Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Kerbala
College of Veterinary
Medicine

Evaluation Effect of *Aloe Vera* Against Hyperglycemia and Hyperlipidemia in Male Rats Exposed to Dexamethasone

Thesis

Submitted to the council of the College of Veterinary Medicine at University of Kerbala as a Partial fulfillment of the Requirement for the Degree of Master in the Sciences of Veterinary Medicine/ Physiology.

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1444 A.H **2022 A.D**

بسم الله الرحمن الرحيم

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We certify this thesis entitled was **(Evaluation Effect of Aloe Vera Against Hyperglycemia and Hyperlipidemia in Male Rats Exposed to Dexamethasone)** has been prepared by ***Amna Mohammed Hamza*** under our 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 Veterinary Physiology, Biochemistry and Pharmacology.

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Declaration

I hereby declare that this thesis is my origin 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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/ / 2022

DEDICATION

I present fragments of my humble research as a gift to my master, the Awaited Alimam Mahdi (may God bless him and grant him peace).

To the one who strives to comfort me and make me happy …. my father.

To my loves, merciful, Candle that light my way ..... my mother.

To my dear husband who supported me , In every step of the research. There are no words to express my thanks for him.

To my companion on the journey of searching my life and soul ….my dear daughter (Mina).

To My brother, and sisters you are the bright moons, you are a blessing from the sky.

... Who was my partner in every …

To the flowers in my life …. my dear friends

I would like to thank all those who supported me to complete successfully my research.

Amna Mohammed Hamza

Acknowledgments

First of *all*, I would like to express my grateful thanks to ***Allah,*** who has given me everything.

Great thanks for ***Prof. Dr. Wifaq Jabori AL-Bazi*** / Dean of College of Veterinary Medicine University of Karbala for her help in encouragement.

I would like to express my sincerely grateful and deep appreciation to my supervisor **Asst. Prof. Dr.Mayada Sahib Hassan and prof. Dr.Rana Fadhil Mussa** for their guidance and advisement through the period of the project.

Finally, I am also indebted to all persons who exerted any effort in helping me in this work and I had forget their name

Amna Mohammed Hamza

Table of Contents

List of Tables

Table of Figures

List of abbreviations

Abbreviations	Full word
ACE	Angiotensin Converting Enzyme
AOM	Acute otitis media
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
DXM	Dexamethasone
ELISA	Enzyme Linked Immunosorbent Assay
HDL	High-Density Lipoprotein
HPA axis	Hypothalamus-pituitary-adrenal axis
HSP 70	Heat Shock Protein 70
LDL	Low-Density Lipoprotein
MDA	Malondialdehyde
MMP	Mellatopeptidase
PCOS	Polycystic ovarian syndrome
POAL	Probiotics originating from Aloe leaf
PPAR	Peroxisome proliferator-activated receptor
TBA	Thiobarbituric acid
VEGF	Vascular endothelial growth factor
VLDL	Very Low-Density Lipoprotein

Abstract

Chronic administration of dexamethasone (DXM) causes hyperglycemia and hyperlipidemia, so the present study was undertaken to observe the effect of the aqueous leaf extract of *Aloe Vera* gel in the reduction in blood glucose, lipid level in hyperglycemia and hyperlipidemia in male rats. The study was conducted at University of Kerbala / College of Veterinary Medicine during period from November 2021 to April 2022.

Twenty four adult male rats used in the present study and divided into four groups, first group (G1) is considered as control group received normal saline, the second group (G2) received dexamethasone (1mg/kg/bw) intraperitoneally, while the third group (G3) received dexamethasone (1mg/kg/bw) intraperitoneally combined with Aloe Vera leaf gel extract (300 mg/kg/bw) in aqueous solution daily using an intragastric tube. The fourth group (G4) received dexamethasone (1mg/kg/bw) intraperitoneally combined with *Aloe vera* leaf gel extract (500 mg/kg/bw) in aqueous solution daily using an intragastric tube, at the end experiment blood was collected to assessment glucose, and, lipid profile (cholesterol, triglyceride, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL). Levels of malondialdehyde (MDA), heat shock protein 70 (HSP70), and angiotensin converting enzyme (ACE). Pancreas and liver isolated to study of histological changes. The current results showed a significant decrease ($p<0.05$) in serum glucose at the (G3) and (G4) groups respectively compared with the (G2) group. A significant decreased ($P<0.05$) were noticed in the serum concentration of cholesterol, triglyceride, VLDL and LDL at the (G3) and (G4) groups respectively in comparison with the (G2) group. HDL increased significantly ($P<0.05$) in the same groups. A significant decreased ($P<0.05$) was noticed in the concentration of MDA, HSP70 and ACE in the (G3) and (G4) groups respectively compared with the (G2) group.

Histological changes in liver and pancreas of the rats demonstrate that dexamethasone treated group showed significant structural changes and damage. In addition, Aloe Vera 500 mg/kg/bw working better than Aloe Vera 300 mg/kg/bw leaf gel extract-treated rats were improved the harmful effect of dexamethasone in the histopathological studies in

liver and pancreas of the rats when compared to the group that was injected only with dexamethasone

In conclusion of our results, we conclude that Dexamethasone leads to side effects in high sugar and high fat, which leads to harmful effects on the liver and pancreas. While taking Aloe Vera Gel with Dexamethasone improves this studied information.

Chapter One: Introduction

1.Introduction

Hyperglycemia is clinically realized as a blood glucose level > 11 mmol/L (200 mg/dl) that persists for more than 2 hours (Wolfsdorf *et al.,* 2018). Acute hyperglycemia is often benign and may persist without any clinically significant signs or symptoms (Rehman *et al.,* 2011). Diabetes affects one in ten people worldwide. Understanding the condition is the first step to preventing and managing it. Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Goguen & Gilbert, 2018). A numerous pharmacological agents have an impact on glucose homeostasis, causing either hypo- or hyperglycemia.

Steroids are drugs that have been widely used to treat a variety of conditions. Several protocols are being researched to detect patients at risk of steroid-induced hyperglycemia. This is based on the hypothesis that in pre-diabetic individuals, abnormalities in insulin secretion and loss of beta cell function can be exacerbated by an increase in insulin requirements caused by glucocorticoids exposure (Tamez-Pérez *et al.,* 2015). Use of corticosteroids is very common in clinical practice for treating and controlling inflammation and inflammatory conditions (e.g., rheumatoid arthritis and temporal arteritis), and inducing immunosuppression and for their chemotherapeutic effects, at the same time glucocorticoids have a number of side effects, the most common and prominent of which is hyperglycemia (Tamez-Pérez *et al.,* 2015). It is well known and remarkable that glucocorticoid use in people may elevate blood glucose levels with or without diabetes results in hyperglycemia (Rehman *et al.,* 2011), and larger total corticosteroid dose and longer duration of use are associated with increased risk of new-onset diabetes (Clore & Thurby-Hay, 2009). Corticosteroids blunt the action of insulin and promote hepatic gluconeogenesis (Friedman *et al.,* 1997 & Patel *et al.,* 2011). Clinicians should be aware that patients taking glucocorticoid therapy may be at an increased risk of developing hyperglycemia because glucocorticoids impair insulin sensitivity and beta-cell function and contribute to gluconeogenesis (van Raalte *et al.,* 2010). Glucocorticoids provide a substrate for oxidative stress metabolism increasing lipolysis, proteolysis, and hepatic glucose production (van Raalte *et al.,* 2009). Drug-induced changes in serum glucose were observed by Abdelmannan *et al.* (2010)

reported the use of a "stress test", in which the administration of 8 mg dexamethasone provides timely detection of increases in serum glucose.

Many plants are known to have both economic and therapeutic benefits. Depending on the species, plants typically have a variety of chemical compositions. Plant extracts represent a continuous effort to find new compounds against pathogens. *Aloe vera* is one of the oldest known medicinal plants gifted by nature and it works as antiseptic, antibacterial, antiviral, etc… (Ayyavoo & Ramasamy, 2013; Fakhrildin & Sodani, 2014). The antioxidant activity of *Aloe vera* has been reported, that could effectively ameliorate the oxidative stress inflicted by free radicals (Rajasekaran *et al.,* 2005). Tiwari and Upadhayay, (2018) reported that the polysaccharides in *Aloe vera* gel have properties like anti-oxidant effects, immunostimulation, anti-inflammatory effects, stimulation of hematopoiesis, wound healing, promotion of radiation damage repair, anti-viral, anti-fungal, anti-diabetic and anti-neoplastic activities, and anti-bacterial. The researchers indicated that *Aloe vera* can be utilized as a good natural antioxidant source, due to the antioxidant activity of *Aloe vera* depending on its total phenolic content (Zareie *et al*., 2021). Many studies reported that the antioxidant activity of *Aloe vera* could ameliorate oxidative stress due to diabetes conditions in kidney tissues and hepatic (Rajasekaran *et al.,* 2005 ; Sharma *et al.,* 2013). *Aloe vera* plants showed excellent antioxidants with free radical scavenging activity (Patel *et al.,* 2012). Gupta & Rawat, (2017) found that aloe plant polysaccharides have the potential to control blood sugar, stimulate the body's own antioxidant production and even lower cholesterol. Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids (Surjushe *et al*., 2008). *Aloe vera* extracts have anti-hyperglycaemic effects and may be useful in treating type I and Type II diabetes mellitus by reducing the levels of fasting blood sugar and glycated hemoglobin (Ajabnoor, 1990; Tanaka & Matsuda, 2006) as well as increasing plasma insulin levels (Can *et al.,* 2004).

Aims of Study: -

Reducing the harmful effect resulting from excessive intake of dexamethasone treatment, such as high blood sugar and hyperlipidemia, by giving aloe vera gel and studying its impact on these risks using two different doses of aloe vera gel, by the following these parameters

1- Glucose
2- Lipid profile: cholesterol, triglyceride, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL).
3- Liver enzymes: angiotensin converting enzyme (ACE), heat Shock Protein 70 (HSP 70), and level of malondialdehyde (MDA).
4- Histopathological section of liver and pancreas.

Chapter Two: Review of The Related Literature

2. Review of The Related Literature

2.1. Hyperglycemia

The term hyperglycemia is derived from the Greek hyper (high) + glykys (sweet/sugar) + haima (blood). Hyperglycemia is blood glucose greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 hours postprandial. A patient has impaired glucose tolerance, or pre-diabetes, with fasting plasma glucose of 100 mg/dL to 125 mg/dL. A patient is termed diabetic with a fasting blood glucose of greater than 125 mg/dL (Villegas-Valverde *et al.*, 2018; Hammer *et al.*, 2019).

The incidence of hyperglycemia has increased dramatically over the last two decades due to increased obesity, decreased activity level, and an aging population. The prevalence is equal between men and women. The countries with the greatest number of patients with diabetes included China, India, United States, Brazil, and Russia. Hyperglycemia is more prominent in low to medium-income households. The latest data released by the Centers for Disease Control and Prevention indicate that there are nearly 30.5 million Americans with diabetes and nearly 84 million Americans with prediabetes. These numbers are set to increase significantly over the next decade (Jacobsen *et al.*, 2014; Rawlings *et al.*, 2019).

Hyperglycemia in a patient with type 1 diabetes is a result of genetic, environmental, and immunologic factors. These lead to the destruction of pancreatic beta cells and insulin deficiency. In a patient with type 2 diabetes, insulin resistance and abnormal insulin secretion lead to hyperglycemia. According to recent studies, metabolic disturbances like type 2 diabetes mellitus increases the risk of cognitive decline and Alzheimer dementia. Alzheimer dementia is also a risk factor for diabetes type 2. Recent studies have indicated that these diseases are connected both at clinical and molecular levels. Like peripheral insulin resistance leading to type 2 diabetes, brain insulin resistance is linked to neuronal dysfunction and cognitive impairment in Alzheimer dementia (Kubis-Kubiak *et al.*, 2019).

2.2. Hyperlipidemia

Hyperlipidemia is a condition that incorporates various genetic and acquired disorders that describe elevated lipid levels within the human body. Hyperlipidemia is extremely common, especially in the Western hemisphere, but also throughout the world. Alternatively, a more objective definition describes hyperlipidemia as low-density lipoprotein (LDL), total cholesterol, triglyceride levels, or lipoprotein levels greater than the 90th percentile in comparison to the general population, or an HDL level less than the 10th percentile when compared to the general population (Fredrickson, 1971). Lipids typically include cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, Apo lipoproteins, and HDL (Ballantyne *et al.*, 2000).

Through a vast array of trials and studies, it has been consistently shown that elevated levels of LDL cholesterol increase a person's risk for the development of atherosclerotic plaques and subsequent vascular disease. In stark contrast, high-density lipoprotein (HDL) cholesterol assists in regulating cholesterol levels to prevent imbalances that would increase the risk of atherosclerotic vascular disease. Each patient's LDL cholesterol goal is conditional on their overall cardiovascular risk, and medical therapy should be independently tailored to the patient. Managing risk factors, such as hyperlipidemia, to diminish the risk for atherosclerotic cardiovascular disease is referred to as "primary prevention." The grounds for lowering LDL cholesterol derives from widespread epidemiologic data that reveals a positive, continuous correlation between LDL cholesterol levels, cardiovascular events, and patient mortality (Fredrickson, 1971).

Complications from undertreated or untreated hyperlipidemia include all types of vascular disease, which may prove fatal down the road. These include, but are not limited to, coronary artery disease, peripheral artery disease, cerebrovascular accidents, aneurysms, type II diabetes, high blood pressure, and even death (Ford *et al.*, 2016).

Hyperlipidemia is often a life-long disease process, but one that is typically quite manageable. However, if hyperlipidemia is left untreated, the disease is progressive and will often lead to severe underlying vascular disease processes, which can prove fatal. Ongoing persistent exposure to high serum lipid levels throughout early adulthood

increases the person's subsequent risk of coronary heart disease in a dose-dependent fashion (Vallejo-Vaz *et al.*, 2017).

2.3. *Aloe vera*

Common Names: aloe

Latin Names: *Aloe vera, Aloe africana, Aloe arborescens, Aloe barbadensis*

Aloe vera, a member of the Liliaceae family, is a perennial plant with turgid green leaves joined at the stem in a rosette pattern. The *Aloe vera* leaves are formed by a thick epidermis (skin) covered with cuticles surrounding the mesophyll, which can be differentiated into chlorenchyma cells and thinner walled cells forming the parenchyma (Femenia *et al.*, 1999). The parenchyma makes up the majority of the leaf by volume containing the *Aloe Vera* gel, synonymous with the inner leaf, inner leaf fillet, or *Aloe* fillet (Boudreau & Beland, 2006; Guo & Mei, 2016).

Figure (2-1) *Aloe vera*

Aloe is used topically (applied to the skin) and orally. Topical use of aloe is promoted for acne, lichen planus (a very itchy rash on the skin or in the mouth), oral sub mucous fibrosis, burning mouth syndrome, burns, and radiation-induced skin toxicity. Oral use of aloe is promoted for weight loss, diabetes, hepatitis, and inflammatory bowel disease (a group of conditions caused by gut inflammation that includes Crohn's disease and ulcerative colitis) (Braun & Cohen, 2015).

2.3.1. History of *Aloe Vera*

Aloe barbadensis Miller, commonly referred to as *Aloe vera*, is one of more than 400 species of *Aloe* belonging to family Liliaceae that originated in South Africa, but have been indigenous to dry subtropical and tropical climates, including the southern USA (Reynolds & Dweck, 1999). Recently, only a few species of *Aloe* have been considered for commercial importance, of which *A. Vera* is considered the most potent and, thereby, the most popular plant in the research field (Eshun & Qian, 2004).

A. vera has been used in folk medicine for over 2000 years, and has remained an important component in the traditional medicine of many contemporary cultures, such as China, India, the West Indies, and Japan (Foster, 2011). Ancient Greek scientists believed that *Aloe vera* was a widely used panacea, and Egyptians referred to aloe as "the plant of immortality." (Grindlay & Reynolds, 1986؛Amar *et al.*, 2008).

Aloe is a cactus-like plant that grows in hot, dry climates. It is cultivated in subtropical regions around the world, including the southern border areas of Texas, New Mexico, Arizona, and California. Historically, aloe has been used for skin conditions and was thought to improve baldness and promote wound healing (Akhtar *et al*., 2021).

2.3.2. Composition structure of *Aloe vera* (*Aloe barbadensis* Miller)

Aloe vera gel consists of about 98.5%–99.5% water with the remaining solids containing more than 200 different components, polysaccharides being the most abundant compounds (Femenia *et al*., 1999). Other interesting chemical compounds such as soluble sugars, glycoproteins, phenolic anthraquinones, flavonoids, enzymes, minerals, essential,

and nonessential amino acids, sterols, saponins, and vitamins have also been identified (Eshun & He, 2004; Rodríguez-Sandoval *et al*., 2010).

It is important to highlight that *Aloe Vera* has enjoyed a long history of providing a myriad of health benefits, being one of the herbal remedies most frequently used in the treatment of different diseases, which have been associated mainly to polysaccharides and phenolic compounds, the main bioactive components present in *Aloe vera* (Guo & Mei, 2016; Minjares-Fuentes *et al*., 2016; Pothuraju *et al*., 2016). Nevertheless, the geographic location (including soil and climate), growth periods, horticultural conditions, and postharvest treatments might play a critical role determining the compositional and structural features of the main bioactive compounds from *Aloe vera*, which in turn might result in the modification of its beneficial effects (Ray & Aswatha, 2013; Rodríguez-Sandoval *et al*., 2010). Finally, the most relevant scientific evidence of the beneficial effects of *Aloe vera* on health has also been revised. The *Aloe vera* gel is made up of water, amino acids, vitamins, lipids, sterols, tannins, and enzymes and also contains phenol, saponin, anthraquinones components, which have antiviral, antibacterial, and antifungal properties.

2.3.3. Clinical Efficacy and Mechanism of Action

2.3.3.1. Burn Wound Healing Effect

Aloe is known as *the healing plant*. *A. Vera* has been used for traditional medical purposes in several cultures (Grace *et al*., 2008). *In vitro* extracts of *A. vera* stimulate the proliferation of several cell types. Many studies have shown that treatment with whole *A. vera* gel extracts resulted in faster healing of wounds (Tarameshloo *et al*., 2012). *A. vera* may have a direct effect on the wound healing process as a whole, which is manifested by increase in rate of contraction of wound area (Khorasani *et al*., 2009) and has confirmed the effect of *A. vera* on increasing wound contraction and collagen synthesis. This property is attributed to the mannose-6-phosphate known to be present in *A. vera* gel (Liu *et al*., 2010). Polysaccharides from *Aloe* promote both the proliferation of fibroblasts and the production of hyaluronic acid and hydroxyl proline in

fibroblasts, which play important roles in extracellular matrix remodeling during wound healing (Chantarawaratit *et al.*, 2014).

Acemannan, significantly increases periodontal ligament cell proliferation, upregulation of growth/differentiation factor 5, type I collagen and alkaline phosphatase activity in primary human periodontal ligament cells (Chantarawaratit *et al.*, 2014). In a clinical study, to check the efficacy of *A. vera* gel compared with 1% silver sulfadiazine cream as a burn dressing for the treatment of superficial and partial thickness burns, healing of burn wounds were remarkably early in *A. Vera* treated patients than those patients treated with 1% silver sulfadiazine (Shahzad and Ahmed, 2013). Polysaccharides isolated from *A. vera* induce matrix metallopeptidase (MMP)-3 and metallopeptidase inhibitor-2 gene expression during the skin wound repair of rat, which directly helps to regulate the wound healing activity of *A. vera* gel (Tabandeh *et al*., 2014).

2.3.3.2. Immunomodulatory Effect

A. vera gel has strong immunomodulatory activity where in it downregulates lipopolysaccharide-induced inflammatory cytokine production and expression of NLRP3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome in human macrophages (Budai *et al.*, 2013). *A. vera* could inhibit the inflammatory process following burn injury, as characterized by the reduction of leukocyte adhesion, as well as pro inflammatory cytokines (Duansak *et al*., 2009).

Aloe polysaccharides pretreatment can attenuate the cerebral ischemia and reperfusion injury in severe traumatic–hemorrhagic rats by first entering high altitude through inhibiting systemic inflammatory response and leukocyte aggregation and lipid peroxidation in the brain (Liu *et al*., 2012). Administration of *A. vera* has been universally demonstrated to result in marked increase in phagocytic and proliferative activity of the reticuloendothelial system (Im *et al*., 2005).

A. vera directly inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production (Park *et al*., 2009) which plays an important role in inflammation. *Aloe* also contains anthraquinones and chromone in the inner gel, which possess strong anti-inflammatory effects as shown in murine macrophages (Picchietti *et al*., 2013 ; Park *et al*,

2009). This report suggests that *Aloe* as a whole has anthraquinones (aloin) and chromone (aloesin) components, and *Aloe* gel has pharmacological activity to alleviate inflammatory responses in inflammatory bowel disease (Langmead *et al.*, 2004). A recent report of a clinical study evaluated the therapeutic effect of *A. vera* gel wherein 2% oral gel is not only effective in decreasing the pain score and wound size in recurrent aphthous stomatitis patients but also decreasing the aphtha's wound healing period (Babaee *et al.*, 2012).

2.3.3.3 Intestinal Absorption

Aloe material has been used for drug absorption enhancement for drugs with low bioavailability due to extensive efflux (Carien *et al.*, 2013*). Lactobacillus brevis* strains were isolated from naturally fermented *A. Vera* gel which inhibited the growth of many harmful enteropathogens without restraining most normal commensals in the gut and hence were named POAL (probiotics originating from *Aloe* leaf) strains; these exhibit discriminative resistance to a wide range of antibiotics (Kang *et al.*, 2014). Aloin, present in the gel, is metabolized by the colonic flora to reactive *Aloe*-emodin, which is responsible for the purgative activity.

Aloe-emodin isolated from *A. vera* inhibits colon cancer cell migration by down regulating MMP-2/9 and also inhibits *ras a* homolog family member B and vascular endothelial growth factor (VEGF) via reducing DNA binding activity of nuclear factor κ-light-chain-enhancer of activated B cells (Suboj *et al.*, 2012*). A. vera* gel has been shown to contain five phytosterols, which are able to reduce visceral fat accumulation influences the metabolism of glucose, and lipids in animal model experiments, where they reduced large-sized intestinal polyps and ameliorated reduction in plasma. High molecular weight adiponectin levels in adenomatous polyposis coli gene-deficient multiple intestinal neoplasia mice fed high-fat diet. Further, an *in vitro* study has shown that *A. vera* gel and whole leaf extract were able to reduce significantly the trans epithelial electrical resistance of the Caco-2 cell monolayers and thereby showed the ability to open tight junctions between adjacent cells. Hence, *A. vera* gel and whole leaf extract solutions

significantly enhanced the transport of insulin across the Caco-2 cell monolayers (Chen *et al.,* 2009).

2.3.3.4. Antidiabetic Effect

Clinical studies have suggested that *A. vera* gel may act as a safe anti hyperglycemic and anti-hyper cholesterolemic agent for type 2 diabetic patients without any significant effects on other normal blood lipid levels or liver/kidney function (Huseini *et al.,* 2012). *In vivo* and *in vitro* studies strongly demonstrate that the water soluble fraction of *Aloe* spp. possesses glucose-lowering activities and some of its components modulate glucose transporter-4 mRNA expression (Kumar *et al.,* 2011). In a randomized controlled trial, *A. vera* gel complex reduced body weight, body fat mass, insulin resistance in obese prediabetes, and early non treated diabetic patients (Devaraj *et al.,* 2013). Further, in a pilot study, two *Aloe* products in patients with prediabetes over an 8-week period, tended to revert the impaired fasting glucose and impaired glucose tolerance observed in conditions of prediabetes/metabolic syndrome (Devaraj *et al.,* 2013).

Aprevious study discussed the efficacy of aloe-emodin-8-*O*-glycoside isolated from *A. vera* gel in enhancing glucose transport by modulating the proximal and distal markers involved in glucose uptake and its transformation into glycogen (Anand *et al*., 2010). Tanaka *et al.* (2006) reported reductions in both fasting and random blood glucose levels of db/db diabetic mice chronically treated with the same phytosterols from *A. Vera* gel**.** Jain *et al.* (2010) found that *A. vera* gel has significant antidiabetic and cardio protective activity as it significantly reduced oxidative stress in streptozocin induced diabetic rats and improved antioxidant status. *A. vera* gel also helps to improve the carbohydrate metabolism, with a recent report suggesting that it helps to improve metabolic condition in obese prediabetes and early non treated diabetic patients by reducing body weight, body fat mass, fasting blood glucose, and fasting serum insulin in obese individuals (Choi *et al.,* 2013).

Shin *et al*. (2011) showed that dietary *Aloe* formula also reduced obesity-induced glucose tolerance not only by suppressing inflammatory responses but also by inducing

anti-inflammatory cytokines in the white adipose tissue and liver, both of which are important peripheral tissues affected by insulin resistance**.**

A. vera also has shown improvement in the function of isolated rat pancreatic islets wherein it increased survival of the islet cells, their mitochondrial activity, and insulin levels at the same time as reducing production of reactive oxygen species (Rahimifard *et al.,* 2014).

2.3.3.5. Antioxidant Effect

A. vera contains substantial amounts of antioxidants including α-tocopherol (vitamin E), carotenoids, ascorbic acid (vitamin C), flavonoids, and tannins (Hamman, 2008), and it has been suggested that antioxidant action may be an important property of plant medicines used in treatment of various diseases. Topical *A. saponaria* treatment has shown anti nociceptive and anti-inflammatory effects in ultraviolet B-induced sunburn model via its antioxidant components present in gel (Silva *et al.,* 2014). *Aloe* gel is able to scavenge the free radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and nitric oxide in a concentration-dependent manner, as seen in an *in vitro* study of the radio protective efficacy of *A. vera* gel (Saini & Saini, 2011**).** Administration of ethanolic extract of *A. vera* gel on tissue antioxidants led to reduction in blood glucose level in diabetic rats, which helps to prevent excessive formation of free radicals through various biochemical pathways and also reduces the potential glycation of the enzymes (Rajasekaran *et al.,* 2005; Kammoun *et al.,* 2011). *In vitro* and *in vivo* antioxidant potentials of a polysaccharide isolated from *A. vera* gel were investigated.

Enzymatic extracts were prepared from *A. vera* gel using 10 digestive enzymes including five carbohydrases and five proteases. Results suggested that *Aloe* polysaccharides exhibited a protective effect against 2,2′-azobis (2-amidinopropane) dihydrochloride-induced oxidative stress and cell death in kidney epithelial cells (Vero cells) as well as in an *in vivo* zebrafish model (Kang *et al.,* 2014). One study determined the total phenolic content of *A. vera* leaf skin extracts and a significant correlation were established between the total phenolic content and the

antioxidant capacity (Kammoun *et al.,* 2011). The methanol extracts of leaf skins and flowers of *A. vera* were also screened for their antioxidant and anti mycoplasmic activities, and *in vitro* antioxidant activities of both extracts exhibited antioxidant activity, with the leaf skin extract being the most active (Lopez *et al.,* 2013).

2.3.3.6. Hepatoprotective Effect

Isolated phytosterols, namely lophenol and cycloartanol, have the ability to induce the downregulation of fatty acid synthesis and a tendency for upregulation of fatty acid oxidation in the liver, which favors the reduction in intra-abdominal fat and improvement of hyperlipidemia. Further, addition to sterol regulatory element-binding transcription factor 1/peroxisome proliferator-activated receptor (PPAR)-α ratio was decreased; metabolic syndrome-related disorders were improved and liver steatosis in *Aloe*-sterol-treated Zucker diabetic fatty rats (Misawa *et al.,* 2012).

Aloe formulas also suppress obesity-induced inflammatory responses by reducing levels of the proinflammatory cytokines, PPARγ/liver X receptor α, and 11β-hydroxysteroid dehydrogenase 1, and enhance anti-inflammatory cytokines in white adipose tissue and liver. The beneficial effects of *Aloe* formula with respect to obesity-induced insulin resistance and hepatic steatosis have been associated with its action on PPARγ/liver X receptor α (Rahimifard *et al.,* 2014). Saito et al showed that *A. Vera* gel extract prevents ethanol-induced fatty liver by suppressing mRNA expression of lipogenic genes in the liver. The combination of probiotic *Lactobacillus rhamnosus* GG and *A. Vera* gel have a therapeutic potential to decrease cholesterol levels and the risk of cardiovascular diseases (Kumar *et al.,* 2013).

2.3.3.7. Anticancer Activity

Aloin, an anthraquinone being a natural compound and the main ingredient of *Aloe* have been documented for its remarkable potential therapeutic options in cancer, wherein it showed chemo protective effects against 1,2-dimethylhydrazine-induced preneoplastic lesions in the colon of Wistar rats (Hamiza *et al.,* 2014). Aloin treatment could inhibit the

secretion of VEGF in cancer cells. VEGF is one of the most important proangiogenic cytokines known and well characterized as an inducer of tumor neovascularization.

Aloin treatment significantly inhibited *in vitro* VEGF-induced angiogenic response of human endothelial cells, causing an inhibition of proliferation and migration of endothelial cells (Pan *et al.,* 2013). *Aloe*-emodin (AE), is also a subtype of anthraquinone, a natural compound that has traditionally been found to have diverse biological activities including anticancer functions. AE (1,8-dihydroxy-3-hydroxymethyl-9,10-anthracenedione) is an herbal anthracenedione derivative from *A. vera* leaves. Recent reports have shown that AE possesses antiproliferation effects on some types of cancer cells, such as lung, squamous, glioma, and neuroectodermal cancer cells (Lin *et al.,* 2011; Masaldan & Iyer, 2014). The inhibitory effect of AE on the activity and gene expression of *N*-acetyl transferase, which plays an initial role in the metabolism of aryl amine carcinogens, was found in human malignant melanoma cells (Lin *et al,* 2005; Lin *et al.*, 2006). Lin *et al.* (2006) demonstrated that AE-induced apoptosis in T24 human bladder. Aloin, derived from *A. vera* leaves, has been shown to possess anticancer potential activities, as it inhibits tumor angiogenesis and growth via blocking signal transducer and activator of transcription 3 activation, with the potential of a drug candidate for cancer therapy (Jackson *et al.,* 2013).

Anthraquinone derivatives such as emodin-like natural (emodin, rhein, and aloin) and synthetic (anthraquinone-2-sulfonic acid) anthraquinones have recently been shown to protect in models of amyloid β and τ aggregation-induced cell death through anti aggregation properties, and/or enhancing the phosphatidylinositol-3-kinase/protein kinase B survival mechanism, which suggests that anthraquinone-2-sulfonic acid could be a new neuroprotective compound and a novel caspase inhibitor (Das *et al.,* 2011).

2.3.3.8. Antimicrobial Activity

A. vera has been described as an antibacterial agent. The *Aloe* protein of 14 kDa from the *A. vera* leaf gel was isolated and the purified *Aloe* protein exhibited a potent antifungal activity against *Candida paraprilosis, Candida krusei,* and *Candida albicans* (Pandey & Mishra, 2010). *A. vera* has anthraquinones as an active compound, which is

structural analogue of tetracycline. The anthraquinones acts like tetracycline that inhibits bacterial protein synthesis by blocking the ribosomal A site (where the aminoacylated tRNA enters). Therefore, the bacteria cannot grow in the media containing *A. vera* extract. Pandey & Mishra established the susceptibility of Gram-positive and Gram-negative bacteria to an extract of the inner gel of *A. vera* (Habeeb *et al.*, 2007; Ferro *et al.*, 2003; Lawless & Allan, 2000). Polysaccharides of *A. vera* gel have been attributed direct bacterial activity through the stimulation of phagocytic leucocytes to destroy bacteria (Pugh *et al.,* 2001). *A. vera* contains pyrocatechol a hydroxylated phenol, known to have toxic effect on microorganisms (Kametani *et al.,* 2007; Cowan, 1999). A recent study demonstrated that the *A. vera* inner gel expresses antibacterial properties against both susceptible and resistant *Helicobacter pylori* strains and impact on the antimicrobial resistance phenomenon of *H. pylori*, proposing the *A. vera* inner gel as a novel effective natural agent for combination with antibiotics for the treatment of *H. pylori* gastric infection (Tan *et al.*, 2011).

2.3.3.9. Antiviral Activity

Many reports have suggested that *A. vera* gel has antiviral activity that prevent virus adsorption, attachment, or entry to the host cell. An *in vitro* study has shown that crude extract of *A. vera* gel has antiviral activity against herpes simplex virus type 2 strain (Cellini *et al.,* 2014). Anthraquinone derivatives, such as *Aloe*-emodin, emodin, and chrysophanol, reportedly exhibit antiviral activity wherein their inhibitory mechanism and effect against influenza A virus with reducing virus-induced cytopathic effect and inhibiting replication of influenza A (Li *et al.,* 2014). Preliminary trials have suggested that *A. vera* consumption may help to HIV-infected individuals as it improves the immune system by increasing the CD4 count (Olatunya *et al.,* 2012).

Many methods have been developed for the successful transformation and regeneration of *A. vera* wherein *Aloe* able to produced IFNα2. This experiment was assessed using an antiviral assay with A549 cells wherein these cells treated with extracts from both the rind and pulp fractions of the shoot and subsequently infected with the lytic *Encephalomyocarditis* virus. This experiment demonstrated that *A. vera* was capable

of expressing a human protein with its biological activity namely interferon alpha 2 (IFNα2) (Lowther *et al.,* 2012).

2.3.10. Effect on estrogen status

Isolated emodin and aloe-emodin from *A. vera* gel specifically suppress breast cancer cell proliferation by targeting estrogen receptor-α protein stability through distinct mechanisms, which suggests a possible application of anthraquinones in preventing breast cancer cell proliferation through estrogen receptor-α inhibition (Huang *et al.,* 2013). *A. vera* gel also helps to maintain ovarian steroid status in polycystic ovary-like condition wherein steroidogenesis altered and disturbed estrogen: testosterone ratio (Maharjan *et al.,* 2010).

2.3.11. Antihyperlipidemic activity

A. vera is known for its antihyperlipidemic property wherein it has beneficial effects on the prevention of fatty streak development and may help to reduce the development of atherosclerosis through modification of risk factors. *A. vera* leaf gel efficacy has been checked in hyper lipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial wherein it reduced total cholesterol and LDL levels significantly (Huseini *et al.,* 2012). A recent study also demonstrated that administration of phytosterols isolated from *A. vera* gel reducing visceral fat mass and improves hyperglycemia in Zucker diabetic fatty rats (Dana *et al.,* 2012).

Dried pulp of *Aloe succotrina* leaves produced significant anti hyperlipidemic effect in high-fat diet- and fructose-induced hyper lipidemic rats, where it significantly decreased serum levels of total cholesterol, total triglycerides, low-density lipoprotein–cholesterol, very low-density lipoprotein, and high-density lipoprotein–cholesterol (Dhingra *et al.,* 2014). Previous reports also suggested that *A. vera* gel-treated polycystic ovarian syndrome (PCOS) rats exhibited significant reduction in plasma triglyceride and LDL cholesterol levels, with an increase in high-density lipoprotein–cholesterol PCOS condition wherein hyperlipidemia is one of main consequences. The gel treatment also caused reversion of abnormal estrous cyclicity, glucose intolerance, and lipid

metabolizing enzyme activities, bringing them to normal. It has phytocomponents with antihyperlipidemic effects and has shown efficacy also in management of PCOS but also the associated metabolic complications (Maharjan *et al.,* 2010; Desai *et al.,* 2012).

2.3.12. Antiulcer activity

A. vera is an herbal remedy widely used for a variety of illnesses; *A. vera* leaf extracts have been promoted for digestion and are used in the treatment of peptic ulcer for cytoprotective action whereby *A. vera* gel expresses antibacterial properties against both susceptible and resistant *H. pylori* strains and acts as a novel effective natural agent for combination with antibiotics for the treatment of *H. pylori* gastric infection (Babaee *et al.,* 2012). A previous study demonstrated that newly formulated aloe- and myrrh-based gels proved to be effective in topical management of minor recurrent aphthous stomatitis and was superior in decreasing ulcer size, erythema, and exudation; myrrh resulted in more pain reduction in a randomized, double-blind, vehicle-controlled study (Mansour *et al., 2014).*

2.4. Dexamethasone

DXM administered alone or in combination with other antiemetic drugs has proven efficacious in preventing nausea and vomiting after different types of surgery and when morphine is used for patient-controlled analgesia In addition, it is used in an attempt to decrease brain oedema, alleviate nerve damage and inhibit the inflammatory response It also reduces pain induced by administering i.v. propofol (Singh *et al.,* 2005).

However, DXM, even after single-dose administration, has been shown to increase blood glucose during surgery. This effect may be related to an increase in neoglucogenesis and the development of insulin resistance, which have been demonstrated in both animals and humans. Hyperglycaemia is known to be a significant risk factor of adverse outcome in patients at risk of ischaemia. Hence, it may be of interest to determine factors that may influence blood glucose concentrations during the perioperative period. Finally, DXM has been reported to increase blood glucose

concentrations in non-diabetic patients but has not been investigated in diabetics (Hans *et al.*, 2006).

2.4.1. Indications

DXM has a wide variety of uses in the medical field. As a treatment, DXM has been useful in the treatment of acute exacerbations of multiple sclerosis, allergies, cerebral edema, inflammation, and shock. Patients with conditions such as asthma, atopic and contact dermatitis, and drug hypersensitivity reactions have benefited from the use of DXM (Corssmit & Dekkers, 2019).

2.4.2. Mechanism of Action

DXM is one of the most potent glucocorticoid preparations that downregulates a variety of inflammatory mediators. Similar to all glucocorticoids, DXM binds to the intracellular glucocorticoid receptor α after dissociation of the receptor from heat shock protein 90 (Coursey *et al.*, 2015; Villanueva *et al.*, 2017). This promotes translocation of the complex to the nucleus where it acts as a transcription factor to induce the expression of genes with anti-inflammatory effects, such as lipocortin, IL-1 receptor antagonist, IL-10, and IκBα genes (Mogensen *et al.*, 2008; Prabhu *et al.*, 2015). In addition, DXM inhibits upstream signaling through NF-κB and AP1 pathways, which prevents production of inflammatory cytokines (ie, TNF-α, IFN-γ, IL-6, etc.), chemokines (ie, CXCL-10, CCL5, etc.), and metalloproteinases (ie, MMP-1, MMP-2, MMP-3, MMP-9, etc.) (Mogensen *et al.*, 2008). In various types of experimental and clinical ocular inflammatory situations, there is an increase in prostaglandins in the aqueous humor and tear film (Kulkarni & Mancino, 1993; Kulkarni & Srinivasan, 1989). Importantly, it is known from prior studies that prostaglan-dins play an important role in mediating pain, hyperemia, photophobia, lacrimation, and decreased vision from cystoid macular edema, symptoms that are commonly exhibited in post-cataract eyes (McGhee *et al.*, 2002; Abadia *et al.*, 2016). DXM, similar to all corticosteroids, inhibits the production of prostaglandins by blocking the enzymatic activity of phospholipase A_2-mediated release of arachidonic acid from cell membranes (Masferrer & Kulkarni, 1997). Experimental studies of inflammation have established that prostaglandin production is significantly

higher in inflamed eyes compared to the non-inflamed baseline state (Masferrer & Kulkarni, 1997). For instance, in a study of endotoxin-induced uveitis in rabbits, a 60-fold-induction in the amount of prostaglandin was detected in the aqueous humor (Kulkarni & Mancino, 1993). In contrast to cyclooxygenase-1 (COX-1) enzyme which is responsible for prostaglandin synthesis under baseline physiologic conditions and appears to maintain homeostasis, cyclooxygenase-2 (COX-2) is increasingly expressed after stimulation with proinflammatory cytokines, such as interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-alpha) and endotoxin in many cell types, including endothelial cells and monocytes/macrophages (Raz *et al.*, 1989). Therefore, one of the most important anti-inflammatory roles of DXM is suppression of COX-2 mediated production of inflammatory prostaglandins. In animal models of endotoxin-induced inflammation, simultaneous administration of DXM resulted in a five-fold decrease in prostaglandin synthesis (Kulkarni & Mancino, 1993). Consequently, through various mechanisms of action, DXM reduces some of the inflammatory-induced eye symptoms that are commonly reported by patients following cataract surgery.

2.4.3. Administration

DXM is available in various formulations. As a tablet, it is available in strengths ranging from 0.5 mg to 6 mg. Other forms of administration are as an injectable suspension or as an oral solution (Sharma *et al.*, 2021).

In the treatment of inflammation, it is advisable to start with low doses of 0.75 mg/day, which may titrate to 9 mg/day, with dosing divided into 2 to 4 doses throughout the day. This applies to intravenous, intramuscular, and oral administrations. Less may be used when directly administered to the lesion or tissue with dosing ranging from 0.2 to 6 mg per day (Matheson *et al.*, 2021).

2.4.4. Adverse Effects

Although DXM is generally well tolerated, it does have its drawbacks as a medication. The most frequently reported adverse effect by patients is the presence of insomnia after use. Some other frequent adverse effects reported by patients include, allergic reactions Anaphylactoid reaction, anaphylaxis, angioedema, cardiovascular:

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis (Panoulas *et al.*, 2008; Sholter, & Armstrong, 2000).

Dermatologic: Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticarial. Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients. Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention, tumor lysis syndrome (Whitworth, 1987).

Gastrointestinal: Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis. Metabolic: Negative nitrogen balance due to protein catabolism Musculoskeletal: Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures (Warrington & Bostwick, 2006).

Neurological/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, vision blurred Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or

decreased motility and number of spermatozoa, malaise, moon face, weight gain (Polderman *et al.,* 2019).

2.4.5. Contraindications

DXM use is contraindicated if patients have systemic fungal infections, hypersensitivity to DXM, or cerebral malaria. Another contraindicated to administer live or live-attenuated vaccines during the use of DXM as the immune system is being suppressed and will less like form a strong enough immune response placing the patient at risk. It is still permissible to administer killed or inactivated vaccines, although it bears mentioning that immune response may be attenuated, and it is unpredictable if immunity with develop as a result (Orton*et al.,* 2016).

In patients with cirrhosis, diverticulitis, myasthenia gravis, renal insufficiency, or ulcerative diseases such as peptic ulcer disease or ulcerative colitis, it is important to use caution when prescribing DXM. Recommendations include using DXM cautiously during pregnancy as there is an increased risk of oral cleft formations. Clinical experience has shown that large doses can increase blood pressure. In patients with recent myocardial infarction, it is advisable to proceed with caution as an increase in free wall rupture of the left ventricle has been reported with the use of DXM. Suppression of the hypothalamus-pituitary-adrenal axis (HPA axis) occurs with use, and therefore the rapid withdrawal of DXM is not recommended. It is important to gradually increase and/or decrease any corticosteroid due to its effect on the HPA axis. Latent diseases such as fungal (*Candida*, *Cryptococcus*, Pneumocystis), parasitic (Toxoplasmosis, Amebiasis, *Strongyloides*), and bacterial (*Mycobacterium*, *Nocardia*) infections may become active due to suppression of the immune system (Bhimraj *et al.,* 2020). Steroid use may inhibit bone formation and may lead to the formation of osteoporosis. Caution is necessary when prescribing DXM to populations at higher risk for osteoporosis.

2.4.6. Toxicity of Dexamethasone

The toxicity of corticosteroids accounts for one of the most common causes of iatrogenic illness in patients on chronic therapy. No specific reversal agent exists for corticosteroids. Their effect in excess is manageable by gradual taper and addressing the

particular complication (e.g., hyperglycemia, infection, hypertension). If steroid therapy is in place for less than one week, patients can usually stop without tapering. For dosing lasting one to three weeks, tapering should depend on the clinical conditions for which the patient took the medication. Rapid and complete withdrawal can lead to adrenocorticotropic hormone suppression and flare of the underlying disease. Courses over three weeks should have a quick taper to physiologic doses, then slow weaning should follow while evaluating the adrenal function. Long-term, high-dose suppressive therapy can lead to suppression of the hypothalamic-pituitary-adrenal axis for as long as nine to twelve months following withdrawal (Liu *et al.*, 2013).

Chapter Three: Methodology

3. Methodology

3.1. Materials

3.1.1. Equipments and Instruments

Table 3-1: The equipments and instruments which were used in this study

NO.	Equipment & Instrument	Company	Country
1.	Analytical sensitive balance	Sartorius	Germany
2.	Balance	Shimadu company	Japan
3.	Centrifuge	Hettich Roto fix11	Japan
4.	Digital camera	Toup Cam	China
5.	ELISA reader	Bio Kit	USA
6.	ELISA washer	Bio Kit	USA
7.	Eppendorf tube	Biolabse	England
8.	Freezer	Newal	Turkish
9.	Funnel	HBG	England
10.	Gastric tube and scissors	Local	Iraq
11.	Incubator	BINDER	Germany
12.	Insulin syringes	Biolabse	England
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.	**Micropipette 1-100 µl**	**CYAN**	**Germany**
18.	**Optical microscope with table PC**	**OPTICA**	**Italy**
19.	**Plan tube**	**A F M A- Dispo**	**Japan**
20.	**Rack for blood standing**	**Metter company**	**China**
21.	**Spectrophotometer**	**Labomed**	**UK**
22.	**Sterile syringes 2,3,5, 10 ml**	**PROTON**	**Malaysia**

3.1.2. Chemicals

Table 3-2: The chemicals were used in this study and their sources

No.	Chemicals	company	Country
1.	**ACE kit**	**SPECTRUM**	**Egypt**
2.	***Aloe vera* Gel**	**Local**	**Iraq**
3.	**Chloroform**	**Noorbrok**	**England**
4.	**Cholesterol kit**	**Cormay Kit**	**Poland**
5.	**DXM vial**	**Sigma Aldrich Company**	**(USA)**
6.	**Eosin-Hematoxilin Stain**	**Merck**	**German**

7.	**Ethanol 70%**	**Merck**	**German**
8.	**Formalin 10 %**	**TEDIA Company.**	**USA**
9.	**Glucose**	**SPECTRUM**	**Egypt**
10.	**HDL kit**	**Cormay Kit**	**Poland**
11.	**HSP 70 kit**	**SPECTRUM**	**Egypt**
12.	**LDL kit**	**Cormay Kit**	**Poland**
13.	**MDA kit**	**SPECTRUM**	**Egypy**
14.	**Normal saline**	**Labort**	**India**
15.	**Paraffin Wax**	**Merck**	**German**
16.	**Triglyceride kit**	**Cormay Kit**	**Poland**
17.	**VLDL kit**	**Cormay Kit**	**Poland**

3.2 Animals of the Study

The experiment was carried at the laboratory animal's facilities Faculty of University of Kerbala / College of Veterinary Medicine. Twenty-four albino's rats were usual in this study with the age was (10 weeks) old with an average body weight (150-200 mg). These animals were kept in suitable environmental conditions with temperature of around 25-28 C°, relative humidity 40٪ - 60٪ conditions room with a 12:12 h/light light/dark cycle (Meyer *et al*., 1982). The animals were housed in aplastic cage with diameters of 50×35×15cm. The feed given were pellets. The animals were kept for at last 15 days for acclimatization before experiment began.

3.3. Preparation of DXM

DXM vial was obtained from Sigma Aldrich Company (USA).

3.4. Preparation of *Aloe vera* gel

Mature, healthy and fresh Aloe Vera leaves about 75 to 90 cm long were washed with fresh water. The leaves were cut transversely into pieces. Thickened epidermis has been selectively removed. Natural Aloe Vera gel was seen, the outer part of the Aloe Vera leaf was peeled off to obtain Aloe Vera gel directly, using a small spoon, the entire gel was extracted. Then the gel was transferred to a blender to obtain a mixture and foam ready to be dosed to the animals under study (Fani & Kohanteb, 2012).

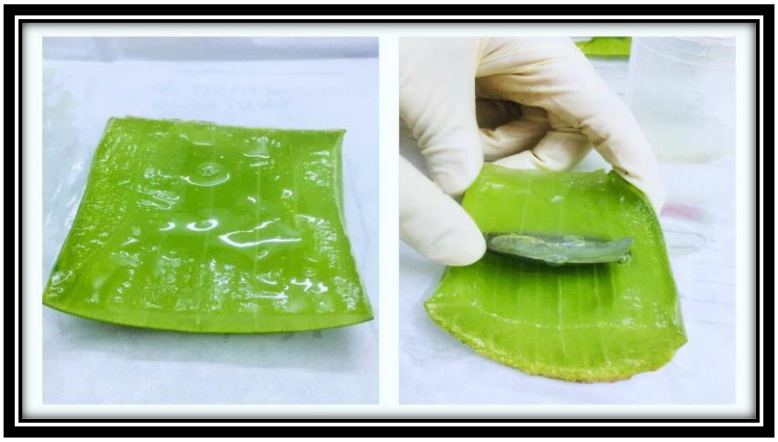


Figure (3-1): Preparation *Aloe vera* gel

3.5. The Experimental Design

The present study was undertaken: Hyperglycemia was induced by intraperitoneal (IP) injection of DXM for week, then fasting rats for 8 hrs. The control rats received the saline alone. Blood glucose level of these rats were estimated a week after DXM administration, hyperglycemia was confirmed by blood samples collected from the tip of the tail using a blood glucometer. Animals with blood glucose level equal or more than 200 mg/dl were declared hyperglycemia and were used in entire experimental group. Twenty-four male rats were divided randomly into four groups as shown in figure (3-2).

1-Group (G1): 6 rats administrating normal saline and animals is euthanized after 28 days.

2- Group (G2): 6 rats administrating of DXM 1mg/kg/bw intraperitoneally for 28 days (Martínez *et al.*, 2016).

3- Group (G3): 6 rats administrating of diabetic rats given DXM 1mg/kg/bw + *Aloe vera* leaf gel extract (300 mg/kg) in aqueous solution daily using an intra gastric tube (Rajasekaran *et al.*, 2005), for 21 days.

4- Group (G4): 6 rats administrating of diabetic rats given DXM 1mg/kg/bw. intraperitoneally + *Aloe vera* leaf gel extract (500 mg/kg) in aqueous solution daily using an intragastric tube (Rajasekaran *et al.*, 2005), for 21 days.

The study done By using 24 adult male rats divided equally into four groups as

Group (G1)	Group (G2)	Group (G3)	Group (G4)
Control group:6 rats has been administratin normal saline and animals is euthanized after 28 day.	DXM group:6 rats has been administrating of DXM -induced hyperglycemia 1mg/kg/bw. intraperitoneally for 28 days.	Experimental group:6 rats has been administrating of diabetic rats given *DXM* 1mg/kg/bw. + *Aloe Vera* leaf gel extract (300 mg/kg) in aqueous solution daily using an intragastric tube, for 21 days.	Experimental group:6rats has been administrating of diabetic rats given *DXM*1mg/kg/bw . intraperitoneally +*Aloe Vera* leaf gel extract (500 mg/kg) in aqueous solution daily using an intragastric tube, for 21 days.

Figure (3-2): Experimental design

3.6. Preparation and Collection of the Samples

At the end of the experiment, the animals were anesthetized by chloroform inhalation. The chest and abdomen, followed by collection of blood to perform biochemical and take the liver and pancreas for histology.

3.6.1. Blood Sample

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.

3.6.2. Organs

Liver and Pancreas was to be removed and the organs were being fixed in to 10% of formalin for histological examination.

3.7. Parameters

3.7.1. Biochemical Parameters

3.7.1.1. Determination of Serum Heat Shock Protein 70 (HSP70 ng/ml)

The kit is a sandwich enzyme immunoassay for in vitro quantitative measurement of HSP70 in rat serum, plasma, tissue homogenates, cell lysates, cell culture supernates and other biological fluids (Breuninger *et al.*, 2014).

Reagents and Materials Provied:

Reagents	Quantity	Reagents	Quantity
Pre-coated, ready to use 96-well strip plate	1	Plate sealer for 96 wells	4
Standard	2	Standard Diluent	1×20mL
Detection Reagent A	1×120μL	Assay Diluent A	1×12mL
Detection Reagent B	1×120μL	Assay Diluent B	1×12mL
TMB Substrate	1×9mL	Stop Solution	1×6mL
Wash Buffer (30 × concentrate)	1×20mL	Instruction manual	1

Reagents Preparation

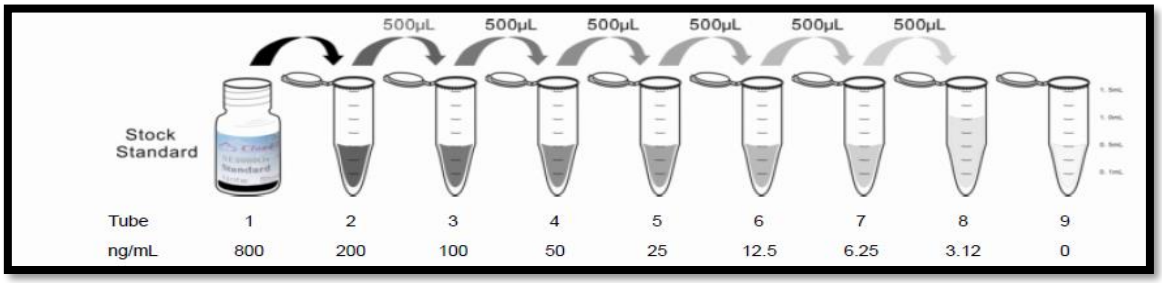
1. Brought all kit components and samples to room temperature (18-25 oC) before used. If the kit will not be used up in one time, please only taked out strips and reagents for present experiment, and leaved the remaining strips and reagents in required condition.

2. Standard - reconstituted the standard with 1.0 mL of standard diluent, kept for 10 minutes at room temperature, shaked gently (not to foam). The concentration of the standard in the stock solution is 800 ng/mL. Pleased firstly dilute the stock solution to 200 ng/mL and the diluted standard serves as the highest standard (200 ng/mL). Then prepared 7 tubes containing 0.5 mL standard diluent and use the diluted standard to produce a double dilution series. Mixed each tube thoroughly before the next transfer. Set up 7 points of diluted standard such as 200 ng/mL, 100 ng/mL, 50 ng/mL, 25 ng/mL, 12.5 ng/mL, 6.25 ng/mL, 3.12 ng/mL, and the last EP tubes with standard diluent is the blank as 0 ng/mL.

3. Detection reagent A and detection reagent B - briefly spun or centrifuged the stock detection A and detection B before used. Diluted them to the working concentration 100-fold with assay diluent A and B, respectively.

4. Wash solution - diluted 20 mL of wash solution concentrated (30×) with 580 mL of deionized or distilled water to prepare 600 mL of washed solution (1.(×

5. TMB substrate - Aspirate the needed dosage of the solution with sterilized tips and do not dump the residual solution into the vial again.



Note:

1. Made serial dilution in the wells directly is not permitted.

2. Prepared standards within 15 minutes before assay, do not dissolve the reagents at 37 ^{o}C directly.

3. Carefully reconstituted standards or worked detection reagent A and B according to the instruction, and avoid foaming and mixed gently until the crystals are completely dissolved. To minimized imprecision caused by pipetting, were used small volumes and ensured that pipettors are calibrated. It is recommended to suck more than 10 μL for one pipetting.

4. The reconstituted standards, detection reagent A and detection reagent B can be used only once.

5. If crystals have formed in the wash solution concentrate (30×), warm to room temperature and mix gently until the crystals are completely dissolved.

6. Contaminated water or container for reagent preparation will influence the detection result.

Samples Prepation

1. Predict the concentration before assaying. If values for these are not within the range of the standard curve, users must determine the optimal sample dilutions for their particular experiments. Sample should be diluted by PBS.

2. If the samples are not indicated in the manual, a preliminary experiment to determine the validity of the kit is necessary.

3. Tissue or cell extraction samples prepared by chemical lysis buffer may cause unexpected ELISA results due to the impacts from certain chemicals.

4. Due to the possibility of mismatching between antigen from other origin and antibody used in our kits (e.g., antibody targets conformational epitope rather than linear epitope), some native or recombinant proteins from other manufacturers may not be recognized by our products.

5. Influenced by the factors including cell viability, cell number or sampling time, samples from cell culture supernates may not be detected by the kit.

6. Fresh samples without long time storage is recommended for the test. Otherwise, protein degradation and denaturalization may occur in those samples and finally lead to wrong results.

3.7.1.2. Determination of Serum Angiotensin Converting Enzyme (ACE) ng/ml.

A-Principle

The kit uses a double-antibody sandwich enzyme-linked immunosorbent one step process to assay Angiotensin Converting Enzyme (ACE) in human serum. The standards, test samples, and HRP-labeled ACE-antibodies have been added to wells that are pre-coated with the ACE-antibodies. After incubation and washing to remove the uncombined enzyme, a chromogen solution A and B have been added. The color of the liquid changed into blue. At the effect of acid, the color finally becomes yellow absorbs at a wavelength of 450 nm. The concentration of ACE in the samples was determined from the linear equation of the log-log plot (Gross *et al.,* 1993).

Reagent preparation

20× wash solution: The solution has been diluted with distilled water 1:20.

Assay procedure

1. Standard addition: 50µl of standards has been added to standard wells.

2. 10 µl of the testing sample has been added. Then, sample diluent 40 µl was added to the testing sample well; nothing added to the Blank well.

3. One hundred microliters of HRP-conjugate reagent were added to each well, then covered and incubated for 60 minutes at 37°C.

4. Each well was washed five times, as previously mentioned.

5.Chromogen solution A (50µl) and chromogen solution B (50 µl) have been added to each well, then mixed and incubated for 15 minutes at 37°C.

6. Fifty microliters of stop solution has been added to each well. The color in the wells were changed from blue to yellow.

7. The OD was recorded at 450 nm by using a microtiter plate reader.

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

Malondialdehyhe was estimated by Thiobarbituric acid (TBA) assay method (Muslih *et al*., 2002) on spectrophotometer.

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.

3.7.1.4. Estimation of Serum Total Cholesterol Concentration (mg/dL)

Cholesterol concentration was measured by using Cormay cholesterol kit produced by PZ CORMAY S.A. company. Oxidation and after enzymatic hydrolysis, the cholesterol is determined in the presence of phenol and peroxidase,4-aminoantipyrine and the hydrogen peroxide forming quinoneimine the indicator (Fasce, 1982).

Principle:

Easter of cholesterol+H2O $Chol.\ estease$ Cholesterol + Fatty acids

Cholesterol +O2 $Chol.\ oxidase$ Cholest-4-en-one+H2O2

H2O+4-Aminophenazone + phenol $peroxidase$ Quinonimine

Reagent:

Reagent (1): Buffer solution: pipes PH 6.9 mmol/L, phenol 26 mmol/L

Reagent (2): Vial of enzyme: cholesterol oxidase 300 U/L, peroxidase 1250 U/L, cholesterol esterase 300 U/L, 4-aminophenazone 0.4 mmol/L

Reagent (3): Cholesterol standard 200 mg/dl

1. Manual procedure: Cholesterol concentration in serum samples was measured according to the following:

a. Reagent and serum samples were brought to room temperature.

b. Serum sample, blank and standard were treated as follow:

- Tube contents were mixed and left to stand for 5 minutes at 37°C before reading.
- The absorbance of the standard was measured and sample was read via spectrophotometer at wavelength 505 nm against the blank.

Tubes	Blank	Standard	Sample
Cholesterol standard (s)	-	10 ml	-
Sample	-	-	10 ml
Working Reagent	1ml	1ml	1ml

Calculation:

Results were calculated according to the following equation: Total Cholesterol concentration = (O.D sample)/ (O.D/ standard) × nn = 200 mg/dl

3.7.1.5. Estimation of serum Triglyceride concentration (mg/dL)

Triglyceride concentration was measured by Cormay triglyceride kit produced by PZ CORMAY S.A. company. Its hydrolyzed to glycerol enzymatically according to the following reaction (Fossati & Prencipe, 1982).

Principle:

Triglyceride $lipoprotein\ lipase$ Glycerol + fatty acid

Glycerol + ATP $Glycerol\ kinase$+ Glycerol-3-phosphate+ADP

Glycerol-3-P+O2 $3{-}G{-}P{-}oxidase$ Dihydroxyacetone ne-p+H2O

H2O2+4-Aminophenazone+p+Chlorophenol$peroxidase$ Quinonimine+ H2O

Reagent:

Reagent (1) buffer solution: pipes buffer PH 7.2, 50 mm0l/L, p- chlorophenol 2 mmol/L

Reagent (2) Enzyme: lipoprotein lipase 150 000 U/I, glycerol kinase 800 U/U/I, glycerol-3-phosphate oxidase 4000 U/I, peroxidase 440 U/I, 4-aminophenazone 0.7 mmol/L, ATP 0.3 mmol/L.

Reagent (3) triglyceride standard (S): Glycerol 200 mg/dl.

Procedure:

Triglyceride concentration in serum samples was measured according to the following:

a. Wave length/filter 505 nm (Hg 546 nm)/green

b. Temperature 37°C/R. T

c. Light path 1 cm

Pipette into clean dry test tubes labelled as Blank (B), Standard (S), and Test (T). Mix well and incubated at 37° C for 5 min or at R. T (25° C) for 15min. measure the absorbance of the standard.

Calculation:

Results were calculated according to the following equation:

Triglyceride concentration mg/dl = (O.D sample) / (O.D standard) × n = 200 mg/dl

Additive sequence	Blank	Standard	Test
Working reagent	1.0	1.0	1.0
Distilled water	0.01	-	-
Triglyceride	-	0.01	-
Standard			
Sample	-	-	0.01

3.7.1.6. Estimation of serum HDL-Cholesterol concentration (mg/dL)

HDL-Cholesterol concentration was measured by using Cormay HDL kit produced by PZ CORMAY S.A. The supernatant contains high density lipoprotein (HDL). The HDL-cholesterol is then spectrophotometrically measured by means of the coupled reaction described (Grove *et al.*, 1979).

Principle:

Cholesterol esters + H2O $Chol.esterase$ Cholesterol + fatty acid

Cholesterol +½O2 + H2O $Chol.oxidase$ Cholestenone + H2O2

2 H2O2 + 4-Aminoantipyrine + DCFS $peroxidase$ Quinoneimine + 4H2O

Reagent

Reagent (1): Good's buffer (pH 6.6)100 mmol/l, cholesterol esterase 1400 U/l, cholesterol oxidase 800 U/l, catalase 600 kU/l, N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline (HDAOS) 0.6 mmol/l.

Reagent (2): Good's buffer (pH 7.0) 100 mmol/l peroxidase 3 kU/l 4–aminoantipyrine (4-AA) 4 mmol/L.

Tubes	Blank	Standard	Sample
Distilled water	50 ml	-	-
Cholesterol Standard (S)	-	50 ml	-
Sample supernatant	-	-	50 ml
Reagent	1.0 ml	0 ml	1 ml

Procedure:

HDL-cholesterol concentration in serum sample was measured according to the following steps: serum sample 40 – 60 mg/dl 1.04 1.55 mmol/l, wave length 600 nm, temperature 37°C CORMAY HDL DIRECT is intended for automated analyzers.

a. Reagent (A, B) and serum sample were brought to room temperature.

b. Serum sample, blank and standard were treated as followed:

c. 0.2 ml of sample was mixed with 0.5 ml of reagent (A) in centrifuge tube and let stand for 10 minute at room temperature.

d. Centrifuged at a minimum of 4000 r.p.m. for 10 minutes.

e. The temperature was collected carefully.

f. Sample supernatant, blank, standard and reagent (B) were treated as the following:

- Tubes contents were mixed thoroughly and incubated for 10 minute at 37 °C.
- The absorbance (A) of the standard was measured and sample was read via spectrophotometerat wave length 500 nm against the blank.

Calculation:

Results were calculated according to the following equation:

HDL-cholesterol concentration in the sample (mg/dl) = (Absorbance of the sample/Absorbance of standard) × concentration of standard × sample dilution factor (1.7).

3.7.1.7. Estimation of Serum LDL-Cholesterol Concentration (mg/dL)

LDL-C was Measured by using Cormay LDL kit produced by PZ CORMAY S.A. company (Alan *et al*., 2006).

Principle:

Cholesterol ester $chol.esterase$ chol. + fatty acid

Cholesterol + O2 $Chol.oxidase$ chol. H2O2

2H2O2 $catalase$ H2O + O2

Reagent

Reagent (1): Good's buffer (pH 7,0) 50 mmol/l, cholesterol esterase 600 U/l, cholesterol oxidase 500 U/l, catalase 1200 kU/l, ascorbate oxidase 3 kU/l, TOOS [N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline] 2.0 mmol/l

Reagent (2): Good's buffer (pH 7,0) 50 mmol/l, peroxidase 5 kU/l, 4–aminoantipyrine (4-AA) 4 mmol/l.

Procedure

Wavelength 600 nm, temperature 37°C, CORMAY LDL DIRECT is intended for automated analyzers. serum/plasma < 100 mg/dl < 2.59 mmol/l.

As LDL cholesterol is affected by a number of factors such as smoking, exercise, hormones, age and sex, each laboratory should establish its own reference ranges for local population.

3.7.1.8 Estimation of serum VLDL-Cholesterol concentration (mg/dl)

VLDL-C was measured by using the following equation **VLDL** = **TG** /5 (FriedWald, 1972).

3.7.1.9. Glucose Estimation

To detect fasting blood glucose in the morning, animals were fasted overnight for 12 hr, and blood samples were obtained from the tail vein. An Accu-Chek compact glucometer was used to detect fasting blood glucose according to (Alonso-Magdalena *et al.*, 2010).

3.8. Histological study

The liver and pancreas of each animal were quickly removed and rapidly weighed then prepared for histological study according to (Mescher method, 2010) with aid of the light microscope as the following steps:

* Fixation

The specimen fixated in the formalin 10 % for 24 – 48 hours.

* 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).

* 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.

* 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.

* 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 (50–55^{o}C), then transferred into glass slides coated with Mayers albumin as adhesive substance and left to dry.

* Staining

The histological sections of the studied organs were stained with Hematoxylin - Eosin stain

3.9. Statistical analysis

The data were analyzed with SPSS (16.0 for Windows) by using a one-way analysis of variance (ANOVA). Differences between means were determined using Tukey's test in which the significance level was designated at ($P < 0.05$).

Chapter four: Results and Analysis

4. Results and Analysis

4.1. Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on blood glucose in adult male rats.

The main value of serum glucose shows a significant (P<0.05) decrease that was noticed at the G3 and G4 groups respectively if compared with the G2 group (table 4-1). On the anther hand G4 was significant decrease compared with the G3

Table 4-1: Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on blood glucose in adult male rats.

Groups / parameter	Control (G1)	Dexamethzone (G2)	Dexamethzone +*Aloe vera* 300 mg/kg/bw (G3)	Dexamethzone +*Aloe vera* 500 mg/kg/bw (G4)
Glucose	**97.83±8.40 C**	**195.50±5.20 A**	**118.00±4.04 B**	**107.83±6.55 C**

Different letters in the same raw represent a significant different at (P<0.05)

4.2. Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on HSP70, ACE and level of MDA in adult male rats.

Significant decrease (P<0.05) was noticed in the concentration of (MDA), (ACE) and (HSP70) in the G3 and G4 groups respectively if compared with the G2 group. On the anther hand G4 was significant decrease compared with the G3 (Table 4-2).

Table 24-: Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on HSP70, ACE and level of MDA in adult male rats.

Groups / parameters	Control (G1)	Dexamethzone (G2)	Dexamethzone +*Aloe vera* 300 mg/kg/bw (G3)	Dexamethzone +*Aloe vera* 500 mg/kg/bw (G4)
MDA nmole/mL	**205.33±3.25 D**	**280.46±7.69 A**	**245.71±7.27 B**	**221.7±5.51 C**
ACE ng/ml	**1.53±0.15 D**	**8.08±0.63 A**	**5.61±0.77 B**	**3.74±0.96 C**
HSP70 ng/ml	**10.10±1.03 D**	**16.25±0.45 A**	**14.29±0.62 B**	**12.46±0.41 C**

Different letters in the same raw represent a significant different at (P<0.05)

4.3. Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on blood lipids profile in adult male rats.

Significant (P<0.05) decrease was noticed in the serum concentration of cholesterol, triglyceride, VLDL and LDL at the G3 and G4 groups respectively if compared with the G2 group, on the anther hand G4 was significant decrease compared with the G3 (Table 4-3). HDL increased significantly (P<0.05) in the same groups.

Table 4-3: Effect of *Aloe vera* gel 300, and 500 (mg/kg/bw) on blood lipids profile in adult male rats.

Groups / parameters	Control (G1)	Dexamethzone (G2)	Dexamethzone +*Aloe vera* 300 mg/kg/bw (G3)	Dexamethzone +*Aloe vera* 500 mg/kg/bw (G4)
Cholesterol mg/dl	**50.59±9.14 D**	**155.16±8.88 A**	**111.33±9.39 B**	**76.66±8.09 C**
Triglyceride mg/dl	**77.00±5.58 C**	**171.83±11.26 A**	**118.00±5.40 B**	**88.66±9.75 C**
HDL mg/dl	**57.04±4.64 A**	**39.45±3.13 B**	**38.94±3.90 B**	**53.40±4.19 A**
LDL mg/dl	**9.11±1.36 C**	**150.37±1.02 A**	**118.35±33.09 B**	**26.61±16.37 C**
VLDL mg/dl	**15.48±1.48 C**	**44.33±8.57 A**	**24.26±3.59 B**	**18.66±2.16 BC**

Different letters in the same raw represent a significant different at (P<0.05)

4.4. The Histological Examinations

4.4.1. Liver

The histological section of the liver is shown in figure (4-1) stained with (H&E, 100X) from the control group, which has the normal hepatic architecture, around central vein, hepatocytes with significant rounded large nuclei. Figure (4-2) group of rats treated with dexamethasone showed the significant degenerative changes of hepatocytes (ballooning), sever dilation and congestion of portal vein and arteriol with inflammatory cells infiltration and remarkable hepatocytes pyknotic nuclei. The histological section in liver treated with dexamethasone + *Aloe vera* 300 mg/kg/bw revealed necrosis and depletion in hepatocytes with cellular vacuolation, and slight to moderate vascular congestion, areas showed histological structure improving to normal tissue with mild degenerative changes, figure (4-3) stained with (H and E, 100X). While the liver of rats figure (4-4) that had been dosed with dexamethasone + *Aloe vera* 500 mg/kg/bw showed improved to the normal morphological structure of portal area components, mild hepatocytes degeneration and vacuolation with nuclear pyknosis in some areas, and slight leukocytic infiltration.

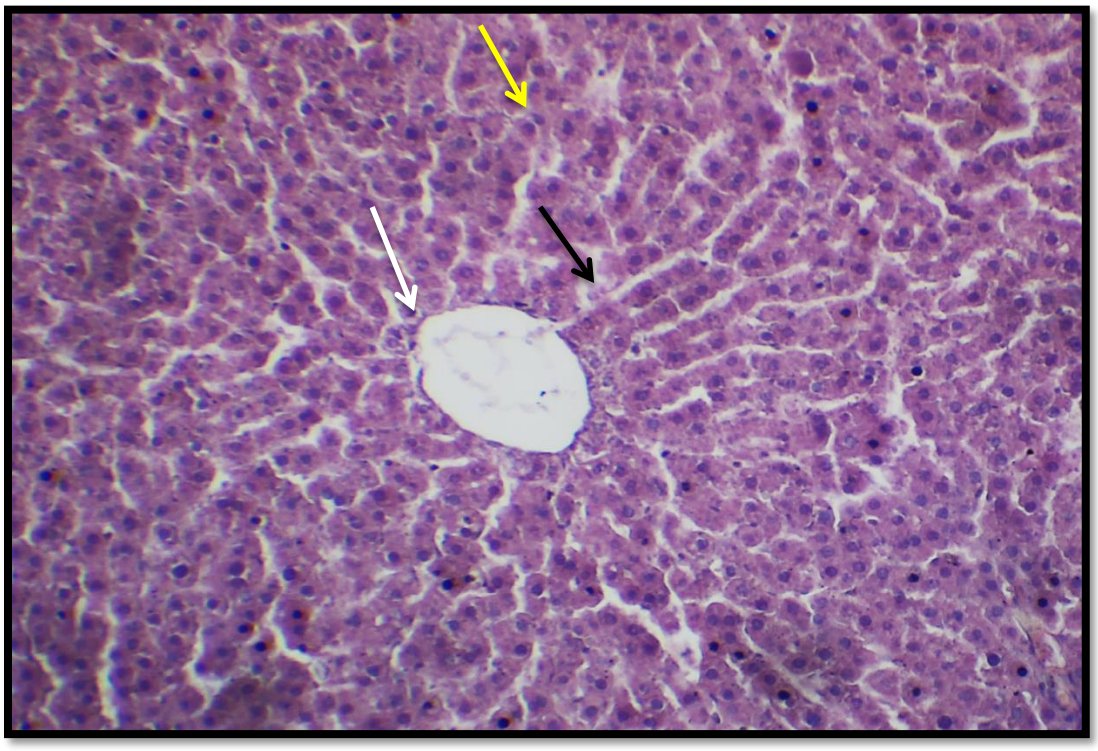


Figure (4-1): Photomicrograph of liver tissue section of a control group animal, showed the normal hepatic architecture (cords) (black arrow), around central vein (white arrow), hepatocytes with significant rounded large nuclei (yellow arrow), (H and E ,100X).

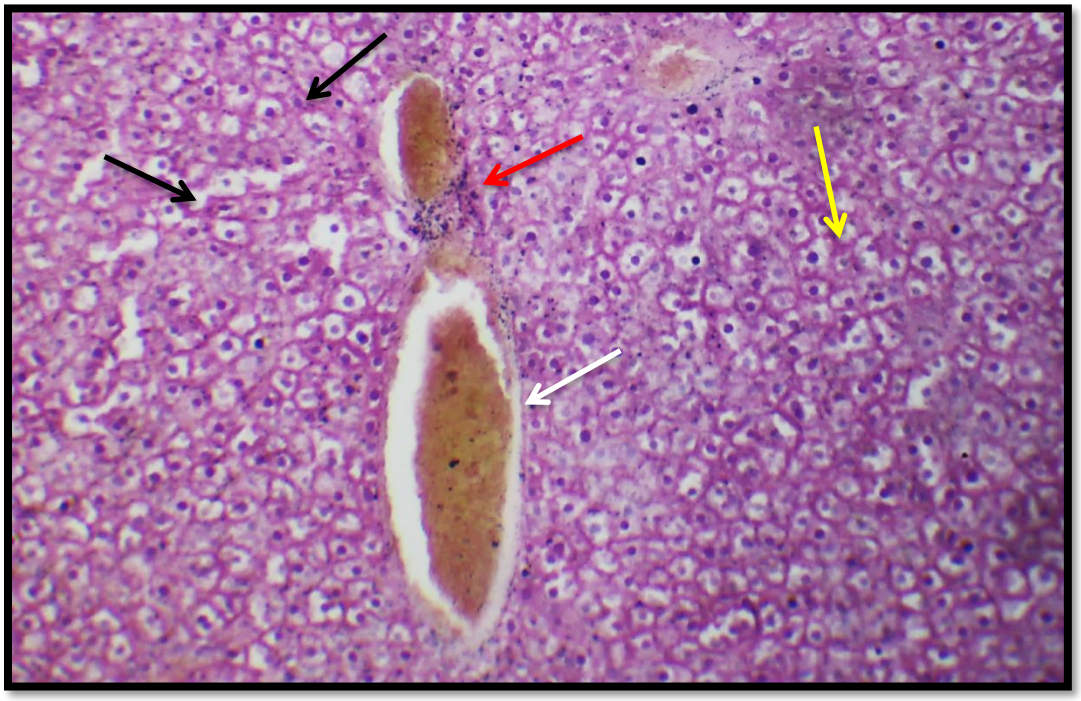


Figure (4-2): Photomicrograph of liver tissue section from dexamethzone group animal showed the significant degenerative changes of hepatocytes (ballooning) (black arrow), sever dilation and congestion of portal vein and arteriole (white arrow) with inflammatory cells infiltration (red arrow) and remarkable hepatocytes pyknotic nuclei (yellow arrow), (H and E, 100X).

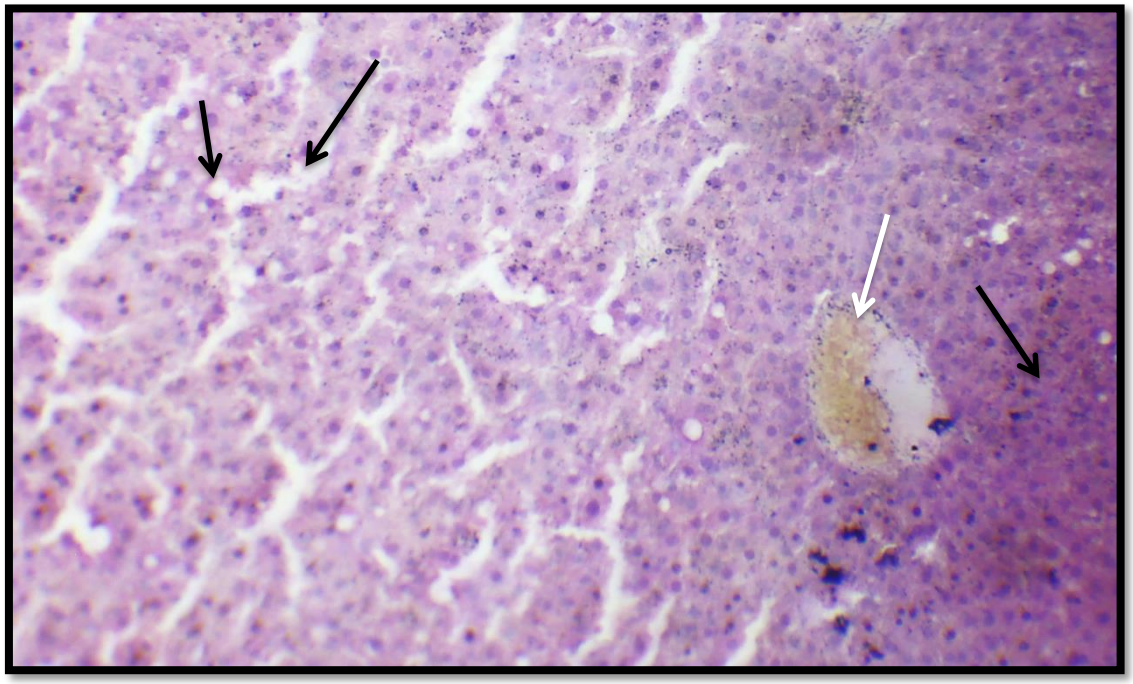


Figure (4-3): Photomicrograph of hepatic tissue section of dexamethasone + *Aleo vera* 300 mg/kg/bw treated group animal, revealed the significant necrosis and depletion in hepatocytes with cellular vacuolation (black arrow), and slight to moderate vascular congestion (white arrow), areas showed histological structure improving to normal tissue with mild degenerative changes (right side), (H and E, 100X).

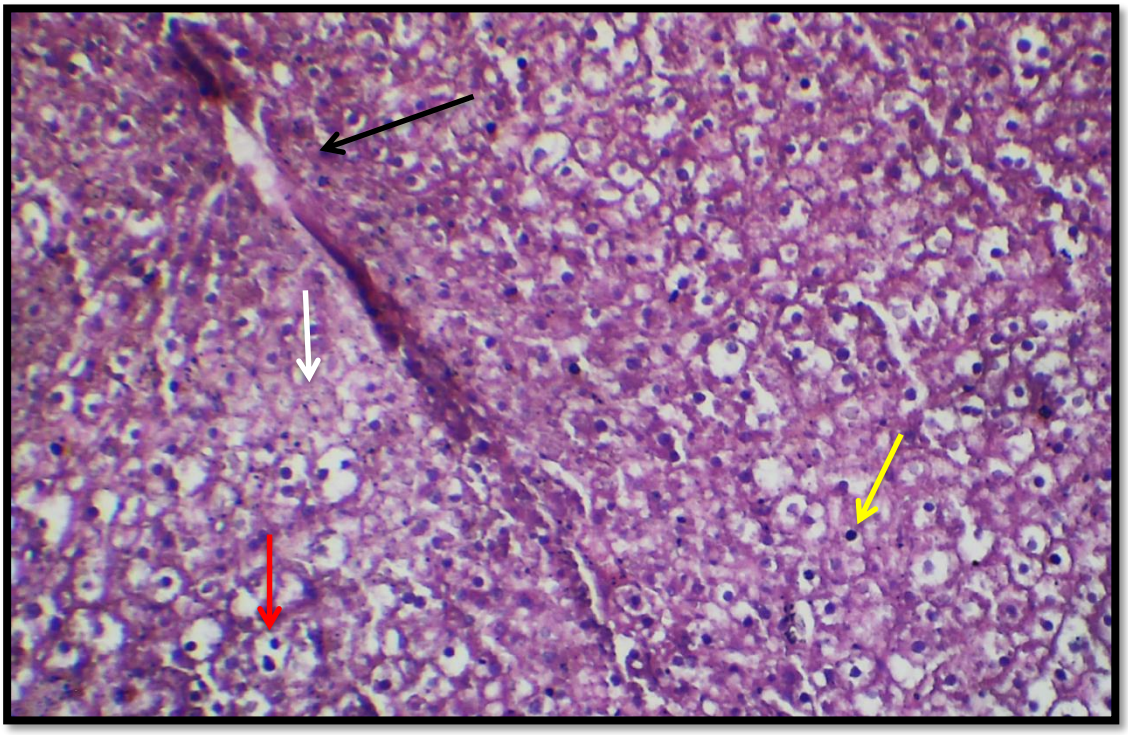


Figure (4-4): Photomicrograph of liver tissue section of dexamethasone + *Aleo vera* 500 mg/kg/bw treated group animal, improved to the normal morphological structure of portal area components (black arrow), mild hepatocytes degeneration and vacuolation (red arrow) with nuclear pyknosis in some areas (yellow arrow), and slight leukocytic infiltration (white arrow), (H and E, 100X).

4.4.2. Pancreas

Pancreas tissue from the control group (figure 4-5) stained with (H&E, 100X) revealed the normal architecture of tissue, normal exocrine acini, and normal islets of Langerhans embedded in exocrine pancreatic acini. Figure (4-6) group treated with dexamethasone only significant structural changes and damage, remarkable pancreatic ductal widening, acinar necrosis with vascular congestion and marked shrinkage islets of Langerhans due to degeneration of cellular components, stained with (H and E, 100X). Pancreas from rats treated with the dexamethasone + *Aloe vera* 300 mg/kg/bw revealed depletion of pancreas tissue with acinar necrosis, moderate vascular congestion, with perivascular inflammatory cells infiltration, and reversible changes ameliorate to normal cellular components of islets of Langerhans, figure (4-7). The pancreas of rats that had been treated with dexamethasone + *Aloe vera* 500 mg/kg/bw in figure (4-8) improved reversion of pancreatic tissue to their normal structure, vascular congestion with periductal inflammatory cells infiltration, and islets of Langerhans ameliorating to normal structure, stained with (H&E, 100X).

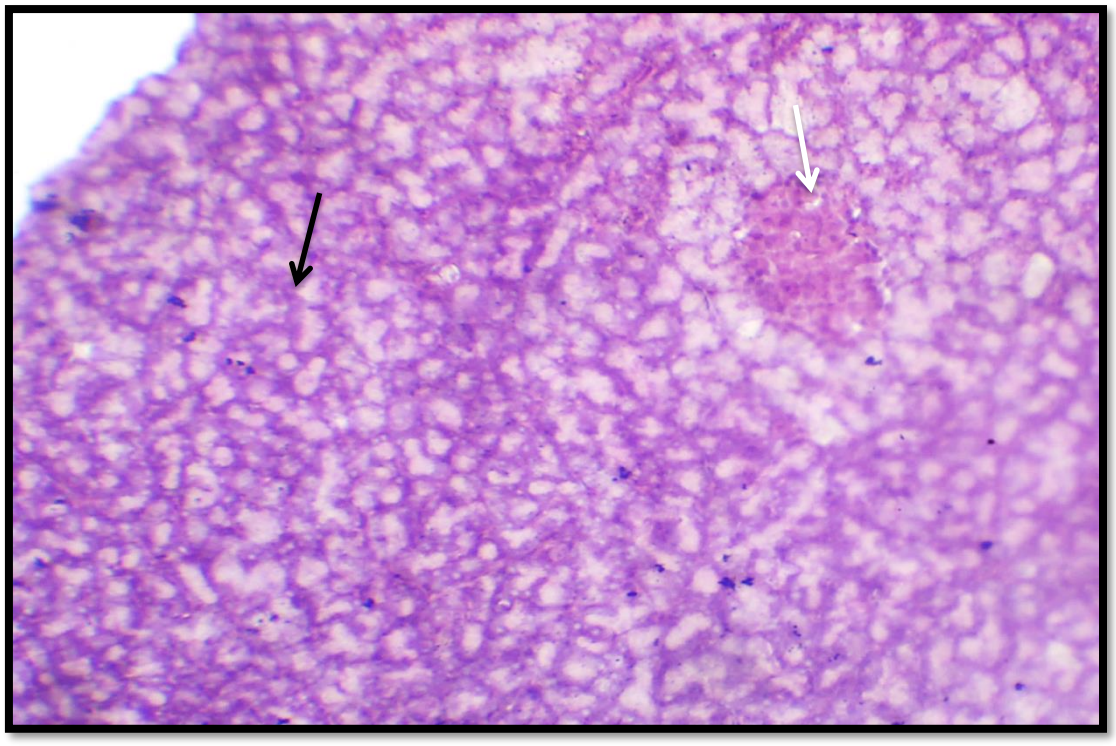


Figure (4-5): Photomicrograph of pancreatic tissue section of a control group animal, revealed the normal architecture of tissue, normal exocrine acini (black arrow), and normal islets of Langerhans embedded in exocrine pancreatic acini (white arrow), (H and E, 100X).

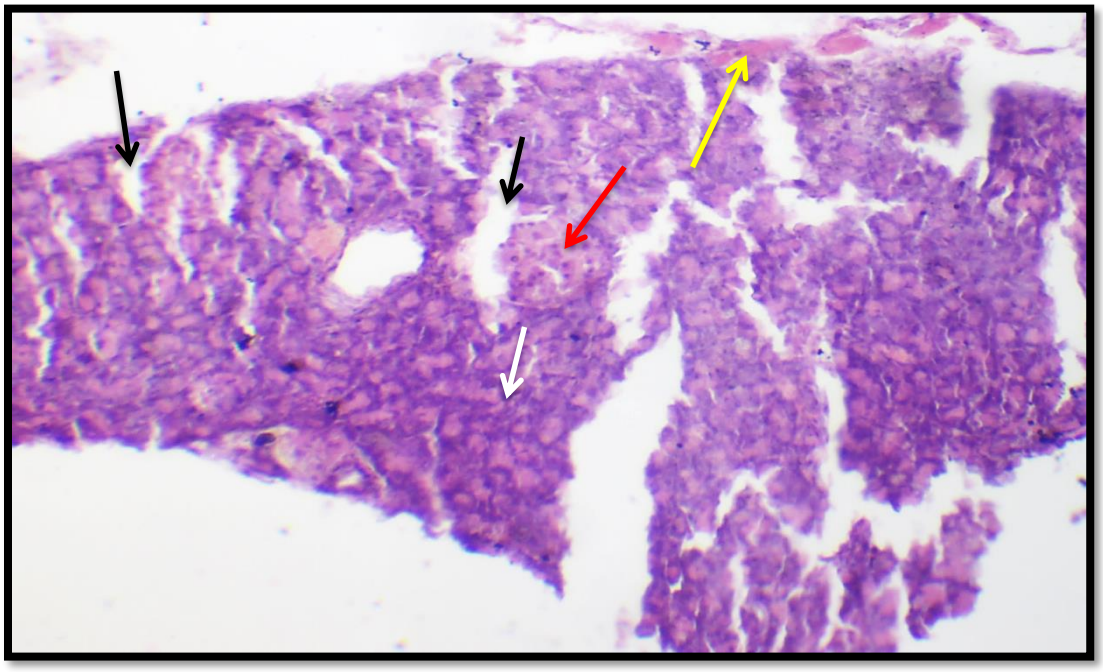


Figure (4-6): Photomicrograph of pancreas histological section from dexamethzone group animal showed significant structural changes and damage, remarkable pancreatic ductal widening (black arrow), acinar necrosis (white arrow) with vascular congestion (yellow arrow) and marked shrinkage islets of Langerhans due to degeneration of cellular components (red arrow), (H and E, 100X).

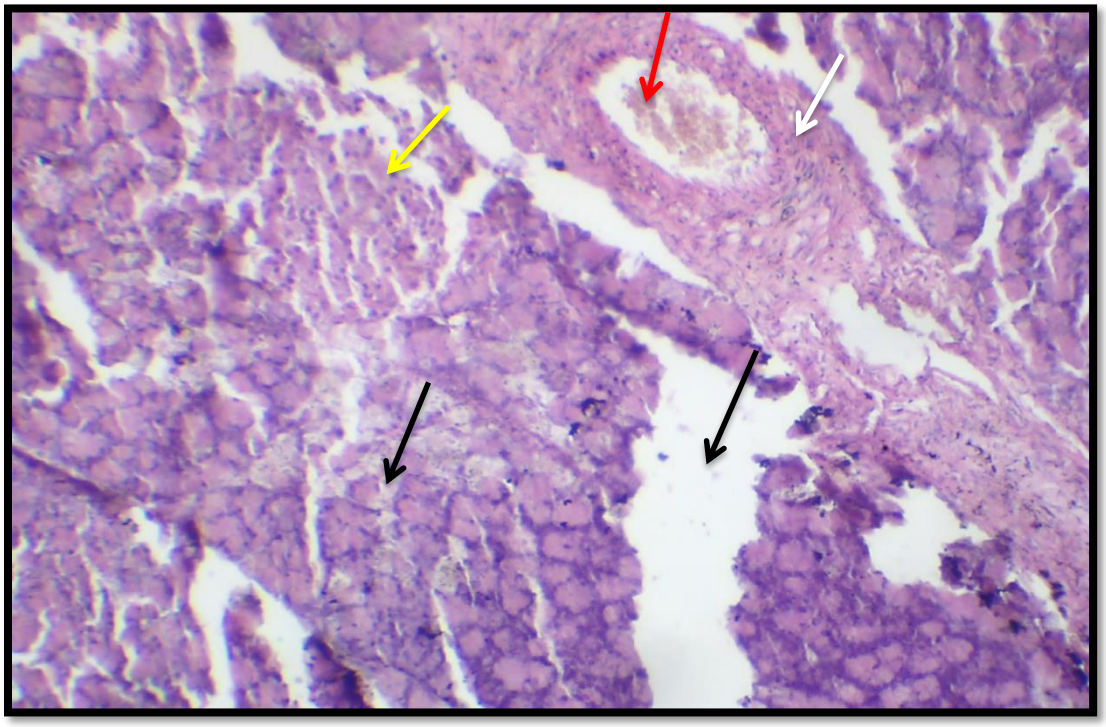


Figure (4-7): Photomicrograph of pancreatic tissue section of dexamethasone + *Aloe vera* 300 mg/kg/bw treated group animal, revealed depletion of pancreas tissue with acinar necrosis (black arrow), moderate vascular congestion (red arrow) with perivascular inflammatory cells infiltration (white arrow) and significant reversible changes ameliorate to normal cellular components of islets of Langerhans (yellow arrow), (H and E, 100X).

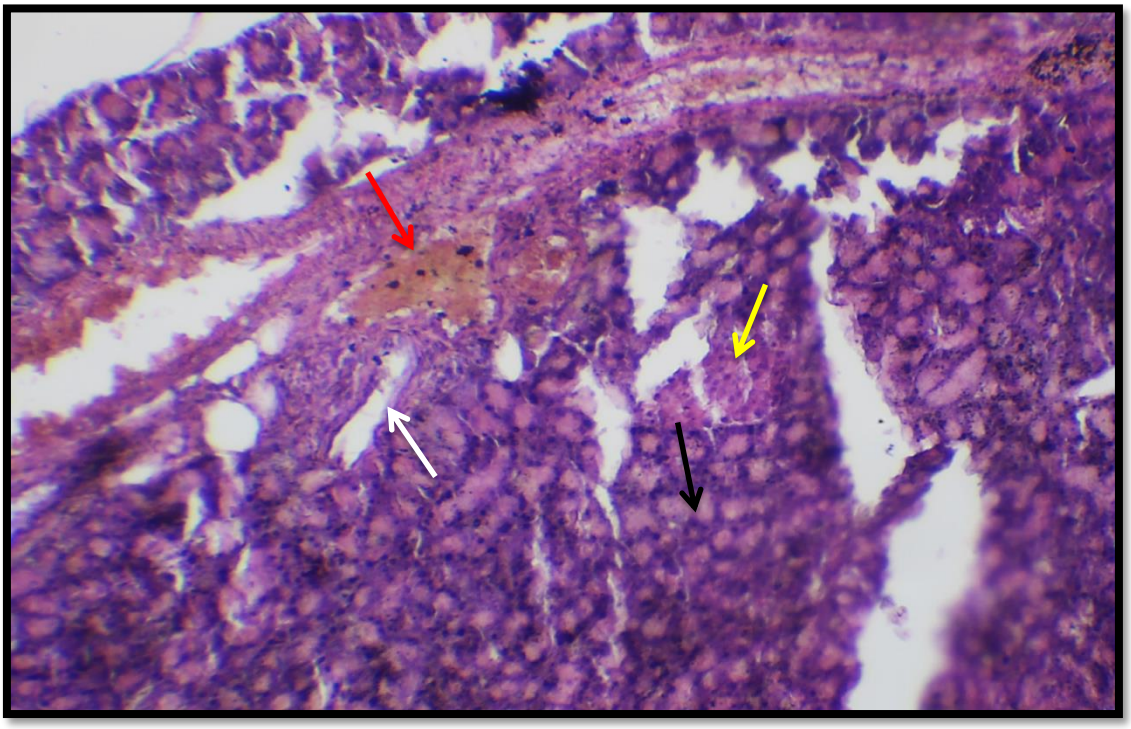


Figure (4-8): Photomicrograph of pancreatic tissue section of dexamethasone + *Aloe vera* 500 mg/kg/bw treated group animal, improved reversion of pancreatic tissue to their normal structure (black arrow), vascular congestion (red arrow) with periductal inflammatory cells infiltration (white arrow) islets of Langerhans ameliorating to normal structure (yellow arrow), (H and E, 100 X).

Chapter five: Discussion

5. Discussion

5.1. Effect of *Aloe vera* on some of biochemical parameters

5.1.1. Effective role of *Aloe vera* dose on blood glucose level

The statistical analysis for the blood glucose level (Table 4-1) shows a significant ($P<0.05$) decrease in the level of glucose in both doses of *Aloe vera* (118.00±4.04 mg/dl, 107.83±6.55 mg/dl) sequentially, compared to its level when given only dexamethasone (195.50±5.20 mg/dl). Also, no significant differences were observed between the two levels of *Aloe vera* on the level of glucose in the blood of rats.

As the high level of glucose leads to serious complications on various organs of the body such as the heart, liver and pancreas, Therefore, in this study, it is decided to observe the side effect of dexamethasone and try to reduce this effect by giving safe doses of *Aloe vera* gel. Indeed, a decrease in blood glucose level was observed when given calculated doses of this gel. It was mentioned in previous studies the effect of administering dexamethasone treatment for long periods and in high doses daily on the level of sugar in the blood. A significant increase in the level of glucose was also observed in diabetic patients which depend on a diet regulated for their glucose, despite its medical importance, (Gerstein *et al*., 2007). Explain the reason for the increase in glucose when this medicine is given to its ability to reduce the activity of insulin secretion as a result of a defect or destruction in the insulin-secreting liver cells and thus its inability to regulate the level of glucose in the blood, which leads to its rise, increase in homeostasis model assessment of insulin resistance and homeostasis model assessment of β cells, respectively is the closest theory to the real cause .This is what we agree with in our study. On the other hand, documented studies found no effect of taking dexamethasone on healthy people compared to its ability to increase the level of glucose on diabetic patients themselves (Marcinkowska *et al*., 2007; Abo-Youssef *et al.*, 2013).

Studying the effect of giving *Aloe aera* gel on the level of diabetes as in our current study, as the mechanism of cactus regulation of glucose level is not known, and it is likely that it plays an important role in restoring the activity of the pancreas and its ability to secrete insulin in an organized manner, as was observed during the results. A primary

preventive measure for this disease is lifestyle modification, which is usually difficult. Therefore, it is necessary to utilize other therapies to reduce the consequences of this disease (Alberti *et al.,* 2009; Grundy *et al.,* 2005).

In the present study, the effects of different doses of *Aloe vera* extract at different time spans were studied on blood glucose and lipids in hyperglycemia patients. The results of this study showed that both the 300 and 500 mg *Aloe vera* within one month significantly reduced fasting blood glucose levels. Also, they significantly decreased lipids by the end of the study. Similar studies indicate that *Aloe vera* extract is effective in increasing insulin sensitivity, reducing fasting blood glucose, and decreasing the level of HbA1C in patients with pre-diabetes during eight weeks (Devaraj *et al.,* 2013). Several human studies have reported the anti-diabetic effects of *Aloe vera* gel extract (Bunyapraphatsara *et al.,* 1996; Fallah *et al*., 2012). In models of type I diabetes laboratory animals, it is shown that *Aloe vera* extract had a similar effect on blood glucose to that of glibenclamide (Rajasekaran *et al.,* 2007). Even in patients who did not respond to glibenclamide alone, consumption of *Aloe vera* extract for 2 weeks could reduce fast blood glucose (Bunyapraphatsara *et al*., 1996).

Other studies have also shown the effectiveness of *Aloe vera* extract on the regulation of blood glucose levels in diabetic animals (Rajasekaran & Aathishsekar, 2007; Kim *et al,* 2009). Few studies have indicated a rise in blood sugar levels after consumption of *Aloe vera* extract (Koo, 1994), which might be related to the use of different parts of the plant (not the gel) or short duration of the intervention (2 times a day for 3 days).

Researchers have also introduced an important element in the hypoglycaemic effects of *Aloe vera* in a substance called Acemannan. This is actually a D-isomer of compound polysaccharide that is extracted from *Aloe vera* leaf gel and has such properties as anti-virus, anti-cancer, digestive, and immune stimulating properties (Devaraj *et al.,* 2013). *Aloe vera* also contains other compounds such as hydrophilic fiber, glucomannan (Yeh *et al.,* 2003), and phytosterol (Tanaka *et al.,*2006) that reduce blood glucose.

Kim *et al.,* (2009), who is suggested that *Aloe vera* can increase insulin sensitivity in the cells with reduce the level of blood glucose. Perhaps the *Aloe vera* can increase the insulin genetics activity in pancreatic beta cells. Studying the effects of anti-diabetic

extract of *Aloe vera* showed that this plant cannot reduce the level of blood glucose in non-diabetic animals which is contrary to the results for hypoglycemic effects of glybenclamid (Okyar *et al.,* 2001).

5.1.2. Effect of *Aloe vera* on ACE, HSP70, and level of MDA

The statistical analysis of the ACE, HSP70, and level of MDA showed a significant decreased ($P<0.05$) was noticed (ACE) 5.61 ± 0.77 ng/ml, (HSP70) 14.29 ± 0.62 ng/ml, and in the concentration level of (MDA) 245.71 ± 7.27 nmole/mL, when we used the concentration of *Aloe vera* gel 300 mg/kg/bw compared with the (G2) group (Table 4-2). Generation within the membrane and lipoprotein of peroxyl and alkoxyl radicals, aldehyde and other products of lipid oxidation affects the liver to a great extent, causing the formation of high molecular mass protein aggregate within the membrane. Hence increased level of MDA and associated products viz conjugated dienes are a factual indicator of lipid peroxidation (Gutteridge *et al.*,1982), which highlight the toxic effect of MDA in liver. Thiols are thought to play a vital role in protecting cells against lipid oxidation (Pryor, 1973).

Among the HSPs, HSP70 is considered to be one of the most conserved and important protein families. In fact, HSP70 refers to a family of 70 kDa chaperone proteins participating in house-keeping functions. These ATP-dependent chaperones are key elements of the cellular protein surveillance network involved in a large variety of protein-folding processes (Rosenzweig *et al.,* 2019). It is well appreciated that under various stress conditions, adaptive synthesis of stress inducible HSP70 enhances the ability of stressed cells to maintain proteostasis by dealing with increased concentrations of unfolded or denatured proteins (Fernández *et al.,* 2018; Xu *et al.,* 2021; Balogi *et al.,* 2019; Clerico *et al.,*2019).

5.1.3. Effect of *Aloe vera* gel on lipids profile of adult male rats

The results of this study showed in (table 4-3) that *Aloe vera* 500 mg/kg/bw was more significantly than 300 mg/kg/bw he managed to reduce the levels of total cholesterol, TG,

and LDL-C, and increase the level of HDL-C significantly during the 28 days drug intake. However, *Aloe vera* 300 mg/kg/bw could only increase the level of HDL-C in 28 days more than before intake it.

However, *Aloe vera* did not affect the level of HDL-C and triglycerides (Fallah *et al*, 2012). The reason may lie with the fact that only the 300-mg capsules of *Aloe vera* were used in that study on a population of type 2 diabetic patients who had high levels of blood glucose.

That high levels of blood glucose can cause complex problems such as oxidative stress that will lead to the development of type 2 diabetes (Rajasekaran *et al.,* 2005). Also, it has been demonstrated could increase the level of serum lipids: cholesterol, triglycerides, LDL, VLDL and decreased levels of HDL (Kim *et al*., 2009).

Aloe vera can bring the distribution of fatty acids in the blood to normal status by controlling the metabolism of lipids in the liver. In fact, Aloe Vera extract can construct non-saturated fatty acids that remove free radicals from blood stream and control the metabolism of lipids in the body (Rajasekaran *et al*., 2007).

Beta Sistostrol, Camposterol, and Stigmosterol are similar to Phytosterols. Besides, it is found that beta Sistostrols chain available in some plants such as *Aloe vera* can significantly decrease the level of plasma total cholesterol, LDL-C, and triglycerides by inhibiting activation of fat absorption mechanisms (Kamal-Eldin & Moazzami, 2009). This is what we support as a reason for the results obtained in our study. In a previous study, it was shown that the use of *Aloe vera* gel extract as much as 200 mg/kg/bw on a daily basis for as long as 100 days can significantly reduce the level of cholesterol, triglyceride, free fatty acids, and phospholipids in normal mice (Joshi & Gajraj, 2006). It is also shown that taking *Aloe vera* extract for 8 weeks in diabetic rats can lower the level of cholesterol and TG (Kim *et al.*, 2009). Nonetheless, *Aloe vera* is beneficial even in short-term intakes (21 days) of 300 mg dose (Rajasekaran *et al.,* 2005).

Some studies have mentioned that maximal dose of 50 mg *Aloe vera* could not improve the level of cholesterol in diabetic rats (Tanaka *et al.,* 2006). This suggests that

the dose of *Aloe vera* that is required to reduce the level of cholesterol of serum is higher than the dose needed for reducing the level of blood glucose.

In a clinical trial conducted on 36 patients with type 2 diabetes, it was found that *Aloe vera* could reduce the level of triglycerides but had no effects on the level of cholesterol after daily use of one tablespoon of *Aloe vera* along with glibenclamide for 6 weeks (Bunyapraphatsara *et al.,* 1996), which are not similar to the results of our study. Perhaps, high blood glucose which may in turn lead to increased levels of blood lipid in the patients may suggest that they were taking lipid-lowering drugs instead of complementary medicine. The patient took *Aloe vera* juice which was not of sufficient accuracy to determine the exact amount of medication received. Devaraj *et al*. (2013) also showed, that taking two 500 mg capsules of *Aloe Vera* on a daily basis was effective in lowering the level of LDL and total cholesterol, is consistent with the results of our study. However, it was not found to be effective in reducing the level of triglyceride and increasing the level of HDL-C of the serum (Devaraj *et al.,* 2013). Perhaps, it was because of the small number of participants in each group (n =15) or the little amount of active ingredients in the gel of, which can be as a result of the specific method of pasteurization and separation of the extract.

It was also reported that a high intake of *Aloe vera* (2 tablespoons three times daily for 12 weeks) could reduce the level of triglyceride of serum without effect on the levels of cholesterol, while no renal or hepatic toxicity was observed (Yagi *et al.,* 2009). Increased activity of hormone-sensitive lipase during insulin secretion defect, increased release of free fatty acids from fat tissue. Thus, it produces more phospholipids and cholesterol in the liver due to accumulation of fatty acids in plasma. These two substances are released into the blood stream as triglycerides which can increase the level of lipoproteins in the blood. Beppu *et al.* (2006). Those are suggested that can reduce the level of lipids in blood by controlling the fat metabolism in the liver.

Another theory is that the *Aloe vera* gel extract can lower the level of blood glucose and lipid in diabetic rats by improving sensitivity of cells to insulin (Kim *et al.,* 2009; Misawa *et al.,* 2012).

To Kim *et al.* (2009) those are well known that *Aloe vera* extract can suppress the adipogenesis gene and suggested that the plant can improve insulin resistance by reducing toxic effects of fat in the liver.

5.2. Histopathological study

5.2.1. Histopathological effect of *Aloe vera* on liver

Histological section for liver done after the rats were scarified and the livers taken at the end of treatments. The dexamethasone intake rats show liver damage and increase vacuolation in the hepatocytes with dilatation in the central vein (figure 4-2).

It was observed through the histopathological sections of a piece of the liver that there was no injury in the control group as in the figure (4-1), while there were injury points in the liver of the group that had been dosed with dexamethasone alone, for the liver is the major site for detoxification and metabolism of most xenobiotics, these effects occur in the liver due to the high dose of dexamethasone may be cased oxidative stress and lead to cellular apoptosis (Alabbood *et al*., 2019), as we show in the same group that there is a vacuolation of hepatocytes and return radial arrangement of liver architecture.

This is what we agreed on with the previously published article (Abo-Youssef *et al.*, 2013). Given that many millions of people take *Aloe vera* every day around the world with no ill effect, hepatotoxicty appears to be a very rare problem, particularly with the decolorized gel, which is purely made from the plant pulp and does not contain any skin of the leaf (Guo & Mei, 2016). It is worth noting though that the skin of the plant is not digestible and can cause liver toxicity; it has therefore not been recommended for human oral consumption (Younes *et al.,* 2018). Therefore, *Aloe vera* should only be consumed from a trusted source, using the fresh inner flesh of the plant, or a decolorized derivative (Younes *et al.,* 2018).

The previous reports of liver toxicity are barring one case, suspected rather than proven (Parlatiet *et al.,* 2017; Lee *et al.,* 2014). It is sometimes difficult to assess the effects of herbal and health food compounds as hepatotoxic agents in the populations of the developed world, given that 25-30% of the western European population have increased liver enzymes from multiple causes such as obesity, diabetes, high cholesterol

levels, consumption of alcohol to excess and the use of a variety of medications which have known liver effects. As there are usually multiple potential reasons for abnormal liver enzymes on blood testing, picking out a single cause does require expert interpretation and in this increasingly obese world, being overweight is becoming the commonest reason.

5.2.2. Histopathological effect of *Aloe vera* on pancreas

In various plant extracts have been claimed to be useful for the cure of diabetes mellitus (Shukia *et al*., 2000; Bolkent *et al*., 2005) but few of them have been tested for their effects on tissues of diabetic animals (Parinandi *et al.,* 1990; Bolkent *et al.,* 2005). Parsley extracts did not cause any morphological changes in pancreatic β-cells (Yanardag *et al,* 2003).

Acute treatment with Aloe leaf pulp resulted in 30 and 34% decreases in blood sugar levels of n0-STZ-diabetic rats, after 2 and 3 hr. of administration of the extract respectively (Okyar *et al*., 2001), and 11 and 14% reductions in blood glucose levels 3 and 4 hr. after administration of *Aloe* leaf-gel extract.

However, these effects could not be repeated with the same extracts in chronic treatment (Okyar *et al.,* 2001).

Changes in the pancreatic sections were more pronounced, and when the dose was began affected, there was a deterioration of pancreatic acini cells as well as in the islets of Langerhans, in addition to a reduction in volume, as well as necrosis of the other islets, with infiltration of inflammatory mononuclear cells. These results were also observed in pancreatic tissue by other investigators after rats were given different doses of the drug for 4 weeks (Ayoub & ElBeshbeishy, 2016; Haroun *et al*., 2020), as we showed.

Based on this work with the mentioned literature, it can be said that dexamethasone when consumed for a long time can cause damage to the pancreas, and this damage increases with increasing dose of consumption. (El Desouky *et al*., 2019) stated that a higher concentration of sugar may alter carbohydrate metabolism resulting in elevated blood glucose and insulin levels accompanied by insulin resistance.

This may explain why the carrots are enlarged in size. Increasing the dose and duration of dexamethasone administration leads to an additional rise in the level of glucose in the blood, which may increase the production of reactive oxygen species that cause oxidative stress and damage to pancreatic tissue (Ayoub & ElBeshbeishy, 2016), as may oxidative stress due to hyperglycemia (Ismail, 2020).

Hyperglycemia, caused by large amounts of dexamethasone, reduces tissue sensitivity to insulin, impairs glucose metabolism, and stimulates the release of stress hormones such as adrenaline (Gonzalez *et al*., 2017). Oxidizing in turn will cause insulin resistance, and destruction of βeta cells of pancreas (Robertson, 2006).

Chapter six: Conclusions and Recommendations

6. Conclusions and Recommendations

6.1. Conclusions

Based on the current research findings, the conclusions are as the following:

1. It was concluded that *Aloe vera* gel extract has an important role in lowering the levels of blood glucose, LDL, VLDL, triglycerides, cholesterol, and increasing the level of HDL.

2. It was concluded that *Aloe vera* gel glucose had an important role in reducing the level of antioxidants ACE, HSP70 and level of MDA.

3. The results of this study revealed that *Aloe vera* at the dose of 300 and 500 mg/kg body weight significantly normalized the elevated blood glucose level and restored serum marker enzymes toward normal values of hyperglycemic and hyperlipidemic rats.

4. The anti-hyperglycemic effect of *Aloe vera* at 500 mg /kg bw dose was found to be more effect than 300 mg/kg bw.

6.2. Recommendations

1. Studying the effect of high doses of the drug on the heart, lung and brain, and taking tissue sections for them to study the effect of dexamethasone on them.

2. A more extensive study on the uses of aloe Vera gel and its effect on the body, such as repairing wounds, hiding traces of burns, and others

3. Study the effect of aloe Vera gel on reactive oxygen species (ROS).

4. Taking more biomarkers than the effect of high doses of dexamethasone, such as hormones, antioxidants, etc.

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الخلاصة

يؤدي الاستخدام المزمن للديكساميثازون (DXM) إلى ارتفاع السكر في الدم وفرط شحميات الدم ، لذلك أجريت هذه الدراسة لتقييم تأثير المستخلص المائي لهلام الصبار في خفض مستوى الجلوكوز والدهون في دم الجرذان المجرعة بالدكساميثازون في ارتفاع السكر في الدم وفرط شحميات الدم في ذكور الجرذان. أجريت الدراسة في جامعة كربلاء / كلية الطب البيطري خلال الفترة من تشرين الثاني 2021 الى نيسان 2022.

تم استخدام أربعة وعشرين من ذكور الجرذان البالغة في الدراسة الحالية وتم تقسيمها إلى أربع مجموعات ، المجموعة الأولى (G1) تعتبر مجموعة ضابطة تلقت محلول ملحي طبيعي ، المجموعة الثانية (G2) تلقت ديكساميثازون (1 مجم / كجم / وزن الجسم) داخل الصفاق ، بينما تلقت المجموعة الثالثة (G3) ديكساميثازون (1 ملجم / كجم / وزن الجسم) داخل الصفاق ممزوجًا بمستخلص جل أوراق الصبار (300 مجم / كجم / وزن الجسم) في محلول مائي يوميًا باستخدام أنبوب داخل المعدة ، وتتلقى المجموعة الرابعة (G4) ديكساميثازون (1 مجم / كجم) / وزن الجسم) ممزوجًا داخل الصفاق مع مستخلص جل أوراق الصبار (500 ملجم / كجم / وزن الجسم) في محلول مائي يوميًا باستخدام أنبوب داخل المعدة ، وفي نهاية التجربة تم جمع الدم لتقييم مستوى الجلوكوز ، وخصائص الدهون (الكوليسترول ، الدهون الثلاثية ، البروتين الدهني منخفض الكثافة (LDL) والبروتين الدهني منخفض الكثافة جدا (VLDL) والبروتين الدهني عالي الكثافة (HDL). مستويات malondialdehyde (MDA) ، بروتين الصدمة الحرارية 70 (HSP70) ، والإنزيم المحول للأنجيوتنسين (ACE). تم عزل البنكرياس والكبد لدراسة التغيرات النسيجية أظهرت نتائج t انخفاضًا معنويًا ($p<0.05$) في جلوكوز الدم في المجموعتين (G3) و (G4) على التوالي مقارنة مع مجموعة (G2). لوحظ انخفاض معنوي ($P<0.05$) في تركيز مصل الدم من الكوليسترول والدهون الثلاثية و VLDL و LDL في المجموعتين (G3) و (G4) على التوالي مقارنة مع مجموعة (G2). بينما زاد HDL معنويا ($P<0.05$) في نفس المجموعات. لوحظ انخفاض معنوي ($P<0.05$) في تركيز MDA و HSP70 و ACE في مجموعتي (G3) و (G4) على التوالي مقارنة مع مجموعة (G2).

أظهرت التغيرات النسيجية في الكبد والبنكرياس في الفئران أن المجموعة المعالجة بالديكساميثازون أظهرت تغيرات هيكلية وتلفًا كبيرًا. بالإضافة إلى ذلك ، يعمل الألوفيرا 500 ملغم / كغم / وزن الجسم بشكل أفضل من الألوفيرا 300 ملجم / كجم / وزن الجسم على تحسين التأثير الضار للديكساميثازون في دراسات التشريح المرضي في الكبد والبنكرياس عند الفئران بالمقارنة مع المجموعة التي تم حقنها بالديكساميثازون فقط.

في ختام نتائجنا نستنتج أن الديكساميثازون يؤدي إلى آثار جانبية في ارتفاع السكر والدهون مما يؤدي إلى آثار ضارة على الكبد والبنكرياس. أثناء تناول جل الصبار مع ديكساميثازون يحسن هذه المعلومات المدروسة.

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة كربلاء

كلية الطب البيطري

تقييم تأثير الصبار ضد ارتفاع السكر في الدم وفرط دهون الدم في ذكور الجرذان المعرضة للديكساميثازون

رسالة

مقدمة إلى مجلس كلية الطب البيطري في جامعة كربلاء كجزء من متطلبات نيل درجة الماجستير في فرع الفسلجة

كتبت بواسطة

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م 2022 **هـ 1444**