and Recommendations

5. Conclusions and Recommendations

5.1. Conclusions

1) Based on the conducted research, it can be concluded that adding cinnamon mix to one's diet can protect the kidney from oxidative damage , For this reason, it is advised to include a limited amount of the blended spices , a dose of 100 mg/kg body weight of cinnamon extract is an effective therapeutic dose for protecting the kidneys.

2) The results of this study demonstrated that cinnamon extract enhanced the lipid profile and decreased the activity of liver enzymes in rats fed a high-fat diet.

3) The main bioactive components of cinnamon, which result in improved levels of GSH and MIDA, as compared to orlistat group suggesting that a supplement could shield the liver from the damaging effects of a high-fat diet

4) A kidney section subjected to a high-fat diet and orlistat showed mild histological improvements in cortical tissue, glomerulous atrophy, dilation of Bowman capsule, infiltration of interstitial inflammatory cells, and significant tubular epithelium degeneration. Histological examination of the renal cortex revealed the normal histological architecture with significant glomeruli and regular renal tubules. In the section about a high-fat diet and cinnamon in combination with orlistat, it was noted that cinnamon showed glomeruli, normal tubules, mild degeneration, and slight infiltration of interstitial inflammatory cells.

5.2. Recommendations

1) The recommends using cinnamon extract to treat orlistat side effects or the effects of taking multiple medications at once on obesity**.**

2) More research is required to fully understand cinnamon's effects on the body, including how it can erase burn scars and heal wounds. Because of its ability to reduce pain and heal wounds, cinnamon may be able to help with postpartum pain.

3) Purification of the cinnamon's active component, which is used to reduce side effects and act on the kidneys**.**

4) Analyzing the effects of orlistat and researching its adverse effects on the digestive system, including any connection to undigested fats passing through the system in addition to disorders or pain in the stomach**.**

5) recommend conducting a study to assess the impact of orlistat on the immune system**.**

6) recommend conducting a study to assess the impact of orlistat on the nerve system.

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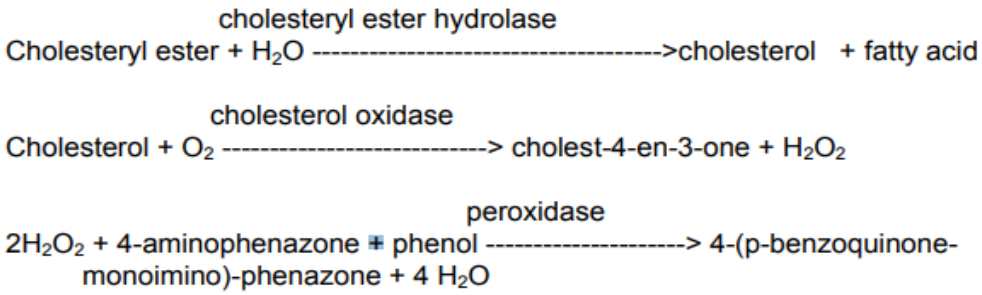
Appendices

Appendia I

Determination of Serum Total Cholesterol (TC) Concentration:

Principle:

Cholesterol is measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol , One of the reaction byproducts, H2O2 is measured quantitatively in a peroxidase catalyzed reaction that produces a color , Absorbance is measured at 500 nm , The color intensity is proportional to cholesterol concentration , The reaction sequence is as follows:



Elevated levels of cholesterol increase the risk for coronary heart disease (CHD) , Cholesterol is measured to help assess the patient's risk status and to follow the progress of patient's treatment to lower serum cholesterol concentrations**.**

Total Cholesterol (TC) was detected by use Enzymatic method described. which reaction scheme is as follows:

Cholesterol esters cholesterol +free fatty acids

Cholesterol +O2 cholesten4 one3 +H2O2

2H2O2+phenol+PAP quinoneimine (pink) +4H2O2

Procedure:

At room temperature Add 1000 µL of reagent and after that add 10 µL of Blank, Standard, Control or specimen CE 129 Let them stand at 37 °C for 5 min record absorbance at 500nm against reagent blank.

Calculation

The result was calculated according to this equation

Total Cholesterol (TC) = $abs(assay)abs(standerd)$ ×standerd concentration $abs(assay)$ = $absorbance\ of\ samble\ abs\ (standerd)$ = $absorbance\ of\ standerd$

Appendia II

Determination of Serum Triglyceride (TAG) Concentration (mg/dl):

it is as follows:

Triglycerides Glycerol + free fatty acids

Glycerol + ATP Glycerol 3 Phosphate + ADP

Glycerol 3 Phosphate + O2 DihydroxyacetonePhosphate + H2O2

POD Lipase GK GPO 130

H2O2 + 4 Chlorophenol + PAP Quinoneimine (pink) + H2O

The absorbance of the coloured complex (quinoneimine), proportional to the amount of triglycerides in the specimen, is measured at 500 nm.

Reagents Preparation

Add promptly the contents of vial R2 (Enzymes), into vial R1 (Buffer). Mix gently and wait for complete dissolution before using reagent (approximately 2 minutes).

Procedure:

The procedure was done as shown in the Table below:

Pipette into well identified test tubes	**blank**	**Standard**	**assay**
Regent	**1ml**	**1ml**	**1ml**
Demineralized water	**10ul**		
Standard		**10ul**	
Specimen			**10ul**

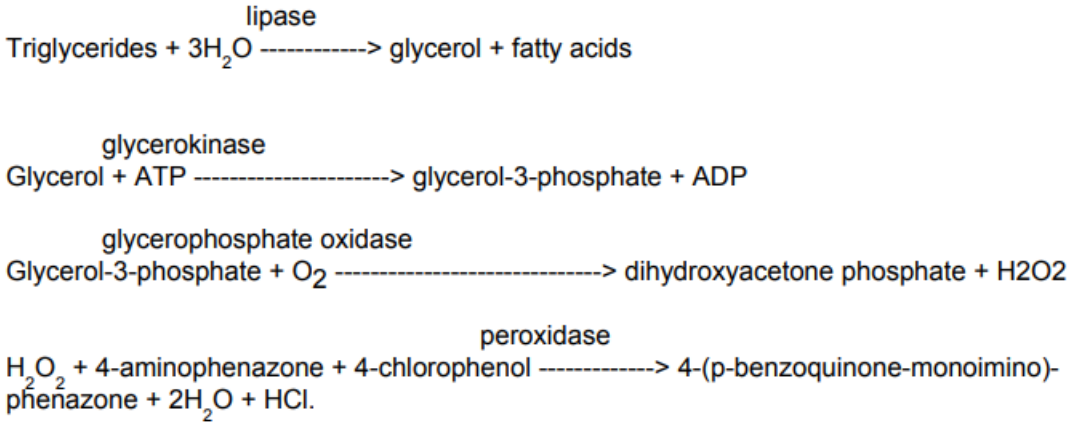
Calculation

The result was calculated according to this equation

Serum Triglyceride (TAG) = $abs(assay)abs(standerd$ ×standerd concentration

Principle:

Triglycerides are measured enzymatically in serum or plasma using a series of coupled reactions in which triglycerides are hydrolyzed to produce glycerol , Glycerol is then oxidized using glycerol oxidase, and H2O2, one of the reaction products, is measured as described above for cholesterol , Absorbance is measured at 500 nm , The reaction sequence is as follows:



High levels of serum triglycerides help mark conditions that are associated with Desirable fasting triglyceride levels are considered to be those below 200 mg/dL, and are further categorized as Borderline, 200-400 mg/dL; High, 400-1,000 mg/dL; and Very High (> 1000 mg/dL) , Very high triglycerides can result in pancreatitis and should be promptly evaluated and treated , Triglycerides are also measured because the value is used to calculate low density lipoprotein (LDL)-cholesterol concentrations

Appendia III

Determination of Serum High-Density lipoprotein-cholesterol

Principle

Accelerator selective detergent methodology. Direct method, without specimen pre-treatment. During the first phase, LDL, VLDL particles and Chylomicrons generate free Cholesterol, which through an enzymatic reaction, produce Hydrogen peroxide. The generated peroxide is consumed by a peroxidase reaction with DSBmT yielding a colourless product. During the second phase, specific detergent solubilizes HDL-Cholesterol. In conjunction with CO and CE action, POD + 4-AAP develop a colored reaction which is proportional to HDL-Cholesterol concentration. The absorbance is measured at 600 nm.

Procedure

The procedure was done as shown in the table below:

Tubes	Blank	Calibrator	assay
Regent 1	300 µL	300 µL	300 µL
Calibrator		3 µL	
specimen			3 µL

Let stand in 37°C for 5 min and Record absorbance of them at 600 nm against reagent blank. Add 100 µL of regent 2 Let stand in 37°C for 5 min and Record absorbance of them at 600 nm against reagent blank.

Calculation

The result was calculated according to this equation

HDL-C-= $\Delta \boldsymbol{abs.assay} \Delta \boldsymbol{abs.calibrator}$ × calibrator concentration

Δ abs.assay = the different between the two record for the assay

Δabs.calibrator= the different between the two record for the calibrator.

Appendia IV

Determination of Serum Low Density lipoprotein-cholesterol

Principle

Direct method using selective detergents without specimen pre-treatment. During the first phase, only non-LDL lipoproteins are solubilised by detergent 1. Such generated Cholesterol, subjected to Cholesterol oxidase (CO) and Cholesterol esterase (CE)

actions, produces a colourless compound. During the second phase, detergent 2 solubilises LDL-Cholesterol. The chromogenic coupler allows for colour formation that is proportional to the concentration of LDL-Cholesterol. The absorbance is measured at 546 nm (520-580).

Procedure

The procedure was done as shown in the table below:

Tubes	Blank	Calibrator	assay
Regent 1	300 µL	300 µL	300 µL
Calibrator		3 µL	
specimen			3 µL

Let stand in 37°C for 5 min and Record absorbance of them at 546 nm against reagent blank. Add 100 µL of regent 2 Let stand in 37°C for 5 min and Record absorbance of them at 546 nm against reagent blank.

Calculation

The result was calculated according to this equation

HDL-C-=Δ $\boldsymbol{abs.assay}\Delta\boldsymbol{abs.calibrator}$ × calibrator concentration

Δ abs.assay = the different between the two record for the assay

Δabs.calibrator= the different between the two record for the calibrator.

Appendia V

Determination of Serum Very Low-density lipoprotein-cholesterol

VLDL-c concentration

was determined by dividing triglycerides values (mg /dl) on equation

VLDL-c conc. (mg/dL) = Triglycerides conc. /5

Principle

Direct method using selective detergents without specimen pre-treatment. During the first phase, only VLDL-C are solubilised by detergent 1. Such generated Cholesterol, subjected to Cholesterol oxidase (CO) and Cholesterol esterase (CE) actions, produces a colourless compound. During the second phase, detergent 2 solubilises VLDL-Cholesterol. The chromogenic coupler allows for colour formation that is proportional to the concentration of VLDL-Cholesterol. The absorbance is measured at 546 nm (520-580) .

Appendia VI

Estimation of Urea

Regents and procedure of Urea

A1	Sodium salicylate Sodium nitroprusside phosphate buffer	62 mmol/L 3.4 mmol/L 20 mmol/L pH 6.9.
A2	Urease	> 500 U/mL
B	Sodium hypochlorite sodium hydroxide	7 mmol/L 150 mmol/L.
S	Urea standard	50 mg/dL - 8.3 mmol/L - BUN 23.3 mg/dL

Reagent Preparation

Reagent (B) and Standard (S) are provided ready to use.

Reagent (A): Transfer the contents of one Reagent A2 vial into a Reagent A1 bottle). Mix thoroughly. Other volumes can be prepared in the proportion: 1 mL Reagent A2 + 24 mL Reagent A1.

Additional Equipment

− Thermostatic water bath at 37ºC

− Analyzer, spectrophotometer or photometer able to read at 600 ± 20 nm.

Samples

Serum, plasma or urine collected by standard procedures. Dilute urine 1/50 with distilled water before measurement.

Appendia VII

Estimation of Serum Creatinine

Regents and Procedure of creatinine

R1	Sodium hydroxide	1.6 mol/l
R2	Picric acid	0.35 mmol/l
R3	Standard	2 mg/ dl

Additional reagent (Trichloroacetic acid TCA 10% **)**

Preparation Of Working Reagent

Mix proportionally 1/1 the reagent R1 and R2

Deoroteinisation Procedure

TCA	1.0 ml
Serum or plasma	1.0 ml

Mix well. Centrifuge a 2500 rpm for 10 min. then pour off the supernatant

Procedure

Wavelength	500-550 nm
Cuvette	1 cm light path
Temperature	25 ° C
Measurement	Against blan
Method	Endpoint - increasing

	Blank	**Standard**	**sample**
Distilled water	0.5 ml	-	-
TCA solution	0.5 ml	0.5 ml	-
Standard	-	0.5 ml	-
Supernatant	-	-	1.0 ml
Reagent mixture	1.0 ml	1.0 ml	1.0 ml

Mix let stand for 20 min. at room temperature, read the optical density (O.D.) of sample and standard against blank .

Calculation

Sample concentration = O.D sample × Standard concentration/

O.D standard

Principle

Creatinine reacts with picric acid in an alkaline solution to form a reddish colored complex. The reaction is commonly known as the Jaffe reaction and the red colored product as the Janovski complex. The assay is based on the reaction of creatinine with sodium picrate as described by Jaffe. Creatinine reacts with alkaline picrate

forming a red complex. The time interval chosen for measurements avoids interferences from other serum constituents. The intensity of the color formed is proportional to the creatinine concentration in the sample.

Appendia VIII

Serum Cystatin C level

Test Principle

The test principle applied in this kit is Sandwich enzyme immunoassay. The microtiter plate provided in this kit has been pre-coated with an antibody specific to Cystatin C(Cys-C). Standards or

samples are added to the appropriate microtiter plate wells then with a biotin-conjugated antibody specific to Cystatin C(Cys-C). Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each

microplate well and incubated. After TMB substrate solution is added, only those wells that contain Cystatin C(Cys-C), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in

color. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450nm ± 10nm. The concentration of Cystatin C(Cys-C) in the samples is then determined by comparing the OD of the samples to the standard curve.

Reagent Preparation

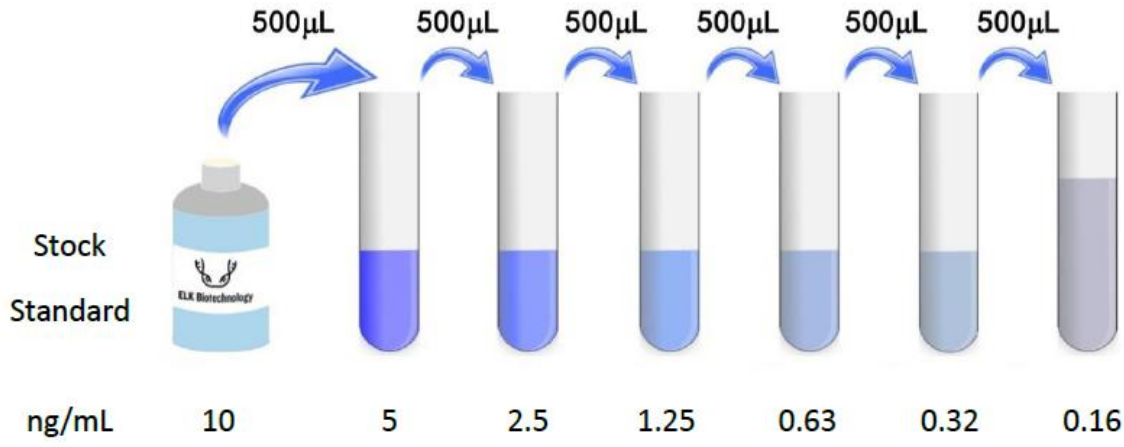
1. Bring all kit components and samples to room temperature (18-25°C) before use.

2. If the kit will not be used up in 1 time, please only take out strips and reagents for present

experiment, and save the remaining strips and reagents as specified.

3. Dilute the 25×Wash Buffer into 1×Wash Buffer with double-distilled Water.

4. Standard Working Solution - Centrifuge the Standard at 1000 × g for 1 minute. Reconstitute the Standard with 1.0 mL of Standard Diluent Buffer, kept for 10 minutes at room temperature, shake gently (not to foam). The concentration of the Standard in the stock solution is 10 ng/mL. Please prepare 7 tubes containing 0.5 mL Standard Diluent Buffer and use the Diluted Standard to produce a double dilution series according to the picture shown below. To mix each tube thoroughly before the next transfer, pipette the solution up and down several times. Set up 7 points of Diluted Standard such as 10 ng/mL, 5 ng/mL, 2.5 ng/mL, 1.25 ng/mL, 0.63 ng/mL, 0.32 ng/mL, 0.16 ng/mL, and the last EP tubes with Standard Diluent is the Blank as 0 ng/mL. In order to guarantee the experimental results validity, please use the new Standard Solution for each experiment. When diluting the Standard from high concentration to low concentration, replace the pipette tip for each dilution. Note: the last tube is regarded as a Blank and do not pipette solution into it from the former tube.



5) 1×Biotinylated Antibody and 1×Streptavidin-HRP - Briefly spin or centrifuge the stock Biotinylated Antibody and Streptavidin-HRP before use. Dilute them to the

working concentration 100-fold with Biotinylated Antibody Diluent and HRP Diluent, respectively.

6) TMB Substrate Solution - Aspirate the needed dosage of the solution with sterilized tips and do not http://www.elkbiotech.com elkbio@8 elkbiotech.com dump the residual solution into the vial again.

Appendia IX

Serum Neutrophil gelatinase-associated lipocalin (NGAL)

Test Principle

The test principle applied in this kit is Sandwich enzyme immunoassay. The microtiter plate provided in this kit has been pre-coated with an antibody specific to Neutrophil Gelatinase Associated

Lipocalin (NGAL). Standards or samples are added to the appropriate microtiter plate wells then with a biotin-conjugated antibody specific to Neutrophil Gelatinase Associated Lipocalin (NGAL). Next, Avidin

conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After TMB substrate solution is added, only those wells that contain Neutrophil Gelatinase Associated Lipocalin (NGAL), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450nm ± 10nm. The concentration of Neutrophil Gelatinase Associated Lipocalin(NGAL) in the samples is then determined by comparing the OD of the samples to the standard curve.

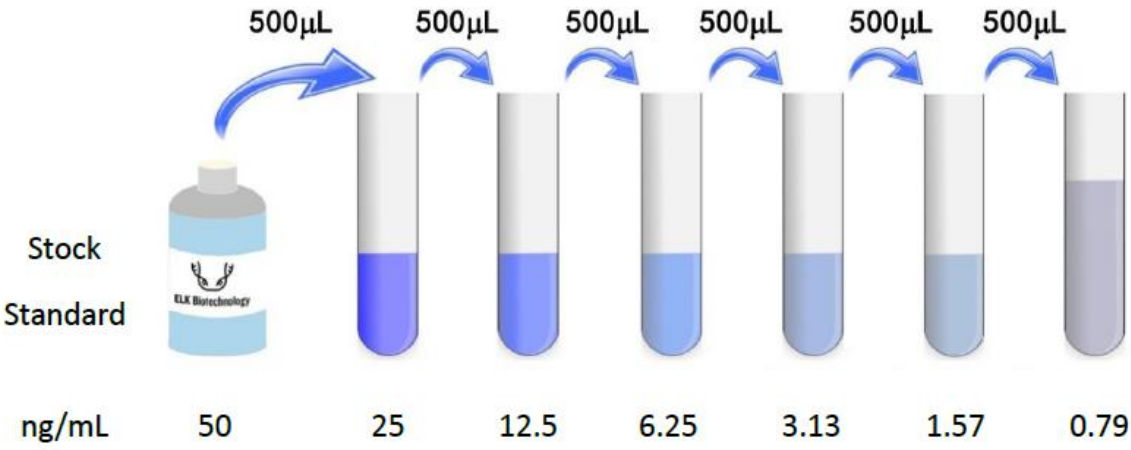
Reagent Preparation

1. Bring all kit components and samples to room temperature (18-25°C) before use.

2. If the kit will not be used up in 1 time, please only take out strips and reagents for present experiment, and save the remaining strips and reagents as specified.

3. Dilute the 25×Wash Buffer into 1×Wash Buffer with double-distilled Water.

4. Standard Working Solution - Centrifuge the Standard at 1000 × g for 1 minute. Reconstitute the Standard with 1.0 mL of Standard Diluent Buffer, kept for 10 minutes at room temperature, shake gently (not to foam). The concentration of the Standard in the stock solution is 50 ng/mL. Please prepare 7 tubes containing 0.5 mL Standard Diluent Buffer and use the Diluted Standard to produce a double dilution series according to the picture shown below. To mix each tube thoroughly before the next transfer, pipette the solution up and down several times. Set up 7 points of Diluted Standard such as 50 ng/mL, 25 ng/mL, 12.5 ng/mL, 6.25 ng/mL, 3.13 ng/mL, 1.57 ng/mL, 0.79 ng/mL, and the last EP tubes with Standard Diluent is the Blank as 0 ng/mL. In order to guarantee the experimental results validity, please use the new Standard Solution for each experiment. When diluting the Standard from high concentration to low concentration, replace the pipette tip for each dilution. Note: the last tube is regarded as a Blank and do not pipette solution into it from the former tube.



5. 1×Biotinylated Antibody and 1×Streptavidin-HRP - Briefly spin or centrifuge the stock Biotinylated Antibody and Streptavidin-HRP before use. Dilute them to the

working concentration 100-fold with Biotinylated Antibody Diluent and HRP Diluent, respectively.

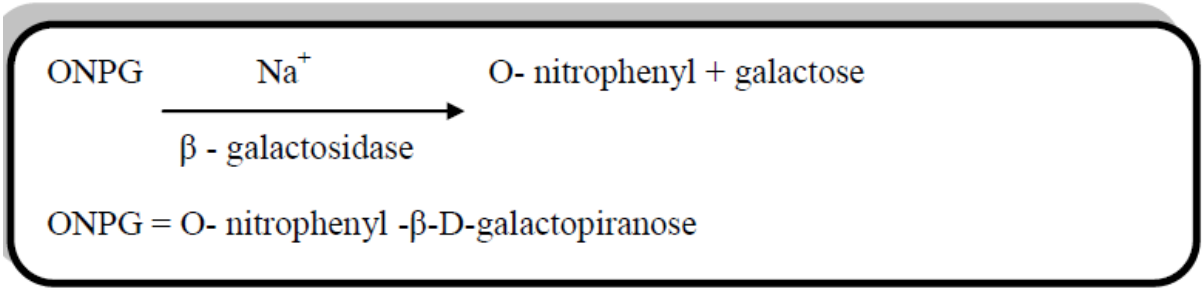
6. TMB Substrate Solution - Aspirate the needed dosage of the solution with sterilized tips and do not http://www.elkbiotech.com elkbio@8 elkbiotech.com dump the residual solution into the vial again.

Appendia X

Determination of Serum Sodium Level (mmol/L):

Sodium measurements are used to monitor electrolyte balance in the diagnosis and treatment of disease conditions characterized by low or high blood sodium levels. Sodium is determined enzymatically via sodium-dependent β - galactosidase activity with ONPG as substrate. The absorbance at 405 nm of the product O-nitrophenyl is proportional to the sodium concentration.

Reaction Principle:



Reaction Composition:

R1 - Good's buffer (pH 8.5), β-D-galactosidase (<8 U/mL), Cryptand (>0.4 mM), proclin 300 (0.02%).

R2 - Good's buffer (pH 6.5), ONPG (>0.5 mM), Proclin 300 (0.02%).

CAL - Sodium / Potassium standard. Sodium (Na+) 160 mmol/L. / Potassium 6.0 mmol/L.

Procedure:

1. Bring reagents and samples to room temperature.

2. Pipette into labelled cuvettes:

Cuvettes	Blank	Sample	Calibrator
R1. Reagent	1.0 mL	1.0 mL	1.0 mL
Sample	- - - - - - -	40 µL	- - - - - - -
Calibrator	- - - - - - -	- - - - - - -	40 µL
R2. Reagent	0.5 mL	0.5 mL	0.5 mL

3. Mix, incubate for 1 minute at 37ºC and read (A1) a 405 nm.

4. Incubate for 2 minutes at 37ºC and read (A2) a 405 nm.

Calculations:

$$\frac{(A_2 - A_1)\ \text{sample}}{(A_2 - A_1)\ \text{calibrator}} \times C\ \text{calibrator} = \text{mmol/L}$$

Principle

The LX system utilizes indirect (or diluted) I.S.E. methodology to determine the concentration of sodium in biological fluids. The LX determines sodium ion concentration by measuring electrolyte activity in solution. When the sample/buffer mixture contacts the electrode, sodium ions undergo an ion exchange in the hydrated outer layer of the glass electrode. As the ion exchange takes place, a change in

voltage (potential) is developed at the face of the electrode. The potential follows the Nernst equation and allows the calculation of sodium concentration in a solution.

Appendia XI

Determination of serum potassium level (mmol/L):

Potassium measurements are used to monitor electrolyte balance in the diagnosis and treatment of disease conditions characterized by low or high blood potassium levels. Potassium is determined spectrophotometrically through a kinetic coupling assay system using potassium dependent pyruvate kinase. Pyruvate generated is converted to lactate accompanying conversion of NADH to NAD. The corresponding decrease of optical density at 380 nm is proportional to the potassium concentration in the serum.

Reagent Composition:

R1 - LDH < 50 KU/L, NADH < 10 mmol/L, sodium azide 0,05% and stabilizers.

R2 - Pyruvate kinase < 50 KU/L, sodium azide 0,05% and stabilizers.

CAL - Sodium / Potassium standard. Sodium (Na+) 160 mmol/L / Potassium (K+) 6.0 mmol/L.

Procedure:

1. Bring reagents and samples to room temperature.

2. Pipette into labelled cuvettes:

Cuvettes	Blank	Sample	Calibrator
R.1 Reagent	1.0 mL	1.0 mL	1.0 mL
Sample	- - - - - - -	25 µL	- - - - - - -
Calibrator	- - - - - - -	- - - - - - -	25 µL

3. Mix, incubate for 5 minutes at 37°C.

4. Add:

R2. Reagent	250 µL	250 µL	250 µL

5. Mix, incubate for 1 minutes at 37ºC and read (A1) at 405 nm.

6.Mix, incubate for 3 minutes at 37ºC and read (A2) at 405 nm.

Calculations:

$$\frac{(A_2 - A_1)\ \text{sample}}{(A_2 - A_1)\ \text{calibrator}} \times C\ \text{calibrator} = \text{mmol/L}$$

Principle

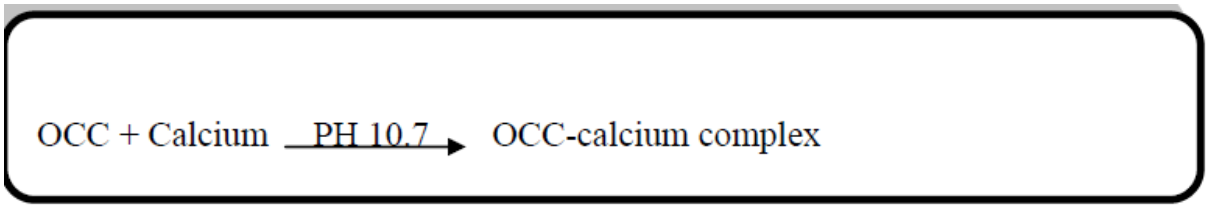
Serum potassium is measured by the use of a flame photometer or ion-selective electrode. The procedure is rapid, simple, and reproducible. In interpreting serum potassium, it should be kept in mind that because the intracellular potassium concentration is approximately fortyfold greater than the extracellular concentration, any maneuver that would result in the release of a small amount of intracellular potassium will erroneously raise serum potassium. These include: (1) tight tourniquet; (2) vigorous exercise of the extremity during blood drawing; (3) hemolysis due to vigorous shaking of the test tube; (4) thrombocytosis (platelet count greater than 600,000); and (5) leukocytosis (WBC greater than 200,000). In the last two situations, the longer the blood stands, the greater the rise in serum potassium will be**.**

Appendia XII

Determination Serum calcium level (mg/dl):

The method is based on the specific binding of cresolftalein complexone (OCC), a metallochromic indicator, and calcium at alkaline pH with the resulting shift in the absorption wavelength of the complex. The intensity of the cromophore formed is proportional to the concentration of total calcium in the sample.

Reaction Principle:



Reagent Composition:

R1 - OCC indicator. O-Cresolphtalein complexone 0.16 mmol/L, HCl 60 mmol/L, 8-quinolinol 7 mmol/L.

R2 - OCC buffer. AMP 0.35 mol/L, pH 10.7.

CAL - Calcium / Magnesium standard. Calcium 10 mg/dL / Magnesium 2 mg/dL. Organic matrix based primary standard. Concentration value is traceable to Standard Reference Material 909b.

Procedure:

1. Bring reagents and samples to room temperature.

2. Pipette into labelled test tubes:

Tubes	Blank	Sample	CAL standard
Working reagent	1.0 mL	1.0 mL	1.0 mL
Sample	- - - - - - -	10 µL	- - - - - - -
CAL standard	- - - - - - -	- - - - - - -	10 µL

3. Mix and let the tubes stand 2 minutes at room temperature.

4. Read the absorbance (A) of the samples and the standard at 570 nm against the reagent blank.

Calculations:

Serum, plasma

$$\frac{A\ \text{sample}}{A\ \text{standard}} \times C\ \text{standard} = \text{mg/dL total calcium}$$

Principle

The measurement of serum calcium is fraught with possible errors. Several means of contamination might lead to false elevations of serum calcium concentration. Falsely low levels are less common, so if several measurements are obtained, the lowest is usually the most accurate. The precision of the SMAC analysis, an automated colorimetric technique, is usually equal or superior to that of manual analysis. Nevertheless, falsely high or low values may be obtained in patients with liver or renal failure or in patients with lipemic or hemolyzed specimens. Venous occlusion of the arm during venipuncture may increase the total concentration of serum calcium by up to 0.3 mmol/L. This results from an increase in plasma protein concentration caused by hemodynamic changes. Another source of error is posture. If the patient stands up from a supine position, there may be an increase of 0.05 to 0.20 mmol/L in serum calcium. Still another possible source of error is hemolysis. Some methods of

measuring calcium are affected by high levels of hemoglobin, and red cells may take up calcium after prolonged contact. If an error is suspected and the measurement is to be redone, the blood should be drawn following an overnight fast because the daily intake of calcium may contribute to the serum calcium concentration as much as 0.15 mmol/L. Still other variations in the level of serum calcium need to be mentioned. Exercise just before venipuncture tends to increase serum calcium, so the patient should be rested for at least 15 minutes prior to sampling. Men tend to have a higher serum calcium by 0.02 to 0.04 mmol/L during summer versus winter. Postmenopausal women, however, have higher levels of calcium in winter as compared to summer. Men 15 to 45 years of age tend to have serum calcium levels 0.02 to 0.05 mmol/L higher than similarly aged women. While these values generally fall for both sexes during this 30-year period, this trend reverses for women after the age of 45 until they reach 75 when serum calcium levels again tend to fall.

Appendia XIII

Determination of Serum Malondialdehyde Level (MDA) Concentration (µ mol/L)

Principle:

This method quantifies lipid peroxides by measuring aldehyde breakdown products of lipid peroxidation. A basic principle of the method is the reaction of one molecule of malondialdehyde and two molecules of thiobarbituric acid to form a red MDA-TBA complex which can be measure at 535 nm.

Stock TCA – TBA – HCl Reagent

It was prepared by dissolving 15% W/V trichloroacetic acid and 0.375% W/V thiobarbituric acid and 0.25 N HCl to make 100 ml (2.1 ml of concentrated HCl in 100 ml). This solution was mildly heated to assist in the dissolution of TBA.

Dissolved 15 gm TCA and 0.375 mg thiobarbituric acid in 0.25 N HCl and volume was made up to 100 ml with 0.25 N HCl.

Procedure:

To 0.4 ml of serum, 0.6 ml TCA-TBA-HCl reagents were added. It was mixed well and kept in boiling water bath for 10 minutes. After cooling 1.0 ml freshly prepared 1N NaOH solution was added to eliminate centrifugation. This absorbance of pink color was measured at 535 nm against blank which contained distilled water in place of serum. In blank 0.4 ml distilled water and 0.6 ml TCA-TBA-HCl reagent was mixed and boiled. Blank was always taken.

Calculation:

extinction coefficient of MDA at 535 nm is = 1.56 × 105

MDA concentration = χ / 0.0624 nmol / ml.

Appendia XIV

Serum Reduced Glutathione Concentration (GSH)

Catalase activity was assessed by incubating the enzymes ample in 1.0 ml substrate (65 mmol/ml hydrogen peroxide in 60 mmol/l sodium–potassium phosphatebuffer, pH7.4)at37 °C for three minutes. There action was stopped with ammonium molybdate. Absorbance of the yellow complex of molybdate and hydrogen peroxide is measured at374nm against the blank.

Reagents

1. Sodium, potassium phosphate buffer (50mM,pH7.4): this buffer is prepared by dissolving 1.1g of Na2HPO4 and 0.27g of KH2PO4 in 100ml distilled water.

2. H2O2 (20 mM) in 50mmol/l sodium, potassium phosphate buffer: this solution is freshly diluted and standardized daily using a molar extinction coefficient of 43.6M_1 cm_1 at 240nm.

3. Ammonium molybdate (32.4mmol/l).

Table 1

Reagents	Test	Control-test*	Standard	Blank
Serum	100 µl	100 µl	–	–
D.W.	–	1000 µl	100 µl	1100 µl
Hydrogen peroxide	1000 µl	–	1000 µl	–
Mix with vortex and incubate at 37 °C for 3 min, after that, add:				
Ammonium molybdate	4000 µl	4000 µl	4000 µl	4000 µl
After that, the tubes were kept at room temperature. Changes in absorbance were recorded at 374 nm against the reagent blank.				

4. Calculation The rate constant of a first-order reaction (k) equation is used to determine catalase activity:

t: time.

S°: absorbance of standard tube

S: absorbance of test tube.

M: absorbance of control test (correction factor).

Vt: total volume of reagents in test tube. Vs: volume of serum.

Appendices XV

Procedure of Histological study

with aid of the light microscope as the following steps:

1) Fixation :- The specimen fixated in the formalin 10 % for 24 – 48 hours.

2) Washing and dehydration :- After fixation the specimens washed with water to remove the fixative in order to avoid the interaction between the fixative and staining materials used later. By dehydration the water had been completely extracted from fragments by bathing them successively in a graded series of of ethanol and water (70 %, 80 %, 90 %, and 100 % ethanol)

3) Clearing :- Bathing the dehydrated fragments in solvent (xylene) for 30–60 minutes, this step was repeated 3 times. As the tissues clearing, they generally became transparent.

4) Infiltration and Embedding :- Once the tissue fragments were impregnated with the solvent, they were placed in melted paraffin in an oven, typically at 52℃. The heat causes the solvent to evaporate and the space within the tissues becomes filled with paraffin.

5) Sectioning :- After holds from the oven, the specimen let at room temperature to be solid and removed from their containers in order to sectioning they were put in the rotary microtome and were sliced by the microtome, a steel blade into sections 5 micrometers thick. The sections were floated on water bath (50–55oC), then transferred into glass slides coated with Mayers albumin as adhesive substance and left to dry.

6) Staining :- The histological sections of the studied organs were stained with Hematoxylin - Eosin stain.

الخلاصة:-

تناولت الدراسة الحالية دراسة التأثيرات للأورليستات وحده وبالاشتراك مع القرفة على التغيرات في أنسجة الكلى لدى الجرذان الذكور البدينات. كما تم تقييم الخواص المضادة للأكسدة والتأثيرات الوقائية لمستخلص القرفة من خلال فحص تأثيراته المحسنة على التغيرات المرضية في أنسجة الكلى الناتجة عن عقار أورليستات، وكذلك التحسن في حالة الإجهاد التأكسدي ومستويات الدهون في الدم وفقدان الوزن.

أربعون جرذ ذكرًا بالغًا مقسمين إلى مجموعتين:- التجربة الأولى (السمنة) لمدة ستة أسابيع لتحريض السمنة، كما هو موضح أدناه المجموعة الضابطة: تلقت 10جرذان فقط نظامًا غذائيًا عاديًا بدون دهون كجرعة يومية لمدة ستة أسابيع، مجموعة النظام الغذائي عالي الدهون: تلقى 30 جرذ فقط نظامًا غذائيًا عالي الدهون يحتوي على (دهن مع الصويا) وقدم يوميًا لمدة ستة أسابيع، بعد هذه الفترة (ستة أسابيع) تم تحديد زيادة الوزن ووزن الجسم والكوليسترول في المصل والدهون الثلاثية والدهون في المجموعتين الرئيسيتين الأولى والثانية للتأكد من التحريض.

التجربة الثانية لمدة ستة أسابيع، استمرت فترة العلاج من الأسبوع 6 إلى الأسبوع 12 بعد التأكد من تحريض السمنة بجرعات يومية عن طريق الفم مع مجموعة الضبط: تم إعطاء 10 جرذان غذاء عادي خالي من الدهون كجرعة يومية لمدة ستة أسابيع، المجموعة التي تناولت غذاء عالي الدهون: تم تقسيم 30 جرذ بعد إحداث السمنة إلى المجموعة التي تناولت غذاء عالي الدهون مع أورليستات 10 جرذان (10 ملجم/كجم/يوم)، المجموعة التي تناولت غذاء عالي الدهون مع القرفة 10 جرذان (100 ملجم/كجم من وزن الجسم)، المجموعة التي تناولت غذاء عالي الدهون مع أورليستات (10 ملجم/كجم/يوم) والقرفة (100 ملجم/كجم من وزن الجسم).

تم تخدير الجرذان بمخدر الكلوروفورم ، ثم تم أخذ عينات دم من القلب لفحصها بفحوصات الدم وأنزيمات الكبد ومضادات الأكسدة، وتم تشريح الحيوانات للحصول على الكلى للفحص النسيجي. كانت قيمة زيادة الوزن ووزن الجسم أعلى بشكل ملحوظ في المجموعة التي تناولت غذاء عالي الدهون مع أورليستات مقارنة بالمجموعة الضابطة. بينما كان هناك انخفاض معنوي في زيادة الوزن ووزن الجسم في مجموعة أورليستات ومجموعة القرفة بالمقارنة مع مجموعة الدهون. كما كان هناك انخفاض معنوي في زيادة الوزن ووزن الجسم في المجموعة المختلطة (أورليستات والقرفة) بالمقارنة مع مجموعة أورليستات ومجموعة القرفة.

أظهرت الإضافة زيادة في الكوليسترول والدهون الثلاثية والكوليسترول الضار وكوليسترول البروتين الدهني منخفض الكثافة (VLDL) بقيمة معنوية بينما أظهرت انخفاض معنوي في كوليسترول البروتين الدهني عالي الكثافة في مجموعة الدهون بالمقارنة مع مجموعة التحكم. كما كان هناك انخفاض معنوي في الكوليسترول والدهون الثلاثية والكوليسترول الضار و VLDL-c بينما أظهرت زيادة معنوية في HDL-c في مجموعة أورليستات ومجموعة القرفة بالمقارنة مع مجموعة الدهون. بينما أظهرت المجموعة المختلطة

(أورليستات والقرفة) انخفاضاً معنوياً في الكوليسترول والدهون الثلاثية والكوليسترول الضار و VLDL-c مع زيادة معنوية في HDL-c بالمقارنة مع مجموعة أورليستات ومجموعة القرفة.

بينما أظهرت دراسة اليوريا والكرياتينين والبوتاسيوم والصوديوم زيادة معنوية في حين أظهرت انخفاضاً معنوياً في الكالسيوم في مجموعة الدهون بالمقارنة مع مجموعة السيطرة. كما كان هناك انخفاض معنوي في اليوريا والكرياتينين والبوتاسيوم والصوديوم مع زيادة معنوية في الكالسيوم في مجموعة أورليستات ومجموعة القرفة بالمقارنة مع مجموعة الدهون. بينما أظهر انخفاض معنوي في اليوريا والكرياتينين والبوتاسيوم والصوديوم مع زيادة معنوية في الكالسيوم في مجموعة الخليط (أورليستات والقرفة) بالمقارنة مع مجموعة أورليستات ومجموعة القرفة.

في هذه الدراسة أظهرت مصل السيستاتين سي والنيوتروفيل جيلاتيناز - ليبوكالين المرتبط (NGAL) زيادة بقيمة معنوية في مجموعة الدهون مقارنة بمجموعة التحكم. كما كان هناك انخفاض معنوي في مصل السيستاتين سي والنيوتروفيل جيلاتيناز - ليبوكالين المرتبط (NGAL) في مجموعة أورليستات ومجموعة القرفة بالمقارنة مع مجموعة الدهون. بينما أظهرت انخفاضًا معنويًا في سيستاتين سي في المصل وليبوكالين المرتبط بالنيوتروفيل جيلاتيناز (NGAL) في المجموعة المختلطة (أورليستات والقرفة) مقارنة بمجموعة أورليستات ومجموعة القرفة.

بينما أظهرت إنزيم الأكسدة ومضادات الأكسدة في الكبد انخفاضًا بقيمة معنوية بينما كانت هناك زيادة معنوية في MDA لمجموعة الدهون مقارنة بمجموعة التحكم. كما كان هناك انخفاض معنوي في GSH وMDA لمجموعة أورليستات ومجموعة القرفة عند المقارنة بمجموعة الدهون. بينما أظهرت زيادة معنوية في GSH مع انخفاض معنوي في MDA في مجموعة مزيج أورليستات والقرفة عند المقارنة بمجموعة أورليستات ومجموعة القرفة.

الفحص النسيجي لقسم الكلى في المجموعة الضابطة أظهر بنية نسيجية طبيعية لقشرة الكلى مع وجود كبيبات كبيرة وأنابيب كلوية منتظمة، كما تم صبغ الفحص النسيجي لقسم الكلى لمجموعة النظام الغذائي عالي الدهون بالهيماتوسيلين والإيوسين، حيث أظهر المظهر غير الطبيعي لقشرة الكلى، وتسلل شديد للخلايا الالتهابية في الفراغ الخلالي، وضمور كبيبي كبير ونخر أنبوبي، وتغيرات ملحوظة في الكبيبات، كما يتضح من ضمور الالتهاب الخلالي لكل كبيبة. الفحص النسيجي لقسم الكلى لمجموعة النظام الغذائي عالي الدهون والأورليستات تم صبغه بالهيماتوسيلين والإيوسين، حيث أظهر تحسنات نسيجية خفيفة في الأنسجة القشرية، وضمور كبيبي، وتوسع كبسولة بومان، وتسلل الخلايا الالتهابية الخلالية وتنكس ظهاري أنبوبي كبير.

بالإضافة إلى ذلك، في الفحص النسيجي لقسم الكلى لنظام غذائي عالي الدهون ومجموعة القرفة تم صبغها بالهيماتوسيلين والإيوسين، كما أظهرت تحسنات نسيجية كبيرة في أنسجة القشرة الكلوية، الكبيبات الطبيعية، الأنابيب الكلوية الطبيعية، تسلل طفيف للخلايا الالتهابية الخلالية وتنكس خفيف. بينما في الفحص

النسيجي لقسم الكلى لنظام غذائي عالي الدهون ومجموعة القرفة مع أورليستات تم صبغها بالهيماتوسيلين والإيوسين، كما أظهرت بعض التغيرات النسيجية في أنسجة الكلى، الكبيبات الطبيعية مع ضمور طفيف، الأنابيب الكلوية الطبيعية، تسلل طفيف للخلايا الالتهابية الخلالية واحتقان ملحوظ مع تنكس طفيف واحتقان خفيف. من الاستنتاجات أظهرت نتائج هذا البحث أن مستخلص القرفة أدى إلى تحسين مستوى الدهون في الفئران التي تناولت نظامًا غذائيًا عالي الدهون، كما أدى إلى تقليل نشاط إنزيمات الكبد. وبالتالي، قد تكون القرفة مفيدة كعلاج للسمنة وأمراض الكلى.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة كربلاء / كلية الطب البيطري
فرع الفسلجة والكيمياء الحياتية والادوية

التأثيرات الفسيولوجية والنسجية للأورليستات على وظائف الكلى ودور مستخلص القرفة في تحسينها لدى ذكور الجرذان المصابة بفرط الدهون

رسالة مقدمة إلى

مجلس كلية الطب البيطري جامعة كربلاء وهي جزء من متطلبات درجة الماجستير في الطب البيطري / الفسلجة

من قبل

بنان عاد عبد جابر

بأشراف

الاستاذ المساعد الدكتور

وفاء كاظم جاسم

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