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Formulation and Evaluation of a Polyherbal solution and green synthesis of ZnNPs against metabolic disorder associated with experimental diabetes in rats

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بسم الله الرحمن الرحيم

﴿ ثُمَّ كُلِي مِنْ كُلِّ الثَّمَرَاتِ

فَاسْلُكِي سُبُلَ رَبِّكِ ذُلُلًا يَخْرُجُ مِنْ

بُطُونِهَا شَرَابٌ مُخْتَلِفٌ أَلْوَانُهُ فِيهِ شِفَاءٌ

لِلنَّاسِ إِنَّ فِي ذَٰلِكَ لَآيَةً لِقَوْمٍ

يَتَفَكَّرُونَ ﴾ الآية 69 من سورة النحل.

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Abstract

Our study aimed to investigate the effect of polyherb (formulated by some plants) and ZnNPs (formulate by green synthesis) on physiological, biochemical alterations and oxidative stress induced by experimental diabetes in rats.

For this purpose, 24 female albino Wistar rats were randomly divided into 6 groups (n=4); healthy rats (Control), healthy rats treated with polyherb (Polyherb), healthy rats treated with ZnNPs (ZnNPs), diabetic rats (Diabetic), Diabetic rats treated with polyherb (D+Plyherb) and Diabetic rats treated with ZnNPs (D+ZnNPs). All types of treatments were given to rats orally for 21 days. Diabetic in rats was induced by single dose intaperitonially administration of Alloxan (150mg/kg). Various parameters as hematological, biochemical and oxidative stress markers were estimated. Histopathologies of pancreas tissues were observed. In in-vitro study on plant and nanoparticles, some quantitative, qualitative and characterization parameters were analyzed using standard protocols.

In vitro phytochemical analysis results revealed that polyherb contains phenols, flavonoids, alcaloids, terpenoids, tannins and steroids. In vivo results, in diabetic group showed an alteration in lipid profile and biochemical parameters. While, the antioxidant defends system in liver, kidney, pancreas, ovary were affected by increasing the MDA level and decreasing the GSH levels and SOD activities compared to control. Moreover, the hematological parameters revealed that Diabetes induce an anemia in rats by a significant diminution ($P<0.01$) of RBC, MCV and HCT levels. In the other hand, histopathological analysis noted an alteration in pancreas tissues of diabetic rats group compared to control. However, the treatment of Diabetic rats by Polyherb and ZnNPs ensured a partial amelioration and correction of the previous parameters.

In conclusion, the use of Polyherb and Nanoforme of zinc appears to be the dominant limited of development and complication of diabetes which can have a benefic effect against others diseases which oxidative stress plays an important role.

Key words: Diabetes, Oxidative stress, Polyherb, ZnNPs, Rats.

الملخص

الهدف من هذه الدراسة هو دراسة تأثير محلول عشبي (مزيج من عدة مستخلصات عشبية) ونانو الزنك (يتم تخليقه بالطريقة البيولوجية) على التغيرات الفسيولوجية والبيوكيميائية والإجهاد التأكسدي الناجم عن مرض السكري التجريبي عند الفئران.

لهذا الغرض ، تم تقسيم 24 أنثى من جرذان ويستار قسمت بشكل عشوائي إلى 6 مجموعات (ن = 4) ؛ فئران سليمة (مجموعة شاهدة) ، فئران سليمة عولجت بالمحلول العشبي، فئران سليمة عولجت بنانو الزنك ، فئران مصابة بداء السكري (سكري) ، فئران مصابة بمرض السكر عولجت بالمحلول العشبي وفئران مصابة بداء السكري عولجت بنانو الزنك أعطيت جميع أنواع العلاجات للفئران عن طريق الفم لمدة 21 يومًا. تم تحفيز الإصابة بمرض السكر في الفئران عن طريق حقن جرعة واحدة من الألوكسان (150 مغ / كغ). تم تقدير المعايير المختلفة مثل علامات الإجهاد التأكسدي والبيوكيميائية ومعايير الدم. كما تم تحديد نسب اصابة الأنسجة في أنسجة البنكرياس. في الدراسة المخبرية على النبات والجسيمات النانوية ، تم تحليل بعض المعايير الكمية والنوعية والتوصيف باستخدام البروتوكولات القياسية.

أظهرت نتائج التحليل الكيميائي النباتي في المختبر أن المحلول العشبي يحتوي على الفينولات والفلافونويد والقلويدات والتربينويدات والستيرويدات. من جهة اخرى أظهرت النتائج على الجرذان ، في المجموعة المصابة بداء السكري تغييرا في معايير الدهون المعايير البيوكيميائية. في حين أن مضادات الأكسدة التي تدافع عن الجهاز في الكبد والكلى والبنكرياس والمبيض تأثرت بزيادة مستوى MDA واضطراب في مستويات GSH وأنشطة SOD مقارنة بالمجموعة الشاهدة. علاوة على ذلك ، أظهرت معايير الدم أن مرض السكري يسبب فقر الدم في الفئران عن طريق انخفاض معنوي ($P < 0.01$) في مستويات كرات الدم الحمراء وحجم الكريات وHCT من ناحية أخرى، لاحظ تحليل الأنسجة المرضية حدوث تغير في أنسجة البنكرياس لمجموعة الجرذان المصابة بداء السكري مقارنة بالمجموعة الشاهدة. ومع ذلك، فإن علاج الفئران المصابة بمرض السكر بواسطة المحلول العشبي و نانو الزنك اعطى تحسنًا جزئيًا واضحا وعمل على تصحيح المعايير السابقة.

في الختام ، يبدو أن استخدام المحلول العشبي والزنك بحجمه النانوي عمل على الحد من تطور ومضاعفات مرض السكري وهو ما يمكن أن يكون له تأثير مفيد أيضا حتى ضد الأمراض الأخرى التي يلعب الإجهاد التأكسدي دورًا مهمًا فيها.

الكلمات المفتاحية : مرض السكري ، الإجهاد التأكسدي ، المحلول العشبي ، نانو الزنك ، الجرذان .

Figures lisst

Tables list

Abbreviation list

AGE: Advanced glucated end-product.

$AlCl_3$: Aluminum chloride

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

ATP: Adenosine triphosphate

BHT: Butyl hydroxyl toluene

Ca^{+2}: Calcium

Cl^-: Chloride

d: Dilution factor

DHA: Docosahexaenoic acid

DHAP: Dihydroxyacetone phosphate

DNA: Deoxyribonucleic acid

DTNB: 5,5′ -Dithiobis (2-nitrobenzoic acid)

EDTA: Ethylenediaminetetraacetate

FCR: Folin-Ciocalteu Reagent

FDA: Food and Drug Administration

$FeCl_3$: Ferric chloride

FNS: Numeration of the Blood Formula

FRAP: Ferric reducing antioxidant power

g: Gram

GIP: Insulinotropic glucose dependent peptide

GLP-1: Glucagon-like peptide 1.

GluT-2: Glucose transporter type 2

GPx: Glutathione peroxidase

GRx: Glutathione reductase

GSH: Reduced Glutathione

GSSG: Gluthation oxide

H_2O_2: Hydrogen Peroxide

H_2SO_4: Sulfuric acid

H_3PO_4: Phosphoric Acid

HCl: Hydrochloric acid

IC50: Median inhibitory concentration

IR: Infrared spectroscopy

K^+: Potassium

Kg: Kilogram

L: Liter

LDH: Lactate Dehydrogenase

LPO: Lipid peroxidation

MDA: Malondialdehyde

MDH: Malate Dehydrogenase

Mg: Milligram

mL: Milliliter

mM: Millimolar

mmoles: Millimoles mn

Na^+: Sodium

Na_2CO_3: Sodium carbonate

NaCl: Sodium Chloride

NADPH, H^+: Nicotinamide adenine dinucleotide phosphate reduced

$NADP^+$: Nicotinamide adenine dinucleotide phosphate oxidized

NADPH: Nicotinamide adenine dinucleotide phosphate

NaOH: Sodium hydroxide

NBT: Nitro blue Tetrazolium Chloride

NIS: Sodium / Iodide transporter

NOX: NO oxidase

OH: Hydroxyl free radical

OM3: Omega 3

PKC: Protein kinase C

RAGE: Receptor of- advanced glucated end product

RNA: Ribonucleic acid

RNS: Reactive nitrogen species

RONS: Oxygen nitrogen species reagents

ROS: reactive oxygen species

SOD: Superoxide dismutase

TBA: Thiobarbituric Acid

TBG: Thyroid binding globulin

TBS: Tris buffer Saline

TCA: Trichloroacetic acid

TG: Triglyceride

TGO: Glutamo-Oxaloacetate Transferase.

TGP: Glutamo-Pyruvate transferase.

TPO: Thyroperoxidase

TRH: Thyrotropin-releasing hormone

TSH: Thyroid stimulating hormone

Tyr: Tyrosine

WHO: World Health Organization

ZnNPs: Zinc nanoparticles

%: Percentage

° C: Degree Celsius

Summary

Introduction

Introduction

Diabetes is a major health problem and is one of the fastest growing global health emergencies of the 21st century, It has reached alarming levels: currently, nearly half a billion people worldwide live with diabetes, this number is expected to reach 578 million in 2030 and 700 million in 2045 (Saeedi, 2019). Diabetes is a serious and chronic condition that occurs when the body cannot produce enough insulin or that it cannot effectively use the insulin it produces (Rodier, 2001). Diabetes is also characterized by the severity of the complications it causes. Indeed, it is the leading cause of end-stage renal failure, blindness and amputation of the lower limbs, it is also the sixth cause of death (NACEIRI, 2018). This complication has long been thought to be related to increased production of free radicals or impairment of antioxidant defenses causing a state of oxidative stress that occurs when the physiological balance between oxidants and antioxidants is disrupted in favor of the former with potential damage to the organism (Ceriello, 2000).

For this reason, researchers and doctors are looking to find a cure for this big problem, and the success of the treatment will be of great importance, despite the progress of new therapeutic molecules, including insulin and oral hypoglycemic agents (pegonides, sulfonylureas), whose regular consumption causes side effects (Bailey, 2008). Diabetologists recently found evidence that a therapeutic supplement made from herbal extracts is needed to improve the treatment of diabetes, because herbs are a great source of active ingredients that can be used to treat many diseases(NACEIRI, 2018). But one of the Indian traditional medical systems called Ayurveda, which includes the use of natural elements to eliminate the root cause of the disease by restoring balance, at the same time creating a healthy lifestyle. He highlighted the concept of polyherb, which means the multiplicity of herbs due to the great therapeutic efficacy it achieves. This is because the active phytochemical components of individual plants are not sufficient to achieve the desired therapeutic effects, but when combining multiple herbs in a certain proportion, it will give better therapeutic effect and reduce toxicity (Parasuraman,2014).

Recently, nanotechnology has become a well-known field of research and interest in the applications of nanotechnology in various fields has increased (1); This is due to its ability to promote scientific innovation while giving a great advantage to society (Mubarak et al., 2019). Can be noticed,with the increase in the range of applications e (Leng et al., 2018). The plant-mediated or green approach to the preparation of metal particles and metal oxide has also received a great deal of attention due to the ease of preparation and environmental friendliness compared to physical and chemical methods (Enobong et al., 2019). The biosynthesis of nanoparticles using plant extracts is gaining importance in biomedical applications due to their unique properties (Poka et al., 2019). Zinc

is well known as a potential mineral involved in the regulation of metabolism, in which zinc oxide nanoparticles (ZnNP) are considered to be one of the most promising and new magic materials due to their stimulating properties. and unique antimicrobials as well as their low cost and wide application in various fields (Ergun et al., 2006).

Based on these data, the original idea of our work was to study and evaluate the effect of polyherb in diabetic Wistar mice after alloxan injection; As well as studying the protective effects of nano-therapeutic regimens based on treatment using biosynthesized zinc oxide nanoparticles based on polyherb.

In light of these data, in our study, we will first provide some information in the bibliographic section about: diabetes, metabolism, and the role of polyherb (Portulaca oleracea L, Coriandrum sativum and Aquilaria malaccensis) as well as the role of Zn NPs.

Then in the experimental part, the current study was carried out to verify the following two complementary points:

The first part: based on the laboratory study. Extraction of plant extracts, preparation of polyherb, preparation of zinc nanoparticles, quantitative and qualitative characterization of these compounds and evaluation of their biological activity.

The second part: based on an in vivo study to evaluate the protective effect of polyherb and Zn NPs biosynthesized by plant extracts against diabetes in rats.

Bibliographic Part

Chapter I

Diabetic sugar

1. Definition of diabetes

Diabetes mellitus is a metabolic disease that results from impaired metabolism of carbohydrates, proteins and fats (Grimaldi, 2001), resulting from a disturbance in insulin secretion or a disturbance in insulin action or both (ADA, 2009), which leads to chronic hyperglycemia and an increased incidence of complications affecting nearly all tissues (Derouiche and al, 2018).

According to the World Health Organization, diabetes is defined as a state of persistent hyperglycemia with fasting blood glucose greater than or equal to 1.26 g/L (7 mmol) on two occasions and/or greater than 2 g/L (11.1 mmol/L).) at any time of the day (Derouiche , 2016)**.**

2. Types of diabetes

2.1. Type 1 diabetes

Type 1 diabetes mellitus, or insulin-dependent diabetes or juvenile diabetes, is a prevalent autoimmune disease (Pirot et al., 2008). It is also a silent disease that often begins at an early age (infancy or adolescence), and accounts for 5-10% of patients with diabetes (Hennen, 2001). It is caused by the destruction and disruption of insulin-producing beta cells in the islets of the pancreas, in which the islets of Langerhans are infiltrated by mononuclear cells (insulinitis) (Bouhours and Coutant, 2005), resulting in an almost complete deficiency insulin and therefore an increase in blood glucose levels (Chih-Wei, 2017). Clinically hyperglycemia appears, when only 10-20% of functional beta cells remain (Blicklé, 2004; Moussard, 2006).

High blood sugar and prolonged absence of insulin can lead to a buildup of ketones in the blood because the body uses fat for energy instead of glucose, which leads to high acidity of the blood and slows down all body functions. This also leads to coma and eventually death (ADA, 2004; CDER,2008).

This type of diabetes can also lead to hypoglycemia. When hypoglycemia develops, cells do not get enough glucose and patients become confused, unconscious and coma. Even death can occur when the brain is deprived of glucose for a prolonged period (Zimmet, 1992).

2.2. Type 2 diabetes

Often referred to as adult diabetes or insulin-independent diabetes (Simoneau and Garand, 2010), it is the most common form of diabetes, usually seen in adulthood and in the elderly (Morrison et al., 2008). It is a complex endocrine and metabolic disturbance (ADA,1998), mainly due to decreased tissue sensitivity to the effect of insulin, which leads to insulin resistance, and impaired insulin secretion in the response of pancreatic cells to glucose, resulting in hyperglycemia (Durouin B et al, 1999). Hypertension and

dyslipidemia (high triglycerides and low levels of HDL cholesterol; postprandial hyperlipidemia) are often present in these individuals(ADA,1998).

Obesity and being overweight are major factors that lead to the development of insulin resistance and impaired glucose tolerance. Disturbances in other hormones such as glucagon-like peptide-1 (GLP-1) deficiency, hyperglucagonemia, and elevated concentrations of other anti-regulatory hormones contribute to insulin resistance, decreased insulin secretion, and hyperglycemia (Parveen et al, 2017). An individual can also inherit a susceptibility to type 2 diabetes (a genetic factor) (Kaku, 2010).

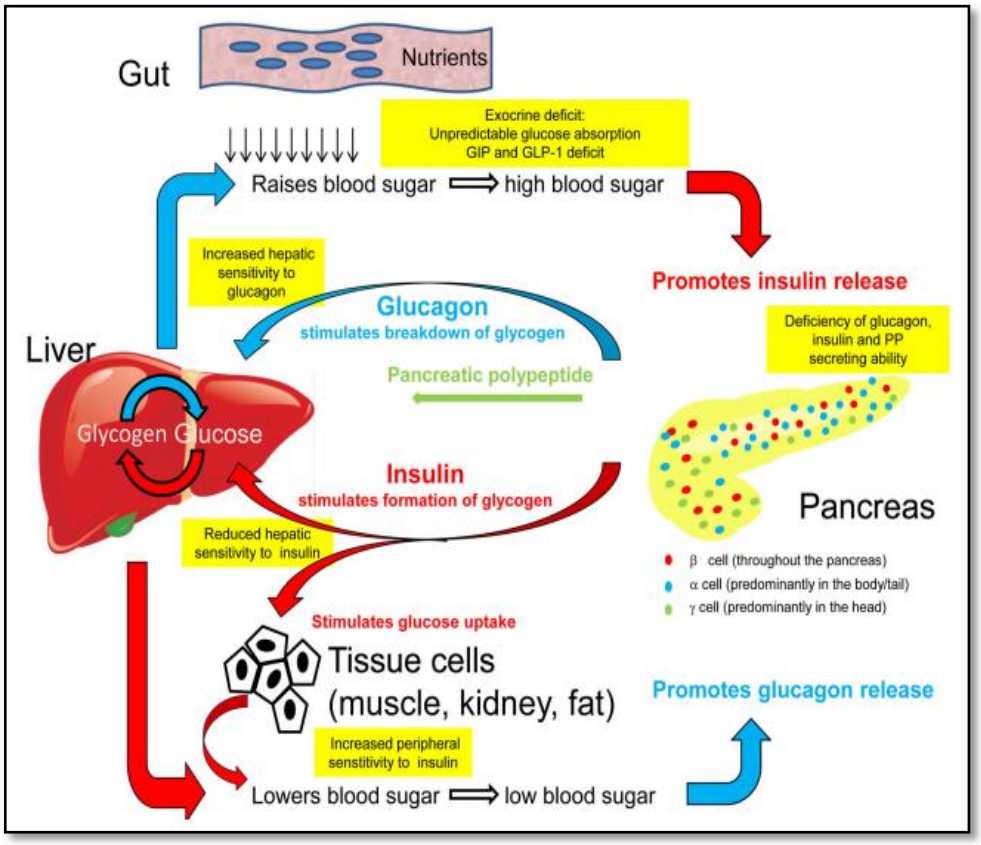

Figure 01: Pathophysiology of pancreatogenic diabetes

3. Symptoms

Clinical symptoms of diabetes mellitus are characteristic and apparent such as frequent urination, polydipsia, weight loss, and sometimes binge eating and vision disturbances, weakness and susceptibility to certain infections (Aouacheri et al., 2015). If no treatment is provided, the situation may develop into ketoacidosis, hyperoxaluria or lactic acidosis (ADA, 2014). The onset of type 1 diabetes can be variable in adults and may not present with the classic symptoms seen in children (William and Cefalu, 2015).

4. Complications of diabetes

Symptoms of diabetes are often invisible, leading to complications in various organs or functions of the body. Permanently present high blood sugar causes gradual disturbances in capillary vessels, as well as the emergence of long-term organic complications affecting the eyes (retinopathy), nerves (neuropathy), kidneys (nephropathy), heart and vessels (macrovascular disease), which causes a very high risk of death, and diabetic foot is also a complication of complications (Raccah, 2004; Schlienger, 2013).

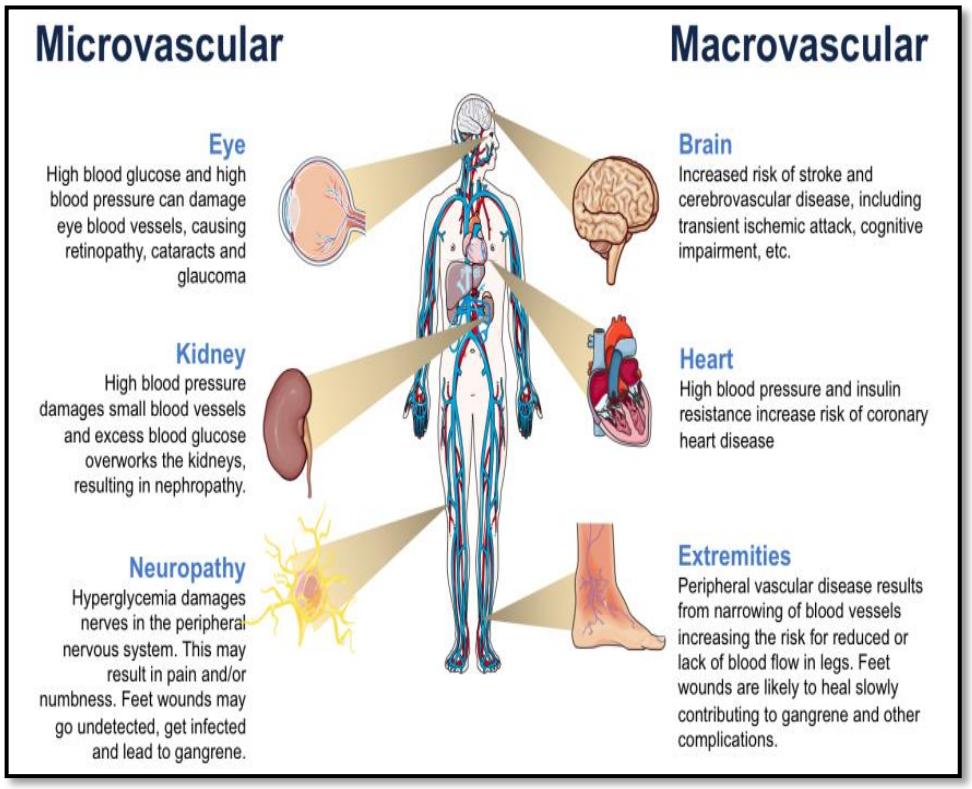

Figure 02: Major complications of diabetes mellitus (Jiang and Dutta,2017)

5. Treatment

For type 1 diabetes, therapeutic management combines a diet adapted to the treatment of hypoglycemia to ensure proper nutritional balance and avoid differences in blood sugar. Insulin therapy is the mainstay of patients with type 1 diabetes, as this treatment requires several Daily injections of insulin because the hormone is broken down in the stomach and cannot be taken orally. The patient learns how to adapt the doses he takes according to his diet on the one hand, and his physical activity on the other (Cornet, 2009).

For type 2 diabetes, therapeutic management should be early and comprehensive. While changes in diet and lifestyle are the mainstay of treatment and management of type 2 diabetes. Insulin is also important in type 2 diabetes when it cannot be controlled.

glycemic control through diet, weight loss, exercise, and oral medications (Tripathi and Srivastava, 2006).

The general goals of treatment are to maintain a normal blood glucose level but also to take responsibility for all the cardiovascular risk factors often associated with diabetes. Treatment also aims to reduce obesity and a sedentary lifestyle (ADA, 2015). There were five types of oral hypoglycemic agents: sulfonylureas (or sulfonamides), glinides, biguanides, thiazolidinediones and alpha-glucosidase inhibitors. The hypoglycemic effect of these five classes of drugs is well established, and their mechanisms of action are different (Nathan, 2007). Two other therapeutic classes have recently been made available, glucagon-like peptide-1 (GLP1) analogs and dipeptidyl peptidase-4 (DPP4) inhibitors (Nauck, 2016).

6. Experimental diabetes

Experimental diabetes mellitus in laboratory animals can be induced using chemical, surgical and genetic/immunological manipulations (Kim et al, 2002), by chemicals that selectively destroy pancreatic cells is very convenient and simple to use. The most common chemicals for induction of experimental diabetes are alloxan and streptozotocin. However, these chemicals are most commonly used to induce type 1 diabetes because they are not able to directly stimulate insulin resistance (Lenzen, 2008).

- **Alloxan-induced diabetes**

Alloxane (2,4,5,6-tetraoxypyrimidine, 5,6-dioxyuracil) is a pyrimidine derivative synthesized by oxidation of uric acid, an agent with cytotoxic activity on beta cells of the islets of Langerhans (Lenzen et al, 1988). It is also an unstable hydrophilic compound with a structure similar to glucose, which makes it penetrate the cells of the pancreas through glucose transporters GLUT2 (Medjdoub et al, 2013).

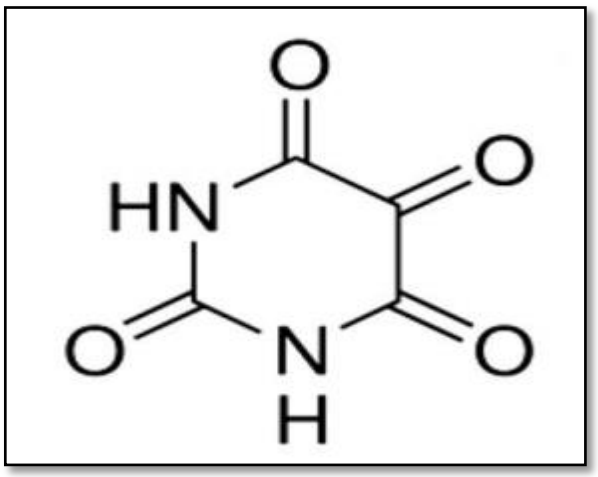

Figure 03: Chemical structure of alloxan (NACEIRI, 2018).

The dose of alloxan needed to induce diabetes depends on the type of animal, method of administration and nutritional status. In rats, the usual intravenous dose is 65 mg/kg. Intraperitoneally and subcutaneously, this dose is two to three times higher (Szkudelski, 2001).

At the level of the cytosol, several substances such as glutathione reductase (GSH) and SH groups of proteins are present that convert Alloxane to dialyuric acid, the latter of which is oxidized again to produce alloxan (A), which generates reactive oxygenated species (OH ·, O_2•⁻) by the Fenton reaction (Derouich, 2016).

Also, Alloxane inhibits the enzyme glucokinase through the formation of a disulfide bridge, resulting from the reaction of thiol groups in the active site of the enzyme with the central carbonyl group present in Alloxane. Inhibition of glucokinase reduces glucose oxidation and ATP generation, which suppresses ATP signaling, which leads to insulin secretion (Szkudelski, 2001).

In addition, intracellular calcium homeostasis is disturbed to constitute an important step in the glycolytic effect of alloxan. Free cytosolic alloxan increases the calcium concentration in pancreatic cells. Calcium influx is driven by the ability of alloxan to depolarize pancreatic cells, which opens voltage-gated calcium channels and improves calcium entry into pancreatic cells. Increased calcium ion concentration can damage pancreatic islet cells with ROS (Ankur and Shahjad, 2012).

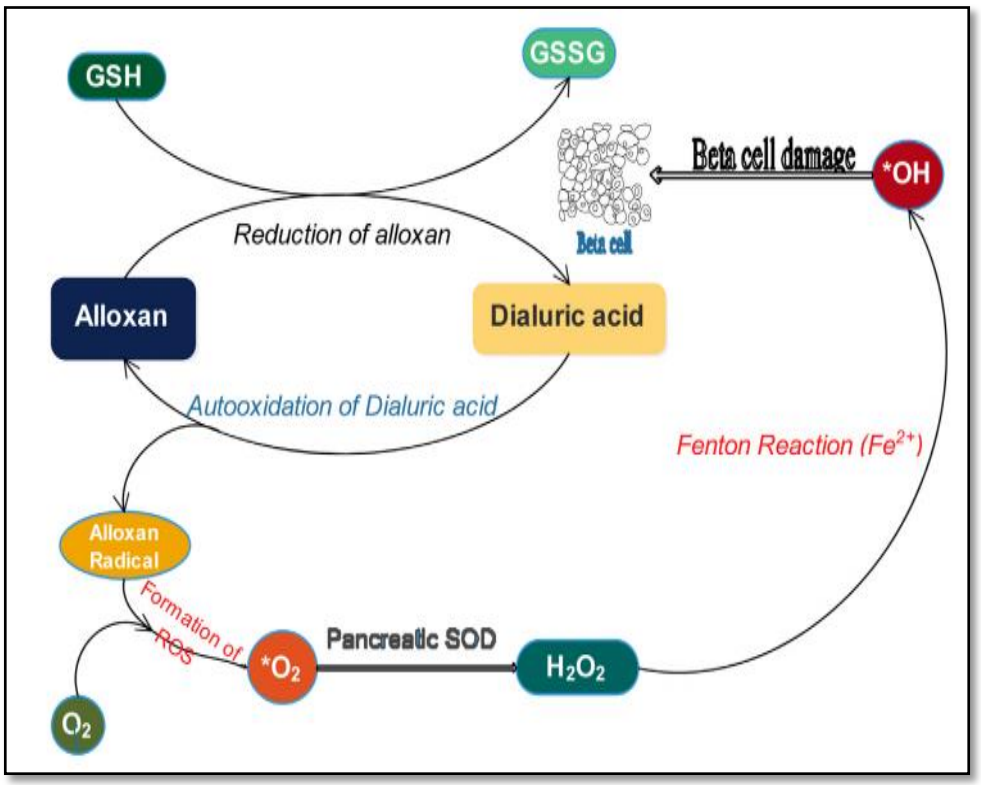

Figure 04: Formation of ROS through redox cycling of Alloxan (Osasenaga, 2017).

Chapter II

Oxidative stress

1. Definition of oxidative stress

In biological systems, oxidative stress is the consequence of an imbalance between the production of free radicals and the destruction by antioxidant defense systems (Kirschvink et al., 2008), that play a major role in protecting against molecular oxidative damage (Derouiche et al., 2018), which leads to irreversible cellular damage by free radicals which can cause significant damage to cell structure and metabolism by degrading numerous targets: proteins, lipids and nucleic acids(Angelos et al., 2005). Oxidative stress is implicated as a pathophysiological mechanism of different diseases and is a topic of growing interest, while oxidative stress is not a disease in itself, it constitutes a favorable ground for the development of various pathologies (Derouiche et al., 2018).

2. Free radicals

2.1. Definition

Free radicals are atoms or molecules capable of having an independent existence containing one or more unpaired electrons, on their external electronic orbitals, giving them great instability (Derouiche and Djouadi, 2017).

In various fields of biology and medicine, free radicals are generally referred to as reactive oxygen species (ROS) or reactive nitrogen species (RNS) (Phaniendra, 2014). Thus, free radicals can be anionic, cationic, neutral, net negative charge, net positive charge or electrically neutral species (Firuzi et al, 2011). Among the most important ROS are (chemical species possessing an isolated electron) such as the superoxide anion $O\bullet_2^-$), the hydroxyl radical (OH•), nitrogen monoxide (NO•) ..., and the oxygen derivatives known as active oxygen species (not possessing a single electron) they are not free radicals but they are also reactive and can be precursors of radicals peroxide anion(O_2^{-2}), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$) (Lanez & Djouadi, 2015), and transition metals such as iron and copper (Betteridge, 2000). Free radicals are produced at the mitochondrial level (Sylvia, 2010).

2.2 Sources of free radicals

Living aerobic organisms stay under the influence of free radicals due to the constant formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by endogenous and exogenous sources (Kruka et al., 2019).

2.2.1. Endogenous sources

The endogenous sources of ROS include mitochondria, cytochrome P-450 metabolism (au cours de la détoxication des xénobiotiques) , peroxisomes, reactions involving iron and other transition metals, inflammatory cell

activation (Macrophages and neutrophils contain a group of enzymes called the NADPH oxidase complex, which, upon activation generates superoxide radicals and hydrogen peroxide) (Bhattacharya, 2014), and la membrane plasmique et le réticulum endoplasmique (Barouki et Morel ,2001).

2.2.2 Exogenous sources

ROS and RNS can also be generated through exposure to external factors such as oral bacteria, ionizing and ultraviolet radiation, food, alcohol, heavy metals, certain chemotherapeutic drugs (Żukowski et al., 2018 ; Santo et al., 2016),ozone, pesticides, anesthetics, industrial solvents (Kumar, 2011) and environmental factors, such as air pollutants or cigarette smoke (Birben et al., 2012), and physiological factors (Mental status like stress, emotion…etc) (Kumar, 2011).

3. Consequences of oxidative stress

An imbalance between free radicals and antioxidants are factors which lead to significant cellular damage via the triggering of breaks and mutations within the DNA, the inactivation of various enzymes, the modification of protein structures, the oxidation of sugars and induction of lipid peroxidation (Adwas et al., 2019).

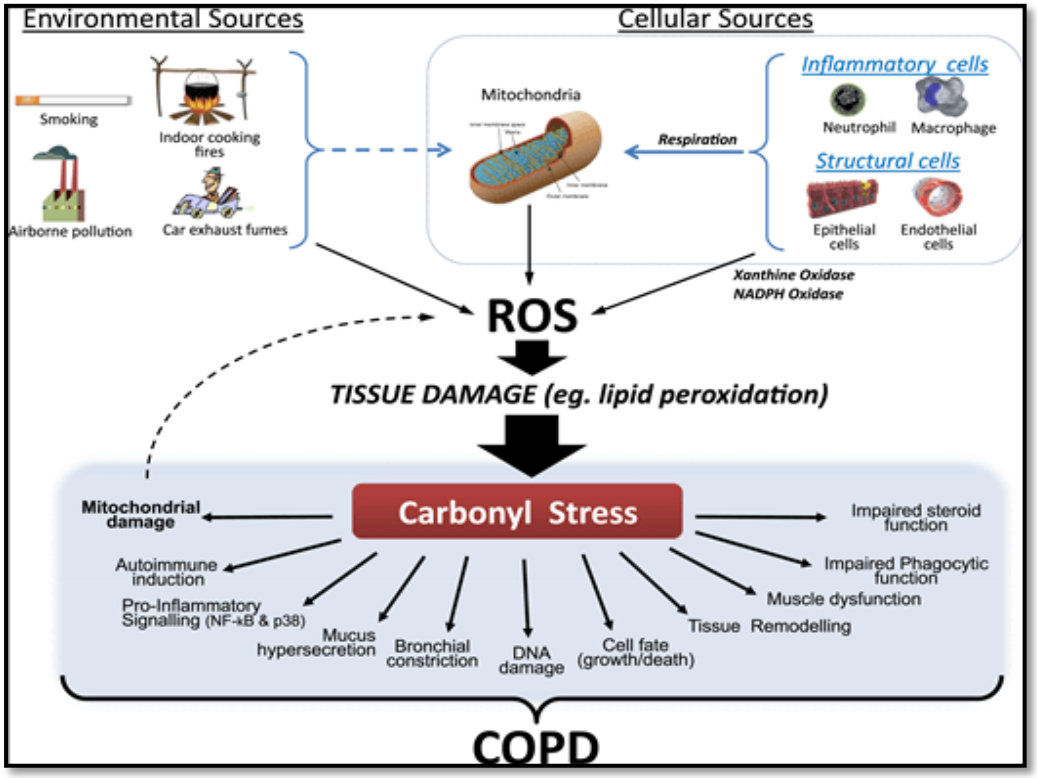

Figure 05: Oxidative stress and the health effect of free radicals (Aleksic, 2019)

4. Anti-oxidant systems

4.1. Definition

Exposure to free radicals from various sources has led in organisms to develop a series of defense mechanisms among these mechanisms the antioxidant defense mechanism (Firuzi, 2001). So, antioxidants are nucleophilic and reductant molecules and stable enough able to react with oxidants, which are generally electrophiles, giving them one or two electrons (Espinosa-Diez et al., 2015). They are diverse in nature and act in synergy either by sacrificing themselves to trap the unmarried electron of a free radical and neutralize it by delocalizing it or by enzymatically reducing the reactive oxygen species (Favier, 2006). Which makes it play a very important role in protecting biological systems from the toxicity and harmful effects of free radicals, reducing them and thus preventing or treating diseases related to oxidative stress (Valko, 2007; Birben et al. , 2012). The antioxidants are present in significant amounts in commonly consumed fruits, vegetables, beverages (juices, tea, coffee), nuts and cereal products (Mirończuk-Chodakowska et al., 2018).

4.2. Classification

4.2.1. Enzymatic antioxidant

The major antioxidant enzymes directly involved in the neutralization of ROS and RNS are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GRx) (Pham-Huy et al., 2008).

Where O_2 is converted by SOD to H_2O_2 because it contains minerals that catalyze superoxide removal, as well as converted by CAT to water and oxygen, which prevents the production of hydroxyl radicals (Krishnamurthy & Wadhwani, 2012; Liguori et al., 2018). While inside the mitochondria there is a glutathione peroxidase that works to reduce H_2O_2 in water and lipid peroxides to the corresponding alcohols (ghodaro & Akinloye, 2017).

4.2.2. Non enzymatic antioxidant

4.2.2.1. Endogenous antioxidants

They are called metabolic antioxidants, as they are produced through metabolism within the body (Gupta et al., 2014). They are molecules that interact with RONS and terminate free radical reactions. It included non-enzymatic antioxidants endogenously produced GSH or nutritional compounds (Zhao et al., 2016). In addition to bilirubin, αtocopherol, albumin (Wu GQ, Kosten and Chang, 2013), L-carnitine, alpha-lipoic acid and coenzyme Q10 (Kedar, 2015; Xuejun et al., 2015).

4.2.2.2. Exogenous antioxidants

Called nutritious antioxidants, they are compounds that cannot be produced in the body and must be provided through foods or supplements (Gupta et al., 2014). They are mainly polyphenolic compounds, which include minerals (selenium, copper, iron, zinc, manganese), vitamins (A, E, C) and phytochemicals (flavonoids, tannins, terpenoids, catechins, carotenoids etc.) (Kadi and Mulvey, 2018).

5. Oxidative stress and diabetes

An imbalance between the levels of different markers of oxidative stress (Leitinger, 2008; Reddy et al , 2009) and decreased antioxidant defense mechanisms (Davi et al, 2005; Lodovici et al, 2009) have demonstrated the presence of oxidative stress in diabetic patients. As oxidative stress contributes to the development of its complications such as nephropathy, neuropathy, atherosclerosis, and coronary artery disease (Zujko, 2014), although it is still unclear whether oxidative stress is a cause or merely a consequence of the onset of diabetes (Fassett et al, 2009; Bonnefont-Rousselot et al, 2004). It is also known that hyperglycemia leads to prolonged production of intracellular reactive oxygen species (ROS), which leads to prolongation of the electrochemical gradient of protons generated in the mitochondrial chain leading to increased production of superoxide, (Kawahito et al, 2009; Brownlee, 2000). Important metabolic pathways in RONS production under hyperglycemic conditions (Rolo et al, 2006; Robertson, 2004):

1) Formation of advanced glycation end products (AGE):

In this pathway, AGE interacts with its cellular receptors (RAGEs), which leads to the activation of NOX (Grossin et al , 2009) and results in a large amount of RONS (Tan et Forbes, 2007) where these stable covalent approaches or AGEs are formed either by:

-The accumulated glucose is converted to glycosylate residues or amidori products, arising from non-enzymatic reactions between glucose and the primary amines of proteins (Thornalley, 2002).

- Intracellular auto-oxidation of glucose to glyoxal (Robertson et al, 2003).

- Dissociation of some glycolytic compounds such as 3-glyceraldehyde phosphate (PGAL) and dihydroxyacetone phosphate (DHAP) into methylglyoxal (Robertson, 2004).

2) Activation of protein kinase C (PKC):

PKC is an enzyme whose regulation depends on the redox state that is activated in the presence of RONS and inhibited by antioxidants (Gopalakrishna et Jaken, 2000). Studies show that the interaction between AGEs and RAGES during hyperglycemia is able to activate PKC (Portilla et al, 1988) which in turn will activate NOx by increasing RONS production (Inoguchi et al, 2000).

3) Activation of the polyol pathway:

In the presence of hyperglycemia, some of the excess glucose is converted to sorbitol, by the enzyme aldose reductase with the cofactor NADPH, as prolonged hyperglycemia reduces NADPH levels, rendering the cell vulnerable to the effect of ROS from During the possible special effects on GSH (Brownlee,2000). In addition, oxidation of sorbitol to fructose via the polyol pathway increases the NADH/NAD+ ratio (NTIMBANE, 2009), inhibits the activity of glyceraldehyde-3-phosphate dehydrogenase, and increases the accumulation of triphosphate (PGAL and DHAP) that will stimulate the formation of AGEs (Robertson, 2004).

The main markers of increased free radicals are increased lipid peroxidation (conjugated diene, fatty acid hydroperoxides and malondialdehyde) (Hartnett et al., 2000). , and a decrease in enzymatic (GPx, SOD, catalase, etc.) or non-enzymatic antioxidant defenses such as GSH or vit E (Maritim et al., 2003).

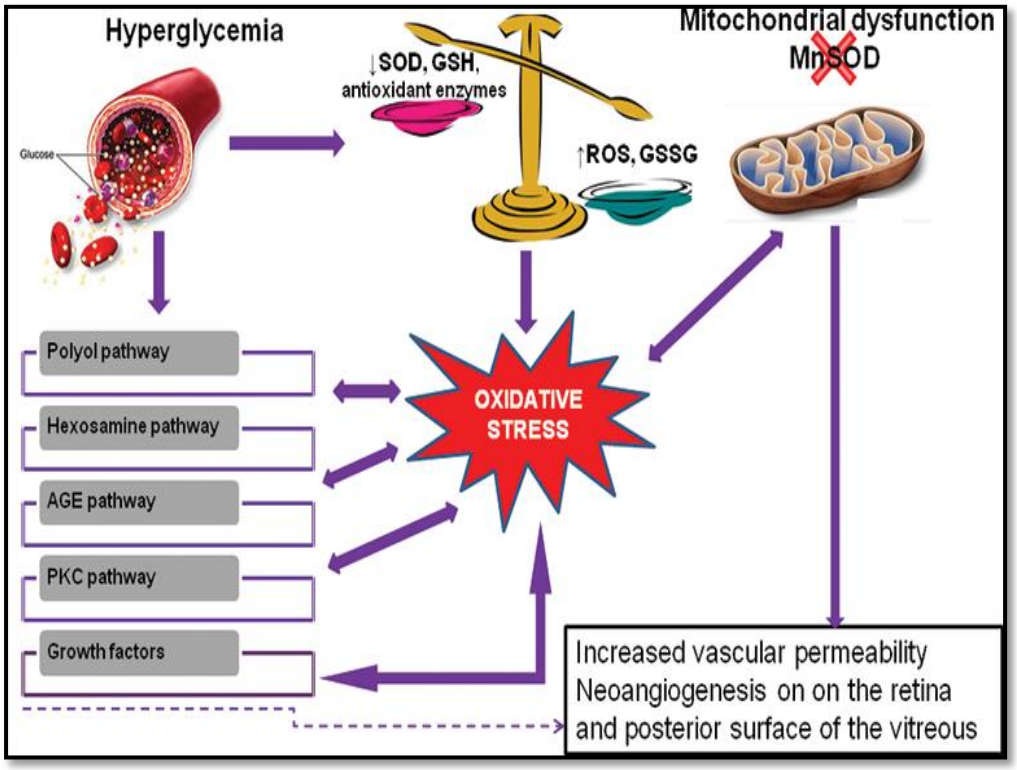

Figure 06: Major pathways implicated in the development of diabetic retinopathy (Cilenšek et al, 2016).

Chapter III
Medical plants

I. Coriandrum sativum

I.1. Definition and localisation

Coriandrum sativum (Coriander) is a glabrous aromatic, herbaceous annual plant, belonging to the family Umbelliferae/Apiaceae (López, 2008) . Its name is derived from the Greek Koris, meaning bedbug, because of the unpleasant, fetid, bug-like odour of the green herb and unripened fruits (Weiss, 2002; Ayanoglu et al., 2002). It displays broad adaptation as a crop around the world, growing well under many different types of soil and weather conditions (Guenther 1952; Purseglove et al.1981; Simon 1990), It is native to the Mediterranean and Middle Eastern regions and has been known in Asian countries for thousands of years, nowadays coriander is grown almost everywhere except Japan. All part of the plants is edible but the fresh leaves and the dried seeds are the most common parts used in cooking (Coskuner et Karababa, 2008). In the traditional medicine, a coriander is used in disorders of digestive, respiratory and urinary system (Nadeem et al., 2013) ,coriander fruit oil is also of great importance since the European Union allowed the use of coriander oil as a food supplement (Mandal et al, 2015).

1 (Pimenov and Leonov, 1993)

Kingdom: Plantae

Subkingdom: Viridaeplantae

Infrakingdom: Streptophyta

Division: Tracheophyta

Subdivision: Spermatophytina

Infradivision : Angiospermae

Class: Magnoliopsida

Superorder: Asteranae

Order: Apiales

Family: Apiaceae

Genus: Coriandrum L. – coriander

Species: Coriandrum sativum L.

I.2.2. Botanical description

Coriander is an annual herb. It is slender, branched, usually measuring 30 to 60 cm in bloom, but can reach 1.4 m (Khan, 2014).

The root is tapering and tapered. The stems are green, erect, slender, cylindrical and striated, sometimes with several lateral ramifications at the level of the first node. Each branch ends in a single inflorescence. The base of the stem of an adult plant is hollow and can reach 2 cm in diameter (Diederichsen, 1996).

The leaves are light green, glabrous and alternate. The basal leaves are stalked, incised and toothed. The upper leaves are sessile, finely cut into strips and provided with a long and broad sheath (Coste, 1937).

The flowers are radial, regular at the center of the umbellule but irregular at the periphery; they have a calyx with 5 unequal sepals, 2 of which are clearly longer than the others and a corolla with 5 petals of white or pink color (Teucscher, 2005).

The fresh fruits are green and give off the same smell as the leaves. They turn beige, then light ocher-brown as they ripen and develop a more aromatic odor. They are schizocarps (diakenes) made up of two hemispherical mericarps joined together, separating only when very dry (Blade, 2008).

Figure 07: Morphology of Coriandrum sativum L.

(A : root, B: leaves, C : flowers, D : fruits)(Ashraf, 2020).

I.3. Chemical composition

Phytochemical examination of the plant showed the presence of essential

oils, tannins, terpenoids, reducing sugars, alkaloids, phenols, flavonoids, fatty acids, sterols and glycosides (Chauhan, 2012; Sreelatha, 2012).

Like many green and fresh plants, the cilantro plant contains carotenoid pigments (provitamin A) (LORENZ, 2001). The Coriandrum sativum L plant has a very important nutritional value and contains many nutrients and minerals, as the chemical examination indicated the presence of eau, energy, protéines, lipides (fat), glucides, fibers, thiamin, riboflavin, niacin (Bhat, 2012, **Anonyme, 2010**).

Coriander contains several antioxidant compounds (Bajpai et al., 2005; Wangensteen et al., 2004), mainly phenolic acids (coffee acid, ferulic acid, gallic acid and chlorogenic acid), but also terpenoids, coumarins, flavonoids (in fruits), and carotenoids in the leaves (carotenes, xanthophylls: lutein, zeaxanthin, cryptoxanthin), the leaves are rich in flavonoids such as the 3-O-glucosides of quercetol and kaempferol, such as quercetol 3-O-glucoronide , rutin and iso quercitrin Alkylphthalides (SAADI, 2017). But also geranyl acetate, geraniol and coumarins (traces), fatty acids were detected, the main fatty acid (saturated, monounsaturated, polyunsaturated being petroselinic acid (65.7% of all esters methyl fatty acids), followed by linoleic acid, isocoumarins have also recently been isolated (Matasyoh et al., 2009). It is also rich in vitamin K, vitamin C and vitamin A (Axel, 1996). In addition to the presence of minerals such as magnesium (Mg), aluminum (Al), silicon (Si), phosphorous (P), sulfur (S), chlorine (Cl), potassium (K), calcium (Ca), and titanium (Ti), manganese (Mn), iron (Fe), copper (Cu) and zinc (Zn) (Al-Bataina et al., 2003).

I.4. Therapeutic effects and uses

The use of coriander dated back to around 1550 BC, and it was one of the oldest spice crops in the world. The whole or ground seed (fruit) was an ingredient of pickling spices, also used to flavor various commercial foods. The fruit essential oil was a common ingredient in creams, detergents, surfactants, emulsifiers, lotions, and perfumes (Da Silva et al., 2018).

Medicinally, it was used in disorders of digestive, and respiratory urinary system, as it has diaphoretic, diuretic, carminative and stimulant. The powdered fruit, fluid extract and oil are chiefly used medicinally as flavoring to disguise the taste of active purgatives and correct their griping tendencies. Also, coriander is used as a stomachic, spasmolytic and carminative because of its essential oil, which also exerts a bactericidal and fungicidal action. It can detoxify the body from heavy metals, because the substances it contains adhere to toxic substances, and allow them to be eliminated through urine and sweat (Cakmak, 2002); (Momin et al., 2012). Coriander has been shown to exert hypoglycemic effects as well as a stimulating action on insulin secretion. In

external use, it is recognized as a muscle relaxant, and as an ingredient in liniments against rheumatism and arthralgia (Wichtl, 2003).

II. Portulaca oleracea L.

II.1. Definition and localisation

Portulaca oleracea L, known as purslane plant is an annual herbaceous plant, the genus Portulaca belongs to the family Portulacaceae, a small family with 21 genera and 580 species (Derouiche et al, 2017). The name Portulaca is thought to be derived from the Latin 'porto' meaning "to carry" and 'lac' meaning milk, since the plant contains a milky juice(Boulos, 1984). It is a cosmopolitan weed, widely distributed in various parts of the world due to its high adaptability in various climatic and harsh conditions, it is found especially in the tropics and subtropics (Jaiswal, 2017; Teixeira, 2009, Uddin et al., 2012). Purslane is an edible plant as a Potherb, and it is also classified as a medicinal herb as it was used as a traditional medicine to relieve a wide range of ailments, because it contains many active substances that are also sources of many nutritional supplements (Derouiche et al., 2019). Several recent studies have indicated that it has many pharmacological effects: hypoglycemic, lipid-lowering, antioxidant, anti-inflammatory and anti-tumor effects (Butnariu, 2018; Khazdair et al., 2019).

II.2. Plant profile

II.2.1. Scientific classification: (Chugh et al., 2019)

Kingdom: Plantae

Subkingdom: Tracheobionta

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Subclass: Caryophyllidae

Order: Caryophyllales

Family: Portulacaceae

Genus: Portulaca L.

Species: Portulaca oleracea L.

II.2.2. Botanical description

Purslane plants are succulent, annual herbaceous, and erect or decumbent up to 30 cm high. Stems are cylindrical, up to 30 cm long, 2-3 mm in diameter, green or red, swollen at the nodes, smooth, glabrous apart from the leaf axils, and diffusely branched, and the internodes are 1.5–3.5 cm in length (Arshiya, 2013). Purslane leaves are alternate or subopposite, flat, fleshy, having variable shapes, obovate, 1–5 cm long, 0.5–2 cm across, obtuse or slightly notched at the apex, tapering at base, sessile or indistinctly petiolate, glabrous, smooth, and waxy on the upper surface, with entire margin, small stipules, and cluster of hairs up to 1 mm long. Leaves are egg to spatula shaped, succulent, and stalkless or have very short stalks, about 5–30 mm long, and sometimes their edges are redtinged. Leaves are green or green with red margin (Beloued, 2005). Cotyledons (seed leaves) are egg shaped to oblong, hairless, succulent, about 2–5 mm long, and sometimes tinged red. Flowers originate as single or clusters of two to five at the tips of stems. The flowers are minute or small having orange yellow, purple, or white pink color with five petals (Grubben et Denton, 2004). Fruit consists of almost round to egg-shaped capsules, usually about 4–8 mm long. Seeds are tiny, less than 1 mm in diameter, circular to egg shaped, flattened, and brown to black (Alam et al., 2014) .

Figure 08: Morphology of Portulaca oleracea L.

(A : plant, B: leaves, C : flowers, D : fruits) (Hwess et al., 2018).

II.3. Chemical composition

Many types of chemical compound has been found present in P. oleracea including alkaloids, terpenoids, organic acids, coumarins, flavonoids, volatile oil and polysaccharides (Sadhana & Deepali, 2017).

The Portulaca oleracea plant is of high nutritional value because it contains biologically active compounds, including flavonoids including kaempferol, apigenin, luteolin, myricetin, quercetin, Portulacanones A, B, C; alkaloids including dopamine; noradrenaline, oleraceins A, B, C, D and E, oleracins I and II, adenosine, thymine and uracil; terpenoids, including portuloside A and B, portulene and lupeol; other compounds such as tannins are also found (Syed et al., 2016; Zhou et al., 2015). It is the uniqueness of purslane as the "richest vegetable source" of omega-3 fatty acids particularly α-linolenic acid (up to 30%) and other essential fatty acids such as palmitoleic, palmitic, linoleic, oleic, stearic eicosapentaenoic and docosahexaenoic acid (Iranshahy et al., 2017) .

It is a succulent plant, rich in antioxidants vitamins A, C, E, beta carotene and glutathione (Abdelwehab et al, 2014). It also contains two types of betalain alkaloid pigments which are the reddish betacyanins visible in the coloration of stem and the yellow betaxanthis that can be seen from the flowers. These two pigments are potent antioxidants and have been found to have anti-mutagenic properties. In addition to containing dietaryminerals such as phosphorus, manganese, iron, calcium, copper are present in root stem and leaf whereas Zinc, selenium, magnesium are present only in the leaves of Portulaca oleracea (Petropoulos et al., 2016).

II.4. Therapeutic effects and uses

For thousands of years, Portulaca oleracea has been used as a food and medicinal plant, as it was listed by the World Health Organization as one of the most widely used medicinal plants and has been given the term "Global Panacea", because it contains many active chemicals. It is also known from herbs (Derouiche et al., 2017). Immunomodulating and antioxidant medicinal, which can be offered to treat many immune disorders. In addition, it can be used as a substitute for synthetic antioxidants in food preservation and may be useful as a food and cosmetic ingredient. Because it contains vitamin C, it plays a role in protecting against cancer of the lung and oral cavity, and it can also have a protective effect against oxidative stress caused by vitamin C deficiency (Arruda et al., 2004). In addition, it is anti-keratolytic and anthelmintic, being rich in mineral salts and has a high content of water (90%) and mucilage, it has emollient and soothing properties to irritate mucous membranes. This plant has traditionally been used as an anti-inflammatory (eyes), anti-diabetic, analgesic (head), anti-bacterial, and anti-fungal (CHERUKURI et al.,2013).

III. Aquilaria malaccensis

III.1. Definition and localisation

Aquilaria malaccensis is one of 13 recognized aromatic resin species produced from Aquilaria in the Indo-Malaysian genus Aquilaria, family Thymelaeaceae (Lee and Mohamed, 2016). It is also called agarwood, as it produces woods impregnated with a dark aromatic resin from the tree when infected with microbes(Subasinghe and Hettiarachchi, 2013) . The resinous compound is believed to be produced by the plant as a self-defense mechanism against fungal infection, but there are also opinions that it is produced by a fungus that pulls raw materials from the plant. The heartwood of the affected plant is very valuable and is used in the manufacture of perfumes, incense sticks, and as a raw material in traditional and modern medicines (Barden et al., 2000). It is native to Southeast Asia, including southern China, India, Cambodia, Vietnam, Malaysia, Indonesia, and Laos (Lee and Mohamed 2016). Nowadays there is local extinction in many areas and this is due to the high demand for agarwood, the affected trees were cut down in an unsustainable manner.

III.2. Plant profile

III.2.1. Scientific classification (Anton., 2007)

Kingdom : Plantae

Phylum : Tracheophyta

Class : Angiosperms

Order : Malvales

Family : Thymelaeaceae

Genus : Aquilaria

Species : malaccensis

III.2.2. Botanical description

sized tree, 20 to 40 m tall, usually with a straight bole, sometimes fluted with thick buttresses up to 2 m high, bole up to 60 cm in diameter (Irnayuli et al., 2011). Young bark is light brown with fi ne hairs, older bark is smooth and whitish in colour. Wood without resin is white, light and soft, while wood with resin is hard, dark and heavy. Leaves alternate, elliptic or lanceo- late, 3-3.5 cm wide and 6-8 cm long with 12-16 pairs of veins (Adelina et al., 2004). Infl

orescence a terminal or axillary umbel. Flowers hermaphroditic, up to 5 mm long, fragrant and yellowish green or white. The tree starts fl owering and fruiting at the age of 5-6 years. Fruit green, egg-shaped capsule, leathery exocarp with fi ne hairs, 4 cm long and 2.5 cm wide. There are two seeds per fruit. Seed ovoid, blackish brown and densely covered with red-brown hair (Irnayuli et al., 2011).

Figure 09: Morphology of Aquilaria malaccensis L.

(a : plant, b: leaves, c : flowers, d : fruits, e: agarwood) (ZAREMSK, 2020).

III.3. Composition chimique

In a phytochemical screening study alkaloids, saponins, flavonoids, tannins, and terpenoids were found from A. malaccensis (Khalil et al. 2013). In addition to containing other major components are 2-(2-phenylethyl)chromone derivatives, aromatics, sesquiterpenes, monoterpenes, sterols and fatty acid methyl esters. Besides chromone, the compounds predominated 4-phenyl-2-butanone, malarial, benzaldehyde and the methyl ester of propanoic acid (Lee Jong et al., 2014), and the presence of various sesquiterpene, sesquiterpene alcohols, oxygen, hydrocarbons and acids. Some of the compounds identified from gaharu included α-agarofuran, β-agarofuran, 10 epi-γ-eudesmol, agarospirol, ginkohol, jinkohol II and valerianol. Jarrow oils of Aquilaria species, including Aquilaria malaccensis, contain various sesquiterpenes, sesquiterpene alcohols, oxygen, hydrocarbons and acids (Azah MAN et al , 2014; Ismail et al , 2013).

III.4. Therapeutic effects and uses

The uses of agarwood are not restricted to incense and perfumery. Currently, the applications of agarwood have been increasingly explored for pharmaceuticals purpose obtained from other parts of the tree (Wang et al., 2018). Studies indicated that leaves from the tree contained great potential of bioactivities such as antioxidant (Begum, 2016), anti-inflammatory (Eissa et al., 2018), anti-hyperglycemic. Also, It is prescribed in traditional medicine to promote the circulation of qi, relieve pain, especially taken during pregnancy, after childbirth and for diseases of the female genital organs, vomiting, arrest by warming the stomach , and to relieve asthma. Agarwood is used in the production of pharmaceutical dyes (Adelina et al., 2004). The plant is used as a stimulant, diuretic, to treat smallpox, rheumatism, spasms especially in the respiratory and digestive systems, abdominal pain, colic, chest congestion, diarrhea, nausea, hiccups, nerves and regurgitation . It is also reported to have remarkable anticancer activity (Tabin et al., 2014).

Chapter IV

Zinc &

Zinc nanoparticles

I. Zinc metal

I.1. Definition

Zinc is a trace elements or metallic trace elements, has the atomic number 30 and is located in group XII of the Periodic Table of the Elements (Samsonov, 1973).

Zinc is an essential element for the life of the organism, but it is found in very small quantities in the body, where the daily requirement of zinc ranges from 10 to 15 mg / day in children and adults, and increases during pregnancy (about 20 mg / day) and during breastfeeding (25 mg / day) (Biomnis, 2013).

Zinc is not made by the body, so it must be provided in sufficient quantities through our diet, and in particular by consuming products rich in zinc such as red meat, fish, seafood (especially shellfish), eggs, dairy products, vegetables, legumes , whole grains and dried fruits (Derouiche, 2016).

I.2. Zinc metabolism

Digestive absorption of zinc occurs mainly in the jejunum. It appears that zinc is taken up by the brush border as a complex and that prostaglandins play a role in this absorption. In the workplace, zinc is mainly absorbed through the lungs in the form of smoke or dust (zinc oxide). Zinc is then distributed in the intestinal cell: part is used in situ by binding to metalloenzymes or membrane proteins, another part is excreted outside the cell by the basolateral membrane and passes into the general circulation. Finally, the last part is stored in the form of metallothioneins (Biomnis, 2013).

I.3. Role of zinc

Zinc is an essential component that plays important roles in various biochemical reactions in many biological systems. Where zinc performs a variety of important functions including DNA and protein synthesis, immunity, neurosensory, cell division, energy metabolism, wound healing, regulation of gene transcription and bone mineralization (DEROUICHE, 2016).

I.4. Zinc and diabetes

Zinc playing a considerable role for the circulation of insulin, it protects insulin from free radical attack, it allows to control the release of insulin after ingestion of food. (derouiche et al., 2017). For type 2 diabetics, a zinc deficiency decreases the sensitivity of peripheral tissue cells to insulin and leads to a decrease in the membrane fluidity of the stability of insulin, zinc is very

important its absence worsens the protein oxidation is This is the reason why we observe in diabetics a degradation of insulin synthesis (DEROUICHE, 2016).

I.5. Zinc and oxidative stress

Zinc is one of the minerals most relevant to human health, due to its antioxidant properties. Zinc acts as a cofactor for important enzymes involved in the proper functioning of the antioxidant defense system such as superoxide dismutase (SOD) (derouiche et al., 2013). In addition, zinc protects cells from oxidative damage, stabilizing membranes and inhibiting the enzyme nicotinamide adenine dinucleotide oxidase (NADPH oxidase). Zinc also stimulates the synthesis of metallothionein, proteins active in reducing hydroxyl radicals and sequestering reactive oxygen species (ROS) produced in stressful situations, such as type 2 diabetes, obesity and cancer (Tandon et al., 2001).

II. Zinc nanoparticles

II. 1. Nanotechnology

During the past few decades, a field called nanotechnology has received great attention due to the wide applications of nanoparticles in various fields of science and technology. Nanoparticles are devices or materials whose scale is at least one nanometer apart, i.e. from 1 to 100 nanometers. Due to their small size, nanoparticles have a high surface-to-volume ratio, which gives distinct features to nanoparticles such as drug delivery, imaging and diagnostics (Bayda et al., 2019).

Nanoparticles consist of two parts: the base material and the surface modifier. Where the basic material is either biological material such as phospholipids, fats, lactic acid, chitosan, and dextran or it may be carbon, chemical polymers, silica or minerals. While the surface modifier is responsible for changing the physicochemical properties of the base materials. Many chemical compounds, drugs, probes and proteins are attached to the surface of nanoparticles with the help of covalent bonds or by adsorption, resulting in a change in the physicochemical properties. Hence, it is possible to change or improve the function of nanoparticles. The efficiency of these particles for any applications also depends on the physicochemical properties of the base materials and surface modifiers. In addition, the composition of the base materials along with the surface modifiers make them biodegradable and biocompatible (Sovan Lal, 2011).

II. 2. Metal nanoparticles

Metal oxide nanoparticles have received remarkable attention in biomedical technology and are extensively used in engineering and medical applications

due to their high surface area. Both the metal and metal oxide nanoparticles hold strong antioxidant and antimicrobial properties, It is also used in the study of biomolecular interactions, the development of bioassays and biomedical devices, and many other biomedical applications such as immunodiagnostics, drug delivery, therapeutics, and gene transfer (Mei & Wu, 2017).

II. 3. Zinc oxide nanoparticles

The ZnNPs are one of the most important metal oxide nanoparticles, are commonly used in various fields (Newman et al., 2009). Zinc oxide nanoparticles (81.38 g / mol, <100 nm) are white odorless solid powders of hexagonal wurtzite crystals. Its small size facilitates the absorption of zinc by the body, which make it attractive in the biomedical application (Jiang et al., 2018). In addition, ZnO is classified as a "GRAS" substance (generally recognized as safe) by the US Food and Drug Administration (FDA) (Rasmussen et al., 2010). In the biomedical field, ZnONPs have been used for development of biosensors for a wide variety of molecules of interest, to improve diagnosis through imaging, controlled drug release, gene delivery and as therapeutic agents (Napi et al, 2019; Martínez-Carmona et al, 2018). There is promising scientific evidence for the treatment of diseases with a high worldwide prevalence where several studies evaluated the anticancer, antidiabetic and antimicrobial activity of ZnONPs (Bisht et al, 2017; Lallo da Silva et al,2019).

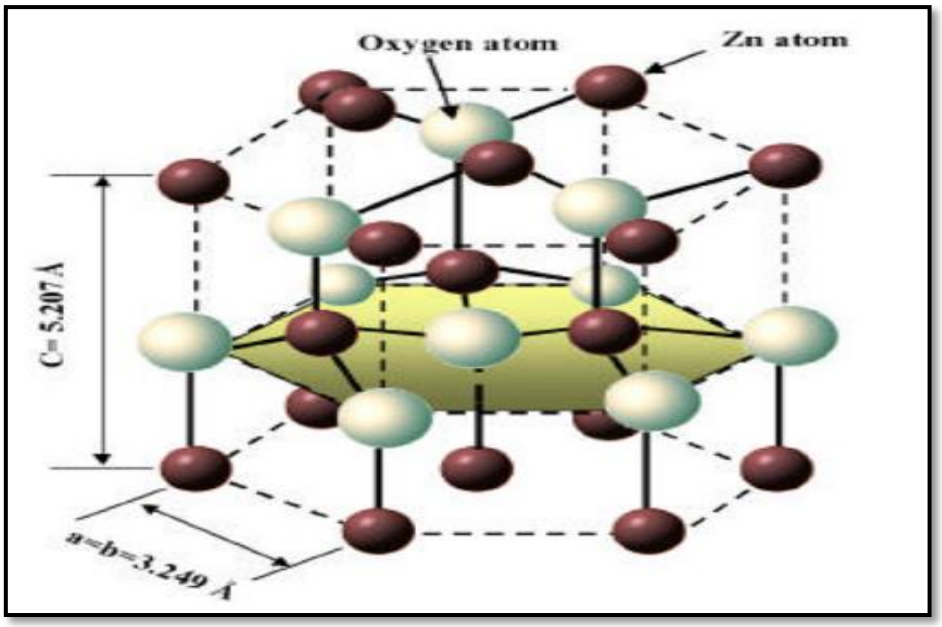

Figure 10: The hexagonal wurtzite structure model of ZnO (Yoon-Bong, 2011).

II. 4. Green synthesis of nanoparticles

In the old days, metallic nanoparticles were manufactured by two different traditional methods: mechanical and chemical methodologies. These mechanisms relied on the use of laser ablation or high-energy ball milling techniques, or the use of sol-gel, hydrothermal, co-precipitation, and micro-emulsion processes, resulting in Nanoparticles are associated with harmful and toxic by-products, and lack of biocompatibility, as well as these traditional methods requires toxic reagents, and expensive instruments. The Green synthesis of nanoparticles is a novel way to synthesize nanoparticles by using biological sources. It is gaining attention and attracted the scientists from different fields due to its simplicity and environment-friendly nature (Chetehouna et al., 2020). The biosynthesis for obtaining nanoparticles using naturally occurring reagents such as vitamins, sugars, plant extracts, biodegradable polymers, and microorganisms as reductants and capping agents could be considered attractive for nanotechnology (Atoussi et al., 2020). The synthesized green nanoparticles showed improvements in their cellular compatibility and biomedical properties compared to their conventional counterparts, becoming excellent antibacterial or anticancer agents (Gunalan et al 2012, Crua et al 2019).

Experimental Part

Chapter I

Materials&Methods

I. Materials

I.1. Biological materials

I.1. 1. Plant material

The plants used in this work are the *Aquilaria malaccensis*, purchased from the local market, then ground with a mixer until a fine powder. Aquilaria powder is stored at room temperature in airtight containers protected from bright light until the start of the experiment. *Portulaca oleracea*, harvested in the Oued Righ region (Touggourt) in. After the plant is restored, the plants are cleaned, and then dried out from sunlight and at room temperature. Then the dry leaves are ground. *Coriandrum sativum* were collected in herbal stores from herbal in local markets of EL-Oued state. Then ground into powder and stored at room temperature until use.

Figure 11: Plants for Polyharb (original photos).

I.1.2. Animal material

I.1.2.1. Animal care

Our study was conducted on twenty-four (24) Wistar Albino female mice weighing between 164 and 208 grams at the beginning of the experiment of the same age with good physiological conditions. These animals were brought from the Institut Pasteur in Algiers, and they were brought up in an animal facility at the level of the Faculty of Natural Sciences and Life at the University of EL-chahid Hamma Lakhdar El Oued, under standard environmental conditions: at a temperature of 19 ± 2 ° C and a light period of 12 hours / 24 hours.

I.1.2.2 Breeding and weighing

The mice are housed in plastic cages, each cage containing four mice. These cages contain sawdust, which is changed twice every week until the end of the experiment. We weighed each mouse regularly, once a week, and measured blood sugar once a week. The animals were fed a diet prepared according to Southon et al, (1984) (Table01), and received distilled water.

Table 01: Standard diet composition (SOUTHON et al, 1984).

Matières premières	Quantité (g/kg)	Pourcentage (%)
Mais	326	32.6
Saccharose	326	32.6
Protéine	168	16.8
Cellulose	40	4
Minéraux	20	2
Vitamine	20	2
Huile	40	4

I.1.2.3 Induction of experimental diabetes in rats

After overnight fasting, diabetes was induced in rats by intraperitoneal injection of a freshly prepared solution of alloxan monohydrate (Sigma) at a dose of 150 mg / kg body weight (Madubunyi et al., 2012). Alloxan is dissolved in physiological solution (NaCl 0.9%). The groups of healthy rats received the same volume of buffer intraperitoneally (NaCl 0.9%). After the injection, the water bottles were replaced by bottles containing 20% of the glucose solution on the first day and 5% of the glucose solution on the second and third days, in order to overcome the hypoglycemia caused by the substance alloxan. This hypoglycemia can be fatal for rats. After 72 hours of the injection, diabetes was confirmed in the rats by measuring blood glucose using a type glucometer (Vital-Check; TECO Diagnostics, Korea). Only the rats with a blood glucose level greater than (14 mmol / l) were considered to be diabetic and retained for this experiment.

I.1.2.4 Treating animals

After induction of diabetes, the groups are kept in the same conditions. Starting treatment with Polyherb aqueous extract. It begins 72 hours after induction of diabetes (Derouiche, 2016). The total duration of treatment is 20 days.

Group 01 (controls): 4 control rats fed a standard diet for 20 days.

Group 02 (non-diabetic rats+ polyherb solution treated): 4 healthy rats subjected to a standard diet and treated with polyherb aqueous extract.

Group 03 (non-diabetics rats+ ZnNPs): 4 healthy mice on a standard diet treated with zinc oxide nanoparticles.

Group 04 (Diabetics): 4 diabetic rats fed a standard diet.

Group 05 (Diabetics+ polyherb): 4 diabetic rats subjected to a standard diet and treated with polyherb aqueous extract.

Group 06 (Diabetics rats+ ZnNPs): 4 rats with diabetes on a standard diet treated with zinc oxide nanoparticles .

I.1.2.5 Sacrifice and collecting blood and organs

At the end of treatment with polyherb and ZnNPs, the animals were fasted for 16 hours, and then anesthetized with chloroform (94%) by inhalation and sacrifice (by decapitation). When mice are sacrificed, blood sugar is measured during the sacrifice period. The blood was also transfused into EDTA tubes for hematology studies, then the blood obtained was centrifuged at 3000 rpm for 10 min, plasma was recovered and then rapidly frozen at -20 ° C until use. Another amount of blood was collected in tubes without anticoagulants for biochemical analysis, and it was placed in a centrifuge at 3000 rpm for 10 minutes to obtain serum frozen at -20 ° C for use in biochemical analysis (urea, creatinine, Triglycerides, cholesterol, TGO, TGP). After dissection, the (liver, pancreas, kidneys, and ovaries) are carefully removed, and adipose tissue stripped from it, and these isolated organs are weighed and rinsed in a 0.9% NaCl solution. Organ congeners are prepared for detection of oxidative stress factors (Malondialdehyde (MDA), Superoxide disutase (SOD) and Reduced Glutathione (GSH). A portion of the pancreas of each rats from each cohort is placed in a formol solution, for preservation and use of tissue sections.

I.2. Matériels technique

I.2.1. Reagents and products

Zinc nitrate, Hydrogen chloride (HCl), methanol, chloroform, sodium chloride (NaCl), Phosphoric Acid (H_3PO_4), Tris, Salicylic acid, 5,5dithiodis-2-nitrobenzoic (DTNB), Gallic Acid, Ferric chloride ($FeCl_3$), Fehling liquor, Sulfuric acid (H_2SO_4), Aluminum chloride ($AlCl_3$), Riboflavin, 1-chloro 2,4- dinitrobenzene (CDNB), Acetic acid, Drajendrof, Trichloroacetic Acid (TCA), Thiobarbituric Acid (TBA), Butylated Hydroxy Toluene (BHT), Phosphate buffer, NBT, Phosphate buffer (KH_2PO_4), Ethanol, FC reagent, Na_2CO_3, Quercetin , Potassium Ferricyanide solution (K_3Fe), Anthrone reagent.

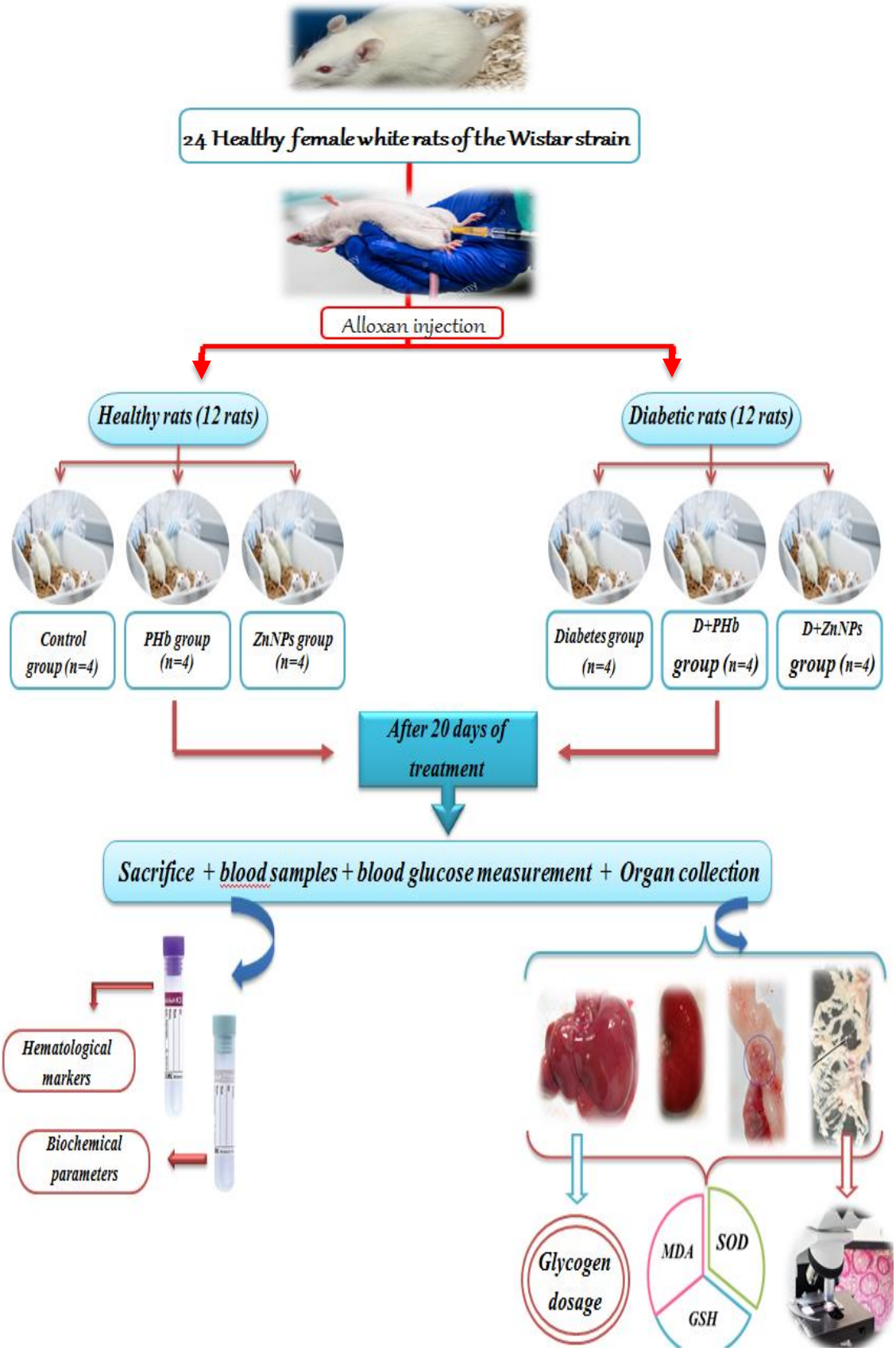

Figure 12: Experimental design of study.

II. Methods

II.1. In vitro study

II.1.1. Development of herbal solution:

a) Local formulation:

The Local Polyherbal formulation was formed based on some local plants according to the table.

Table 02: Composition of Polyherbal formulation

Biological Name
Aquilaria malaccensis
Portulaca oleracea
Coriandrum sativum

b) Herbal solution preparation

The Herbal solution was prepared by adding distilled water to dry herbal powder. After maceration at room temperature, the mixture was filtered by Whatman paper then evaporated by using rotary evaporator (Derouiche et al., 2019).

II.1. 2. Method for preparing zinc oxide nanoparticle

For the synthesis of zinc oxide nanoparticles, we first prepared a herbal solution and then heated it . In the meantime, we add zinc. Then it is left in the oven. To dry, the pale white sediment was removed and washed (Ezealisiji, 2019).

II.1.3. Characterization of ZnNPs

The ZnO nanoparticles prepared by the spectroscopy above method was characterized using FTIR spectroscopy and UV-Vis spectrophotometer. IR analyses were done in department of Process Engineering and Petrochemicals labs by direct reading.

II.1.4. Phytochemical analysis

The phytochemical analysis were carried out on the aqueous extracts prepared from the plant by qualitative characterization method according to (Evans., 2009; Harborne., 1998; Wadood et al, 2013; Harborne, 1973)

- **Phenols**

Introduce 5 ml of extract In a test tube and drops few of natural 5% ferric chloride solution. A dark green color indicates the presence of phenolic compounds

- **Flavonoids**

In a test tube, introduce 5ml of extract, 5ml of diluted ammoniac and 1ml of H_2SO_4. The appearance of a yellow color indicates the presence of flavonoids.

- **Alkaloids**

1 ml of aqueous extract were treated with a few drops of hydrochloric acid then 1–3 drops of Wagner reagent were added. The appearance of brown precipitate reveals the presence of alkaloids in the sample.

- **Tannins**

In a test tube, introduce 5 ml of extract and add 1 ml of a 2% aqueous solution of ferric chloride ($FeCl_3$). The presence of tannins was indicated by a greenish or bluishblackish coloration.

- **Terpenoids**

The formation of a reddish-brown color indicates the presence of terpenoids, through the addition of chloroform (2ml) and concentrated sulfuric acid (3 ml) to 5 ml of plant extract.

- **Reducing compound**

Add Fehling's liquor (1ml of reagent A and 1ml of reagent B) to the extract and incubate the whole in a boiling water bath, the appearance of a brick-red precipitate indicates the presence of reducing sugars.

- **Saponins**

In a test tube, introduce 5ml of extract, mixed with 5ml of distilled and with vigorous manual agitation. The formation of a steady foam indicates the presence of saponins.

- **Steroids**

For 1ml of plant extract, add 0.5ml of acetic acid solution, followed by 0.5ml of concentrated H_2SO_4. If the solution does not give any green color, it proves the presence of unsaturated steroids. In a second tube, the same volume of H_2SO_4 was added. The presence of the red color indicates the presence of steroid derivatives.

II.1.5. Total phenols and flavonoids compounds

II.1.5. 1. Total phenols

Determination of the total polyphenols was carried out according to the Folin Ciocalteu (FC) method (Boizot & Charpentier., 2006): 100 µl of plant extract are mixed with 055µl of the FC reagent and 400 µl of $Na2CO_3$ at 7.5% (w / v). The mixture is stirred and incubated in the dark and at room temperature for ten minutes and the absorbance is measured at 760 nm by a UV spectrophotometer. The results are expressed in mg gallic acid equivalent/ g of dry vegetable material with reference to the calibration curve of gallic acid. Calibration curve is carried out by gallic acid at different concentrations (20 - 40 - 60 - 80 - 100 - 120 µg/ml) under the same conditions and the same steps of the assay. The results are thus expressed in milligrams of gallic acid per gram of dry extract (mg of EAG / g). All measurements are repeated 3 times.

II.1.5.2. Total flavonoids

The determination of total flavonoids was carried out according to the method described by (Dehpour A et al., 2009): 500 µl of each extract, 100 µl $AlCl_3$, 100 µl of 1 M sodium acetate and 2.8 ml of distilled water. The mixture is stirred and then incubated in the dark and at room temperature for 30 minutes. The blank is made by replacing the extract with 95% methanol and the absorbance is measured at 415 nm using a UV spectrophotometer. The results are expressed in mg equivalent quercetin / g of dry vegetable material with reference to the quercetin calibration curve. The quercetin calibration curve is performed by quercetin at different concentrations (20 - 40 - 60 - 80 - 100 – 120 µg/ml) under the same conditions and the same steps of the assay**.**

II.1.6. Antioxidant activity (Ferric Reducing Antioxidant Power Assay "FRAP assay")

- **Principle**

The Antioxidants ability are determined by colorimetry. The ferric-tripyridyltriazine complex is reduced to the ferrous-tripyridyltriazine in presence of the antioxidants; the complex loses its yellow color to a dark blue. This coloration measured at 595 nm is proportional to the concentration of antioxidants present in the samples. The method is standardized by Trolox (Oyaizu, 1986).

- **Procedure**

l. Take 500µl of sample.

2. Add 1.25ml of the buffer solution (0.2 M, PH = 6.6).

3. Incubation during 20 min in a water bath at 50 ° C.

4. Add 1.25ml of the aqueous TCA solution (10%) to stop the reaction.

5. Centrifugation at 3000 rpm for 5 minutes.

6. 1.25 ml of supernatant are then mixed with 1.25 ml distilled water and 250 µl $FeCl_3$ (0.1%). 7. Reading at 700 nm against a blank.

The results expired by IC50, after calculating of the inhibition percentage values according to (Yazdani et al., 2019) as follows:

$$\mathbf{IP}(\%) = 100 - \frac{ODcontrol}{\text{OD sample}} \times 100$$

II.2. In vivo study:

II.2.1. Hematological parameters

The determination of hematological parameters performed using fully Auto Blood Cell Counter (ERMA).

II.2.2. Biochemical parameters

Biochemical parameters were determined by methods using commercial reagent kits from Biomaghreb (Tunisia) using auto-analyzer.

II.2.3. Glycogen and oxidative stress parameters

II.2.3.1 Homogenates preparation

About 1g of each organs was homogenized in 10ml of buffer solution of Tris buffer saline (TBS, pH=7.4). Homogenates were centrifuged at 5000 revolutions/min for 15 min at 4°C, and the obtained supernatant was used for the determination of antioxidant activity.

II.2.3.2 Determination of malondialdehyde (MDA) level

- **Principle**

The principle of this assay is based on the condensation of MDA in an acid medium and under heat with thiobarbituric acid. The reaction leads to the formation of a pink complex between two molecules of thiobarbituric acid which can therefore be measured by absorption spectrophotometry at 532nm (Yagi, 1976).

- **Reagent**

375 mg of TBA, 20g of TCA, 0.01g of BHT, 25 ml of 1 N HCL and 50 ml of distilled water were added to a beaker. The solution obtained was heated to 40°C in a water bath until the TBA was completely dissolved, then transferred to a 100 ml flask and the volume made up with distilled water to the gauge.

- **Procedure**

Pipette into the glass vise test tubes, 200 µl of sample, 800 µl of TBA reagent and close tightly. Heat the mixture in a water bath at 100°C for 15 minutes. Then cool in a cold water bath for 30 minutes, leaving the tubes open to allow the gases formed during the reaction to be removed. Centrifuge at 3000 rpm for 5 minutes and read the absorbance of the supernatant at 532 nm using a spectrophotometer.

- **Expression of results**

The concentration of thiobarbituric acid reactive substances (TBARS) was determined using the molecular extinction coefficient of MDA (å = 1,53.10 M-1 .cm-1). The results were expressed in nmol /mg of prot.

$$\mathbf{MDA}\left(\frac{\text{nmol}}{\text{mg of prot}}\right) = \frac{\text{OD sample}}{1.53} \times 10^{\wedge 5}$$

II.2.3.3. Determination of reduced glutathione (GSH) level

- **Principal**

The level of reduced glutathione is determined according to (Weckbecker & Cory, 1988) by measuring the optical density results from the formation of 2-nitro-5-mercocapturic acid (TNB) from the reduction of dithio-bis-2-nitrobenzoic acid (DTNB) ,which is called Ellman reagent with SH groups exist in GSH briefly.

- **Procedure**

1. 800µl of homogenate samples are add to 200µl of salicylic acid (0.25%).
2. The mixture was centrifuge at 1000 rpm for 5 min.
3. Take 500 ml of supernatant and mixed with 1000µl of tris buffer (tris 0.4mol, 0.02mol NaCl, ph = 8.9) and 25 µl of DTNB (0.01 mol/L).
4. Read the absorbance at λ= 412 nm after 5 min of incubation.

- **Expression of results**

The calculate of GSH concentration expressed in nanomoles per milligram of proteins (nmol/mg of prot) according to the following formula:

$$\text{GSH (nmol/mg of prot)} = \frac{(\text{OD} \times 1 \times 1.525)}{13133 \times 0.8 \times 0.5 \times mg\ of\ prot} \times \text{d}$$

- **OD:** Optical Density.
- **1.525:** total volume of blend an ml.
- **13133:** Absorption constant of SH groups at 412 nm.
- **0.5:** volume of solution float an ml.
- **1:** volume of protein mixture.
- **0.8:** volume of homogeneous solution without protein exists in 1 ml.
- **GSH:** concentration of glutathione.

II.2.3.4. Determination of Super Oxide Dismutase (SOD) activity

- **Principal**

The assay method of SOD activity using the NBT by the superoxide anion ($O_2^{\cdot -}$), is used as a basis for detecting of presence of SOD by measuring the spectrophotometrically absorbance at 560 nm (Beauchamp & Fridovich, 1971).

- **Procedure**

Collect in tubes	Blank	Sample
EDTA-Met (0.1mM, 13mM)	1000µl	1000µl
Sample	-	50µl
Phosphate buffer (50Mm)	1850µl	1800µl
NBT (75µM)	82.5µl	82.5µl

The tubes were incubated for 5 minutes to obtain a constant temperature (25 ° C.), then added 22.5 µl of riboflavin (2 µM), and incubated in a light box for 20 min.

- **Expression of results**

Inhibition percentage of NBT reduction by SOD

$$\text{SOD} = \frac{OD\ blanc - \text{OD sample}}{OD\ blanc} \times 100$$

II.2.4. Determination of glycogen

The determination of glycogen in the tissues is carried out according to the colorimetric method. anthrone reagent is added to the sample (homogenate) then the mixture is placed in a water bath at 800C. a green color develops, the intensity of which is proportional to the amount of carbohydrate present in the sample. Reading the optical density at λ = 620 nm against a reagent blank containing distilled water. The absorbance value is calculated and then converted to carbohydrate concentration equivalent using an established calibration curve, with glucose, under the same experimental conditions (Jean, 1975).

II .2.5. Histopathological study

After the sacrifice of rats, brain and liver were removed and immersed for 48 h in a fixative solution (solution 4% formaldehyde, in phosphate buffer, pH＝7.6), dehydrated in ascending graded series of ethanol, cleaned with toluene, immersed in paraffin, and colored with hematoxylin and eosin. Histopathological evaluation was performed with a light microscope.

II .3. Statistical analysis

The values of the results were expressed as a percentage or an average ± ES (standard deviation). Student's t-test of independent samples was used. All data in this study were examined by Minitab 13.0 software. $P < 0.05$ indicates statistically significant difference.

Chapter II
Results

I. In vitro essays

I.1. Phytochemical study

I.1.1. Qualitative phytochemical analysis

Results of phytochemical essays (Table 03) shows that aqueous extract of plants and Polyherb very rich on different important chemical compounds such as flavonoids, steroids, Phenols, Catechic Tannin, Saponoside, Carbohydrate and Alkaloid but our extract plant is poured from Steroids derivatives.

Table 03: Phytochemical essays of aqueous extract of plants and polyherb studied.

Phytochemical	*Portulaca oleracea*	*Aquilaria Malaccensis*	*Coriandrum sativum*	Polyherbal
Flavonoids	+	+	+	++
Steroids	+	+	+	+++
Phenolic	+	+	+	+
Tannin	+	-	-	+
Saponoside	+	+	+++	++
Reducing compound	+	+	+	+
Alcaloids	+	+	-	+
Terpenoids	+	+	-	+

(+): Present (-): Absent

I.1.2. Total phenols and flavonoids concentration

The results presented in (table 04) showed richness from each of total phenols and flavonoids in Polyherb and plants aqueous extract.

Table 04: Total phenols and flavonoids concentration of plants and Polyherb.

Compounds	Total phenols (mg of EAG/g of extract)	Total flavonoids (mg QE/g of extract)
Portulaca oleracea	34.80 ± 1.50	23.56 ± 0.03
Coriandrum sativum	68.73±0.28	31.86±0.63
Aquilaria malaccensis	209.22±1.65	30.0±0.52
Polyherb	54.34±1.31	14.16±0.03

I.2. Antioxidant activity (FRAP) of Polyherb

The antioxidant activity of Polyherb and acide ascorbic appeared in (Figure 11) show that, IC50 values in the FRAP activity assay of the Polyherb obtained by a percentage inhibition curve as a function of the concentrations of the Polyherb. Also, the percentage inhibition of ascorbic acid, which is calculated by the equation y = 1.57x +51.93 with R^2=0.919, obtained by a percentage inhibition curve as a function of ascorbic acid concentrations.

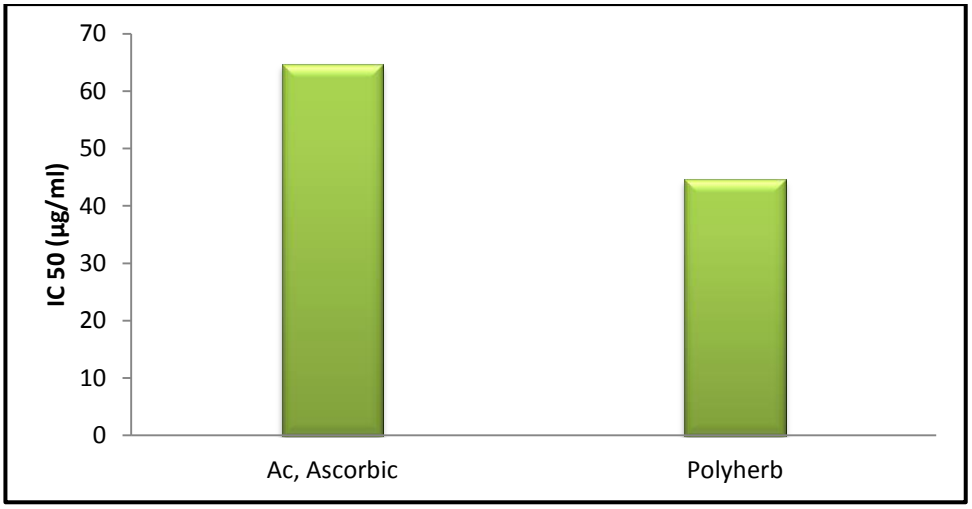

Figure 11: IC50 values of Polyherb and acorbic acide.

I.3. Characterization of ZnNPs

I.3.1. UV–Vis spectroscopy

UV–Vis absorption of green synthetis of ZnNPs is shown in (Figure 12) The presence of peak at 300 nm corresponds to formation of ZnO compound.

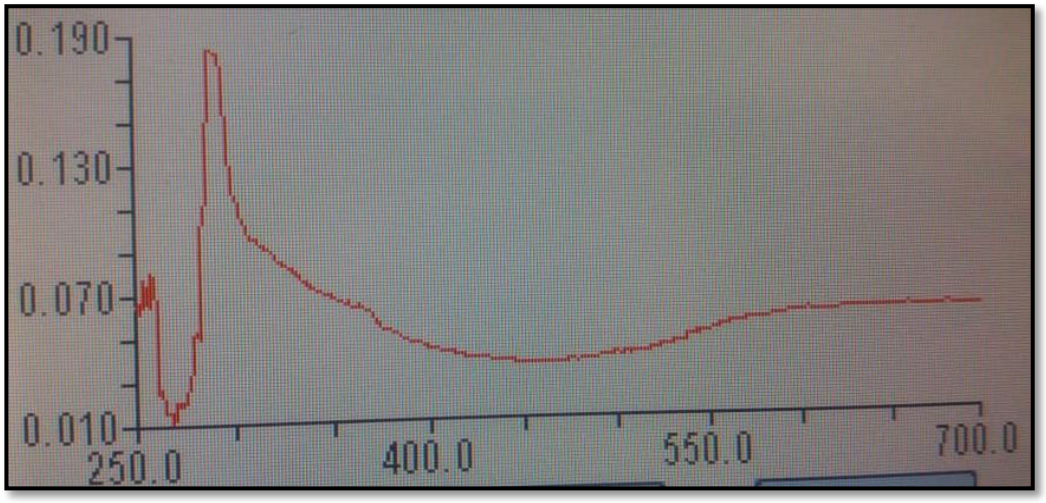

Figure 12: UV-Vis spectrum of ZnNPs.

I.3.2. Infrared analysis of poluherb

In (Figure 13), it was observed that, the presence peak in the rang 400-500 cm^{-1} corresponds to the O-Zn, compound which confirmed the biosynthesis of nanoparticles of zinc.

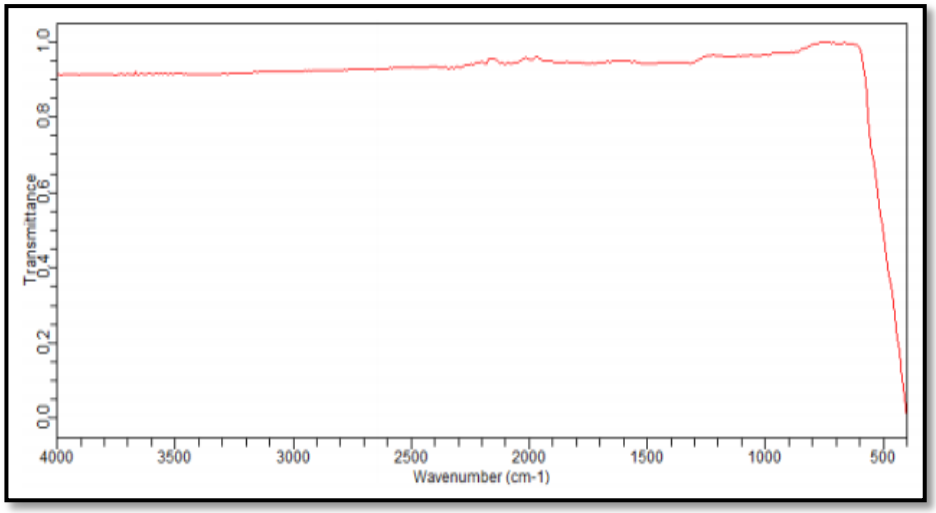

Figure 13: FTIR spectrum of ZnNPs.

II. In-vivo essays

II.1- Study of body growth and the relative weight of organs

The results presented in tabl (05) show a remarkable change of weight in diabetic rats compared to the control and in the treated group compared to diabetic rats. The results obtained for relative organ weights show a highly significant increase ($P<0.01$) in the relative weight of the liver, kidneys, pancreas and ovary in the diabetic groups compared to the control group. On the other hand, the treatment with the polyherb ans ZnNPs has an ameliorate effect ($P<0.05$) on the relative weight of some tissues study and no effect of other compared to diabetic rats (Table 05).

Table 05: Body weight and relative organ weights in control and experimental groups

		Control (n=4)	Polyherb (n=4)	ZnNPs (n=4)	Diabetic (n=4)	D+polyheb (n=4)	D+ZnNPs (n=4)
Initial weight (g)		186.75±9.84	201±18.19*	183±2.93**	200±25.51	161±13.54^{**a}	177±8.32^{*c}
Final weight (g)		175±4.14	189.75±5.01	172±2.97	190±12.3	164.75±9.48	181.50±6.89
Relatie organ weighs (%)	**Liver**	2.68±0.20	2.32±1.36	2.76±0.10***	3.49±0.17	3.17±0.63	3.01±0.58
	Kidneys	0.52±0.02	0.54±0.07	0.56±0.04*	0.79±0.20**	0.69±0.16*	0.62±0.06^{**c}
	Pancreas	0.33±0.03	0.036±0.06	0.36±0.04	0.41±0.11	0.36±0.04^{b}	0.37±0.08
	Ovary	0.02±0.007	0.05±0.02**	0.04±0.01***	0.05±0.01**	0.03±0.01*	0.03±0.009^{**b}

II.2. Biochemical parameters

As for which level illustrates in (Figure 14). Below, the results show high significant increase ($p<0.01$) of blood glucose and decrease of liver glycogen level in diabetic group and non-significant difference in polyherb and ZnNPs group compared to the control. In the other side results shown that blood glucose was significant decreased ($p<0.05$) and the liver glycogen was increased in diabetic rats treated with polyherb and ZnNPs in D+ groups compared to the diabetic no treated group.

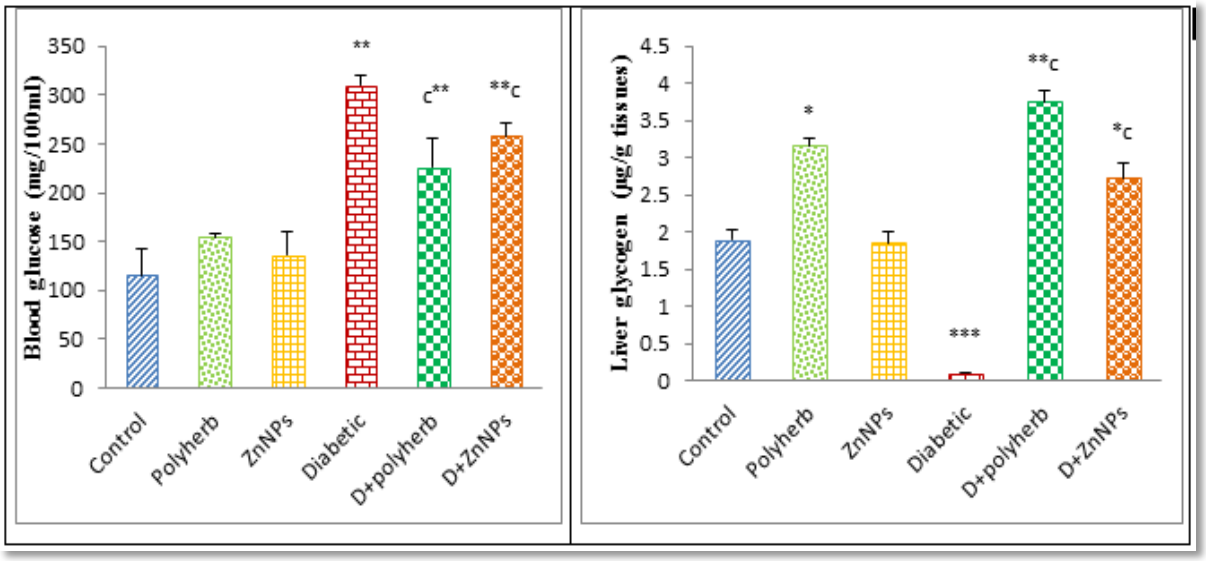

Figure 14: Blood glucose and liver glycogen levels of control and experimental group.
Values are mean ± SEM, n=4. * $p<0.05$, ** $p<0.01$, *** $p<0.001$: significantly different from control group. a $p<0.05$, c $p<0.001$: significantly different from Exp diabetic group.

In table 06, the results show a high increase in total cholesterol, triglycerids, creatinine and urea levels in diabetic group compared to control. Moreover, a significant amélioration of these markers in D+polyherb and D+ZnNPs groups compared to diabetic group. Results of transaminases enzymes activities appeared an increase significantly of GPT but not in GOT activity in diabetic group as compared to the control. In addition, a significant decrease in the level of GPT, in D+polyherb as compared to the diabetic group.

Table 06: Biochemical markers levels of control and experimental groups

paramètre	Control (n=4)	Polyherb (n=4)	ZnNPs (n=4)	Diabetic (n=4)	D+polyherb (n=4)	D+ZnNPs (n=4)
Urea (g/l)	0.38±0.04	0.41±0.03*	0.46±0.03***	0.79±0.25**	0.55±0.12^{**c}	0.47±0.11^{c}
Creatinine (mg/l)	7.15±0.65	7.27±0.96	5.07±0.96***	8.35±1.53*	7.32±1.17^{a}	6.57±0.51^{*c}
Cholesterol (g/l)	0.71±0.24	0.75±0.05	0.81±0.15	0.98±0.30**	0.97±0.28**	0.61±0.19^{c}
Triglyceride (g/l)	0.43±0.12	0.57±0.09**	0.41±0.03	0.87±0.38*	1.14±0.50**	0.57±0.16^{*b}
GOT (UI/l)	44.3±32.5	49.8±34.8	132±20.10	34.25±16.79	55.75±19.79	43.3±33^{b}
GPT (UI/l)	38.50±12.29	46±15.93	42.75±19.16	50.25±9.72**	45±22.03^{a}	54.75±15.85**

Values are mean ± SEM. * $p<0.05$, ** $p<0.01$, *** $p<0.001$: significantly different from control group. a $p<0.05$, c $p<0.001$: significantly different from Exp diabetic group.

II.3. Hematological markers

Concerning erythrocyte and leukocyte line markers, our results in table 07 show a very high significant decrease ($P<0.001$) in Red blood cell (RBC), Mean corpuscular volume (MCV) and high significant decrease ($P<0.01$) in hematocrit (HCT) percentage and no significant change ($P>0.05$) in White blood cell (WBC), Lymphocyte (LYM), PLT, and Hemoglobin **(**HGB), in diabetic group as compared to the controls. On the other hand, there is a very highly significant ($p < 0.001$) decrease in RBC and MCV values and highly significant ($p < 0.001$) increase of HCT in D+ Polyherb group when compared to diabetic group (Table …). Results obtained show also that MCV rates are significant elevate ($p <0.001$) in D+ZnNPs group compared to diabetic group.

Table 07: Leukocyte and Erythrocyte line markers level in control and experimental groups.

paramètre	Control (n=4)	Polyherb (n=4)	ZnNPs (n=4)	Diabetic (n=4)	D+Polyherb (n=4)	D+ZnNPs (n=4)
WBC (10^3/ul)	4.22±1.24	3.80±0.66	4.67±0.82	4.57±0.97	4.45±01.13	2.95±0.93^{**b}
LYM (10^3/ul)	3.40±0.97	2.70±0.52**	3.40±0.77***	3.10±0.82	3.02±0.46	2.22±0.59^{**b}
HGB (g/dl)	11.85±1.26	11.97±0.51	11.65±1.26	11.82±1.15	12.52±1.39	11.32±2.43
RBC (10^6/ul)	6.52±0.41	6.07±0.16**	6.23±0.44	5.63±0.21***	7.02±0.14^{***c}	6.09±1.19
MCV(fl)	55.02±1.38	49±0.99***	48.45±1.73***	48.12±0.90***	56.40±2.66^{c}	55.32±2.43^{c}
HCT(%)	34.67±3.92	30.05±1.39***	28.78±3.56**	29.65±2.64**	37.67±4.80^{b}	34±7.83
Platelet (10^3/ul)	713.7±133.6	476.8±76.6***	564.5±85.9**	671.8±109.9	632.8±100.4	499.5±97.0^{***b}

Values are mean ± SEM. * p<0.05, ** p<0.01, *** p<0.001: significantly different from control group. a p<0.05, c p<0.001: significantly different from Exp diabetic group.

II.4. Oxidative stress parameters

II.4.1. Malondialdehyde (MDA) concentration

Our results (Figure 15) illustrated that there were a significant increase of MDA level in diabetic group in liver (P<0.001), kidney (P<0.01), pancreas (P<0.001), and ovary (P<0.001) organs and very low variation of all tissues studies in polyherb and ZnNPs groups in comparison to control group. In addition as compared to diabetic rats, a significant decrease (P<0.001) of MDA level in the most of tissues studies was observed in D+polyherb and D+ZnNPs groups.

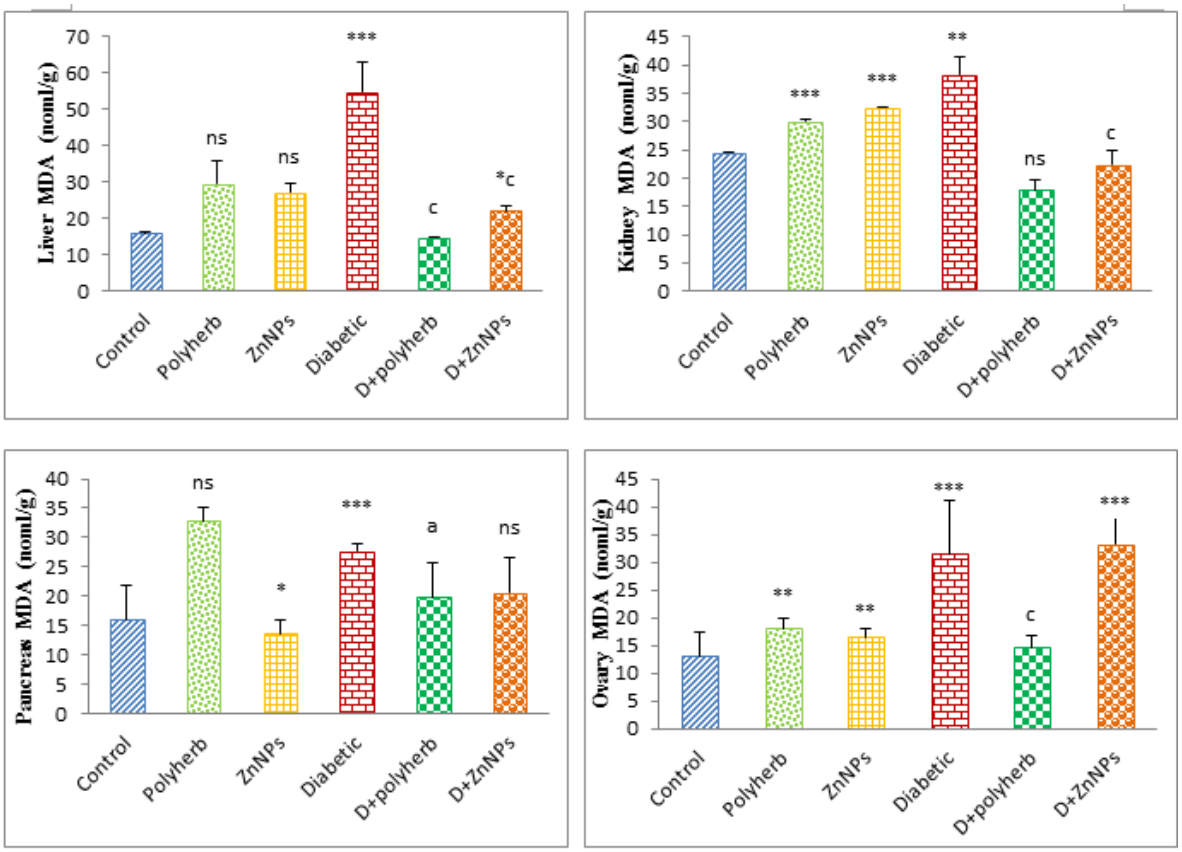

Figure 15: Tissular MDA concentration in control and experimental groups. * p<0.05, ** p<0.01, *** p<0.001: significantly different from control group. a p<0.05, c p<0.001: significantly different from Exp diabetic group. Values are mean ± SEM, n=4

II.4.2. Reduced glutathione (GSH) level

The results of GSH concentration in the tissues for the experimental group is presented in (Figure 16), as compared to the control there were a significant decrease (P<0.001) of GSH level in all tissues of diabetic groups except in Ovary organ when we observed a significant increase (P<0.01) of GSH level in diabetic group compared to control rats group. Furthermore, the tissues GSH concentration of different treatments groups were significantly increased as compared to the diabetic rats except in D+Polyherb group we observed a significant decrease (P<0.001) of GSH level in Ovary organ compared to diabetic group.

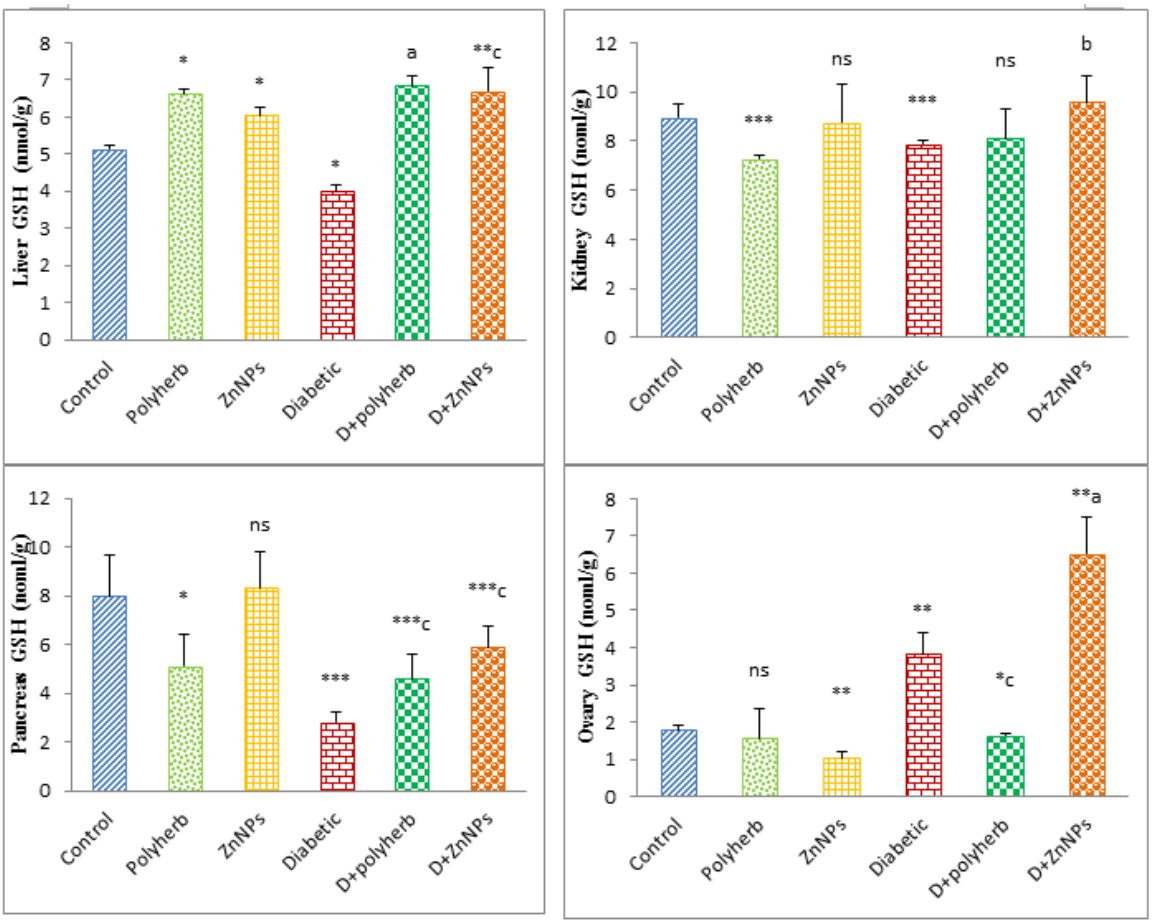

Figure 16: Tissular GSH concentration in control and experimental groups * p<0.05, ** p<0.01, *** p<0.001: significantly different from control group. a p<0.05, c p<0.001: significantly different from Exp diabetic group. Values are mean ± SEM, n=4

II.4.3. Superoxide dismutase (SOD) activity

The histogram results presented in (Figure 17) showed a significant decrease (P<0.001) of liver SOD activity and a significant increase of SOD in kidney and pancease and no significant change of Ovary SOD in diabetic animals as compared to the control. As well, the treatment by polyherb and ZnNPs induce a significant amelioration (P<0.001) in all tissues SOD activities. in comparison to diabetic rats.

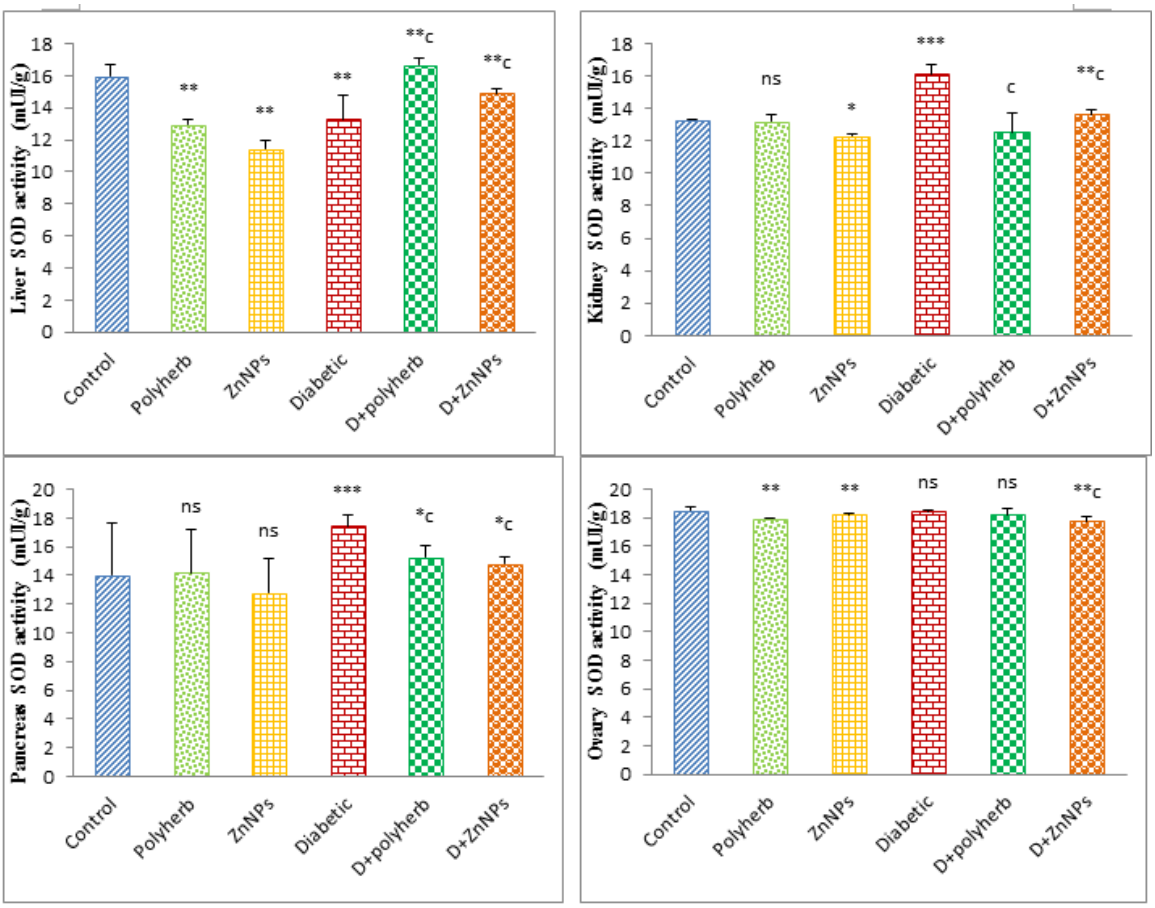

Figure 17: Tissular SOD activity in control and experimental groups * p<0.05, ** p<0.01, *** p<0.001: significantly different from control group. a p<0.05, c p<0.001: significantly different from Exp diabetic group. Values are mean ± SEM, n=4

II.5. Histological analysis

Completed the histopathological studies to determine the severity of diabetes and anti-diabetic effects of Polyherb and zinc nanoparticles (Figure 18). Microscopic examination of the pancreas tissues representing normal histological structure in the control whiles a massive alteration from hemorrhagic, inflammatory, vacualisation and necrosis in pancreas tissue structure of diabetic rats. Furthermore, the treatment by polyherb and ZnNPs improved the ameliorative effect of these histological alterations which have a similar structure from the control.

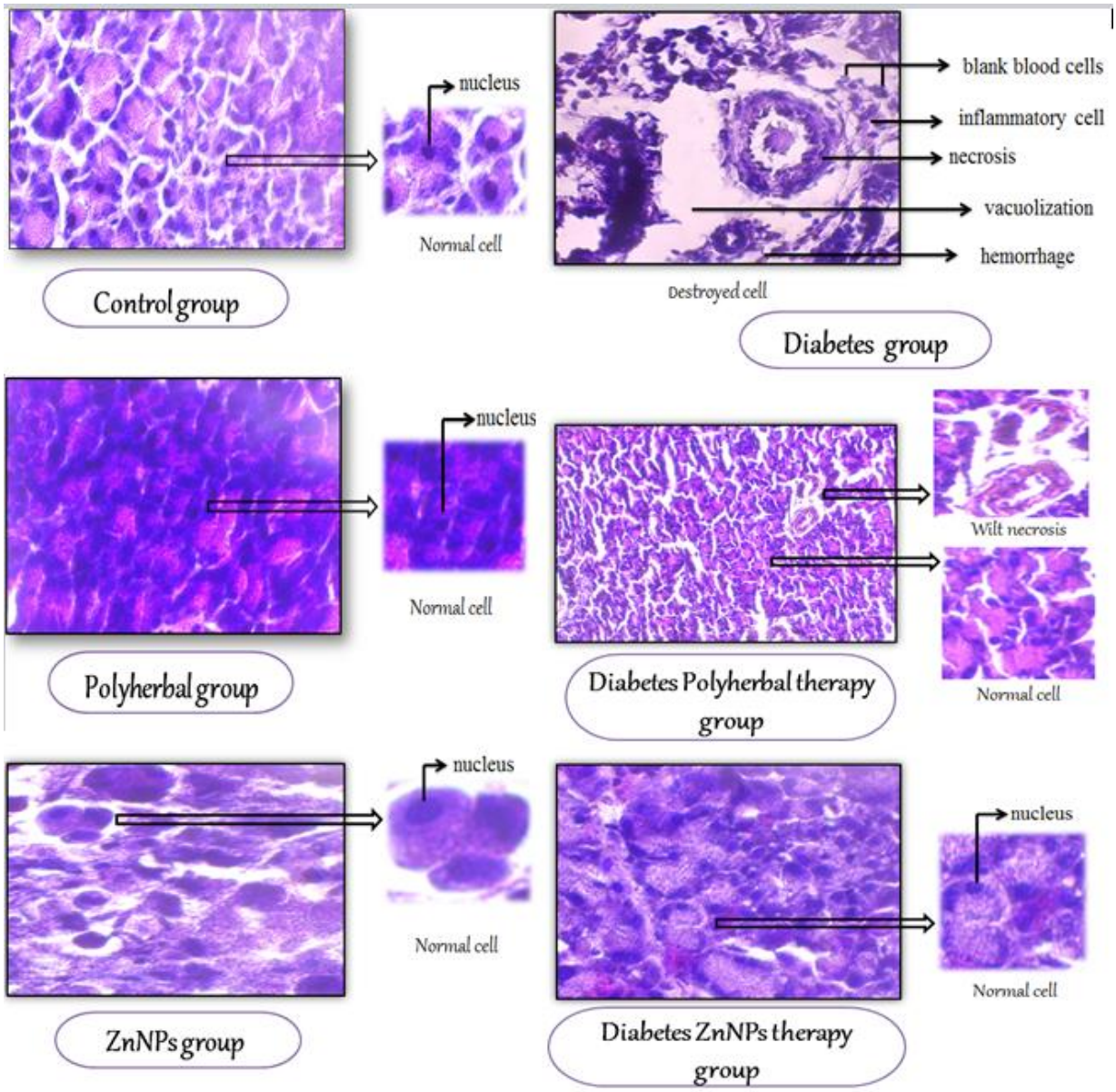

Figure 18: Photomicrograph of the pancreas tissues of control and experimental group (×40).

Chapter III
Discussion

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hypoglycemic disease resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association, 2009). Oxidative stress has been reported to play an important role in the pathogenesis of diabetes and its complications (Asmat et al, 2016). The objective of this work is the study of the antidiabetic and antioxydant activities of polyherb and Zn nanoparticles in rats.

III.1. Part one: in vitro study

III.1.1. Phytochemical Analysis

The results of the phytochemical analysis carried out on the various aqueous extract of the leaf of *Portulaca oleracea*, bark *Aquilaria malaccensis* and seed *Coriandrum sativum* as well as in the polyherb showed the presence of certain bioactive compounds. Saponins, tannins, terpenoids, phenol, alkaloids, flavonoids and reducing sugars have been found in our extracts. In addition, high levels of total polyphenols and flavonoids were estimated. The secondary metabolites produced by these plants have several interesting biological activities, and are sources of pharmacological ingredients active against several pathologies (Dias et al., 2012). Phenolic compounds are well known as antioxidants and directed against free radicals associated with oxidative damage. The presence of these compounds, such as tannins, flavonoids, and phenols in our extracts and polyherb likely to give credibility to its local use for the management of affection induced by oxidative stress. These compounds are interest for the prevention and treatment of various diseases including cancers, inflammatory diseases, diabetes, osteoporosis, cardiovascular and neurodegenerative diseases (Pandey et al., 2009). Tannins are responsible for the hemostatic properties. The presence of tannin suggested the ability of these plants to play a major role as an anti-diarrheal and antihemorrhagic agent (Ren et al., 2012). Therefore, the concentration of this compound can synergistically contribute in the important antioxidant power of this plant and thus can support the topical use for the treatment of the diseases related by radicals. Alkaloids and saponins have a history in pharmacological effects for their analgesic and antispasmodic effects. Thus, the alkaloid plays a detoxifying and antihypertensive role (Fomi et al., 2019).

III.2. Part two: : In vivo study

III.2.1. Study of the weight and relative weight of the organs

Regarding the relative weights of the organs, we notice nephromgaly, hepatic, pancreatic and ovarian hypertrophy. This increase in relative organ weight may be due to alloxan-induced necrosis and apoptosis (Novoselova et al, 2020). The results obtained show an improvement in the weight of the members of the herbal treatment group, and this is due to the presence of some active ingredients in the herb, which led to the reduction of alloxan toxicity and the reduction of the secondary effects of

diabetes on the organs (Shah et al., 2014). For the therapeutic effect of zinc oxide nanoparticles. Noticing an improvement in relative weights due to their size, morphology and porosity which will allow multifunctional power with its application in deferent areas. Metal nanoparticles are considered safe for applications because they are more stable and have essential properties. because it can serve as a useful catalyst for the reduction or elimination of toxic chemicals (Yaqoob et al., 2020) which eliminates the alloxan effect responsible for tissue hypertrophy.

III.2.2. Study of blood sugar and lipid profile

On the other hand, we found that the treatment by polyherb and zinc nanoform for 21 days could play a crucial role in lowering serum glucose, triglyceride and cholesterol levels in diabetic rats, these effects may be due to the presence of several bioactive compounds in this plants, agarwood is contains cafestols which is a type of di terpenes (Lezoul et al., 2020), Cafestols inhibits the synthesis of bile acids and reduces the rate of hepatic triglycerides, adiposity and fatty liver induced by the high fat diet and normalized blood sugar and insulin levels, reduced body weight gain (Alves-Bezerra et al., 2017), It is important to note that the constituents of medicinal plants sometimes play a primary role in improving their medicinal properties including hypoglycemic activity. According to our results the polyherb is very rich in flavonoids and terpenoids, these two molecules can influence pancreatic β cells by stimulating the secretion of insulin (Patel et al., 2012) by activating the enzyme SIRTUIN 1, an enzyme stimulating the signaling chain of insulin secretion, thus this enzyme plays a very important role in the sensitivity of peripheral cells to insulin (Zhou. et al., 2018). In addition, flavonoids inhibit glucose transporters in the intestines, decrease the expression of genes that control gluconeogenesis, increase glucose storage in the liver, and reduce glycogen breakdown. and the conversion to fatty acids at the hepatic level (Alkhalidy et al., 2018). Saponins form micelles with sterols such as cholesterol and bile acids. The hydrophobic part of saponin (aglycon or sapogenin) associates (lipophilic binding) with the hydrophobic sterol core in a stacked micellar aggregation (Moses et al., 2014). Saponins prevent the absorption of cholesterol by interfering with its enterohepatic circulation and by increasing the fecal excretion of cholesterol, which reduces the concentration of plasma LDL cholesterol. This effect is probably the result of the binding of saponin to cholesterol in the bile of the intestine and the prevention of its reabsorption (Jesch et al., 2017). Apigenin is the main compound of polyherb which improved dyslipidemia and hepatic steatosis. These beneficial effects were accompanied by a decrease in the activities of the hepatic enzymes controlling the synthesis of triglycerides and the esterification of cholesterol and by the increase in the expression of the hepatic genes involved in the oxidation of fatty acids (Jung et al., 2016). In addition, Studies have shown that zinc may play a role in improving peripheral insulin sensitivity, because it can potentiate insulin, which stimulates glucose transpor (Derouiche and Kechrid, 2018). Zinc also reduces glucose absorption and synthesis while promoting glucose metabolism and storage. This occurs primarily via the enhanced activity of key enzymes involved in these metabolic processes, such as

alpha-glucosidase, phosphofructokinase (PFK), phosphokinase (PK) and glycogen synthase (Derouiche et al., 2017).

III.2.3. Study of blood serum biochemical parameter

The results show a significant increase in serum urea and creatinine concentration in diabetic group compared to the control. In the diabetic state, hyperglycemia leads to kidney damage which in turn leads to poor renal filtration of urea and creatinine. Poor filtration leads to an increase in the level of urea and creatinine in the blood (Pandya et al, 2016). This can be explained by the accelerated degradation of hepatic and plasma proteins or the degradation of certain body protein compounds by proteolysis due to the administration of alloxan or of food compounds which can be degraded into amino acids and then into urea (Holeček, 2018). Polyherb significantly lowered blood sugar levels and therefore protected kidney tissue from damage that can be caused by prolonged hyperglycemia. hyperglycemia, and proteins modified by hyperglycemia, play a key role in the development of diabetic nephropathy and renal failure (Vallon et al, 2011). The decrease in renal parameters rate after administration of Zinc Oxide nanoparticles this explained by their protective effect. ZnO-NPs is a non-toxic element it has an antioxidant capacity which prevents or slows down oxidation by neutralizing free radicals, thus improving the functioning power of the tissue to stop the disruption of the cell membrane (Lobo et al., 2010).

The results show a significant increase in serum TGP activity in the diabetic group compared to the control group. This is explained by the destruction of hepatic cells (hepatic cytolysis) by toxic substances (hepato-toxic effect of alloxan) (Zebidi et al., 2018). In addition, the increase in transaminases is explained by the accumulation of amino acids such as alanine and glutamic acid in the blood resulting from the breakdown of proteins in the body. Thus, under the action of transaminases, these amino acids can be transformed into carboxylic compounds such as α keto-glutamic acid and pyruvic acid and then into glucose, which reflects the strong enzymatic activity of transaminases (Derouiche and Kechrid, 2016). So our results show that the treatment of diabetic rats with polyherb decreased the enzymatic activity of transaminases compared to untreated diabetic rats, which means that the polyherb inhibits liver damage caused by alloxane. Zinc treatment results in a correction of the enzyme activity of plasma GOT and GPT, which could be attributed to the anti-free radical / anti-oxidant and chelating efficacy of the metals of this element (Derouiche et al., 2017) and stabilization of the cell membrane. Consequently the zinc having protected the hepatic function of the poisoning with nickel, by their hepatoprotective effect in various toxic conditions. These results are in good agreement with those obtained by other studies which postulated the beneficial role of zinc on histological and enzymatic changes in rats (Tizhe et al, 2014).

III.2.4. Study of hematological analysis

Hematological parameters could be an important tool in the assessment of deleterious effect of drugs, as well as medicinal plants (Devaki et al., 2012). Regarding the results of the hematological study, our results showed a decrease in the number of red blood cells, hematocrit and mean globular volume in the diabetic rats against the control rats which signify a hematotoxicity revealed by anemia due to the toxicity of the blood cells. Demirtas et al., (2015) revealed that various hematological parameters and the immune system were reported to be altered during the course of diabetes. The occurrence of anaemia in diabetes mellitus has been reported due to the increased non-enzymatic glycosylation of RBC membrane proteins, which correlates with hyperglycemia (Gabreanu et al., 2016). Oxidation of these proteins and hyperglycaemia in diabetes mellitus causes an increase in the production of lipid peroxides that lead to haemolysis of RBC (Viskupicov et al., 2015). In addition, hyperglecemic environments in diabetics are at the root of many of the consequences including alterations in the structure, shape and function of red blood cells (Szablewski et al., 2017) showed that hyperglycemia increases the level of sorbitol in red blood cells, which interferes with the Na + / K + -ATPase pump, and consequently an osmotic imbalance sets in and leads to cell death (Diseases of the Nervous System, 2017). Thus, the results obtained show that the treatment with polyherb or ZnNPs in diabetic rats induced an improvement in the hematological parameters. Indeed, a polyherb protective effect has been revealed against hematotoxicity, and indicates that these plants can be protected against anemia. Polyherb containing polyphenolic compounds, which have high antioxidant activity, which may explain the decrease in lipid peroxidation and erythrocyte hemolysis. Moreover, The stimulation of RBC formation by zinc signal appears to be common among different animals. However, the zinc concentration for maximum activation of RBCs in rats, zinc is a strong signal common carp to stimulate erythropoiesis which explains this improvement.

III.2.5. Study of oxidative stress markers

Regarding the oxidative stress parameters, the results obtained show a decrease in GSH concentration and SOD activity and an increase in MDA level in the diabetic rats compared to the control rats. GSH forms the first line of defense against oxidative insults by acting as a non-enzymatic antioxidant. Its sulfhydryl (SH) group can interact directly with reactive oxygen species (ROS) or it can be involved in the enzymatic reaction of ROS detoxification as a cofactor or a coenzyme (Ulrich et al., 2019). Hyperglycemia associated with diabetes is a limiting factor for oxidative stress. In diabetes, when the glucose level increases, the hexokinase is then saturated and the excess glucose is partly metabolized via the polyol pathway in the insulin-independent tissues. Aldose reductase reduces glucose to sorbitol using as a cofactor NADPH, H^+ coming from the pentose-phosphate pathway and which will be oxidized to $NADP^+$. The expression of this enzyme appears to be increased in diabetes (Tang et al., 2012). Then the sorbitol dehydrogenase oxidizes a part of the sorbitol formed enfructose using

as cofactor NAD^+. Activation of the polyol pathway also induces an alteration in the redox potential of cells. The formation of sorbitol is accompanied by a decrease in NADPH resources to the detriment of other reactions which also require this cofactor. Among which glutathione reductase requires high levels of NADPH to reduce oxidized glutathione (GSSG) and thus restore endogenous levels of reduced glutathione (GSH) and thus results in the generation of oxidative stress in many tissues and thus contribute to pathogenesis diabetic complications (Espinosa-Diez et al., 2015). Oxidation of lipids makes membranes more rigid and therefore less fluid (Derouiche et al., 2020). The increase in MDA plays a very important role in the alteration of γ-glutamylcysteinesynthetas (γ-GCS), the enzyme responsible for the synthesis of glutathione (Lu, 2008). Furthermore, treatment diabetic rats with polyherb improved MDA, GSH and SOD levels in the tissues studied. Our results suggest that the plants constituting the polyherb possess antioxidant activity based on the elimination of free radicals and the restoration of the oxidant / antioxidant balance during diabetes. The presence of polyphenols and flavonoids in the polyherb could be responsible for the antioxidant activity. In addition, the activity of phenolic acids depends on the number and position of the (-OH) group and (-OCH3) groups (Szwajgier et al., 2013), and flavonoids inactivate and stabilize free radicals thanks to their grouping highly reactive hydroxyl (C3-OH). In addition, the drop in the rate of lipid peroxidation after treatment with polyherb may be due to the presence of antioxidants compounds in the extracts. Preliminary phytochemical screening tests for polyherbs reveal the presence of alkaloids, flavonoids, saponins and tannins. Some phytochemicals have antioxidant activity where they provide protection against damage and risk of developing metabolic diseases (Kibiti et al., 2015). Panche et al., revealed that potent molecule variety like flavonoids was present in the plant possesses significant antioxidant value and also possesses significant scavenging free radicals activity (Panche et al., 2016).

The treatment of diabetic rats with ZnNPs can improve antioxidant activity. Zinc is an essential metal playing an essential role in the defense against oxidative stress. All antioxidant enzymes require a cofactor to maintain their catalytic activity. Thus, mitochondrial SOD needs manganese but cytosolic SOD requires copper and zinc for their activity (Culotta et al., 2006). The mechanism of what could be the ZnNPs enter in the target cells where it dissociates and slowly but consistently released as Zn^{+2} ions (Siddiqi et al., 2018). It is well known that Zn is a powerful antioxidant metal; it is the core constituent of antioxidant enzymes such as SOD and a recognized protector of sulfhydryl groups (Kurutas et al., 2016). The antioxidant activity, which then detoxify the free radicals. These factors protect cells from ROS damaging (Djouadi and Derouiche, 2017).

III.2.6. Histopathological study

Histopathologic study of pancreas from diabetic rats showed almost complete destruction of B cells due to alloxan. This is due to the cytotoxic effect of alloxan, which behaves as a relative enzymatic inhibitor with negative consequences on

pancreatic exocrine secretion, a process accompanied by typical diabetes due to the defection of insulin secretion (Malaisse et al., 1982). Alloxane has been suggested to act as a diabetogenic agent due to its ability to destroy islet cells eventually through excessive free radical formation. Pancreatic β cells are susceptible to damage by oxidative damage generated by free radicals, due to low levels of free radical scavenging enzymes (Elsner et al., 2006). Administration of alloxan caused severe damage to the pancreas (β cells), such as decreased islet cell count, cell damage and death (Bahar et al., 2017). Histological sections of the pancreas of diabetic rats treated with polyherb and ZnNPs show the presence of the islands of Langerhans better delimited with very little cell necrosis. This could mean that the polyherb restored insulin secretion by regenerating Langerhans β cells destroyed by alloxan. This regenerative effect of the islands observed could be due to the presence of the anti-diabetic compounds revealed by the phytochemical study. Indeed, it has been reported that flavonoids had the ability to regenerate B cells in Langerhans and therefore restore insulin secretion in rats rendered diabetic by alloxan. Similarly, flavonoids and several other phenolic compounds have been tested as cytoprotectors and free radical chelators (Soares et al., 2017). Our polyherb solution comprises these families of molecules (flavonoids, triterpenes and tannins), and it is not impossible that one or the other or the synergy of all these compounds is responsible for the cellular (regeneration) of the islands of Langerhans. This observed islet protective effect may be due to enhanced activity of pancreatic antioxidant enzymes, which play a key role in the defense mechanism against pancreatic damage caused by free radicals (Ulusu et al., 2019). This polyherb has an antihyperglycemic effect through the regeneration of pancreatic islets and the secretion of insulin from intact B cells of the islets of Langerhans (Da-Silva, 2018). The presence of an improvement in pancreatic tissues in mice treated with ZnNPs indicates the effectiveness of zinc oxide in protecting pancreatic tissues from damage, which improves the rate of insulin secretion and reduces the metabolic damage caused by diabetes.

Conclusion & Perspectives

Conclusion

Diabetes is one of the oldest diseases known to mankind and its devastating impact is increasing day by day and reaching dangerously the level of an epidemic. Therefore, the main objective of this study was to evaluate the effect of a phytotherapy based on polyherb (Portulaca oleracea L, Coriandrum sativum and Aquilaria malaccensis) as well as treatment with zinc nanoparticles on alloxan-induced experimental diabetes in mice and its complications. inside the body. In conclusion, our data showed that:

The phytochemical findings demonstrate that aqueous extract of plants and polyherb very rich source of phenols, flavonoids, alkaloids, saponins, steroids, Carbohydrate, Catechic, Tannin and terpenoids. This allows us to discover a new source of bioactive molecules that have an important therapeutic effect against several pathologies, and has very important antioxidant activity, which may be linked to hypoglycemic activity.

The green synthesis of ZnNPs using polyherb refer to their potential properties as natural stabilizers of nanoparticles, which characterized by different methods; UV-VIS spectroscopy and FT IR spectroscopy. Also we may be classify these compounds as one of the important biological and medical molecules that can used in various fields due to the powerful in vitro stabilization of cell membrane, antiinflammatory and antioxidant activities.

Intra peritoneal injection of alloxan at 150 mg / kg of body weight in female rats induced disturbances in carbohydrate, lipid and protein metabolism, a process accompanied by histological alterations in the pancreas revealed by degeneration of the islets of Langerhans and cell death by necrosis which is observed by the microscope.

In contrast, our treatment of diabetic mice with polyherb and ZnNPs corrects these disturbances and improves resistance against diabetes and body weight in diabetic mice.

Regarding the lipid balance (cholesterol, triglycerides, ..), the treatment restored the values to normal, which reflects the protective effect of polyherb and ZnNPs against complications related to diabetes.

Polyherb and ZnNPs also protected kidney tissue from the effect of hyperglycemia and manifested as normal uremia and serum creatinine.

The polyherb and ZnNPs effect on liver function results in a significant restoration of liver function parameters; AST, ALT.

Polyherb and ZnNPs by its antioxidant action to decrease lipid peroxidation, all our treatments attenuated the oxidative damages by inhibiting ROS this activity results in the reduction of MDA levels in the organs studied, and to increase non-enzymatic antioxidant defense; reduced glutathione (GSH).

The ability of our treatment to protect high is not limited to the level of biological parameters, but extends to the microscopic level, which indicates its high protection in the stability of cells against pancreatic injury caused by diabetes mellitus. We shed the strong influence of ZnNPs and polyherb in our histological sections. This allows us to consider that these treatments have a potential effect on reducing hyperglycemia.

Finally, based on all of the above, we can conclude that the new approach Polyhere as well as ZnNPs have been shown to be highly effective against the symptoms of diabetes, in all aspects of biochemical, hematological, immunological, histological and oxidative stress, which opens up new avenues, which diabetic patients hope to The possibility of treating them and reducing their future risks.

Perspective

Given the importance of these findings, they open up prospects for experimental and other in-depth studies that will allow us to identify:

- ✓ Going to polyherb treatment in humans to reduce the severity of the disease and reduce these disorders.
- ✓ Conduct a sterile study of nanoparticles and further characterize them.
- ✓ Try to make a specific drug form from the polyherb approach.
- ✓ Improving the efficiency of the polyherb approach and evaluating the impact of its long-term use.
- ✓ We will try to examine the effect of these combination therapies (polyherb + ZnNPs).
- ✓ We will try to reveal all the compounds responsible for the organ function-promoting effect and their appropriate dosages as well as the cellular and molecular mechanism of these molecules to obtain a definitive anti-diabetic drug.

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Annex

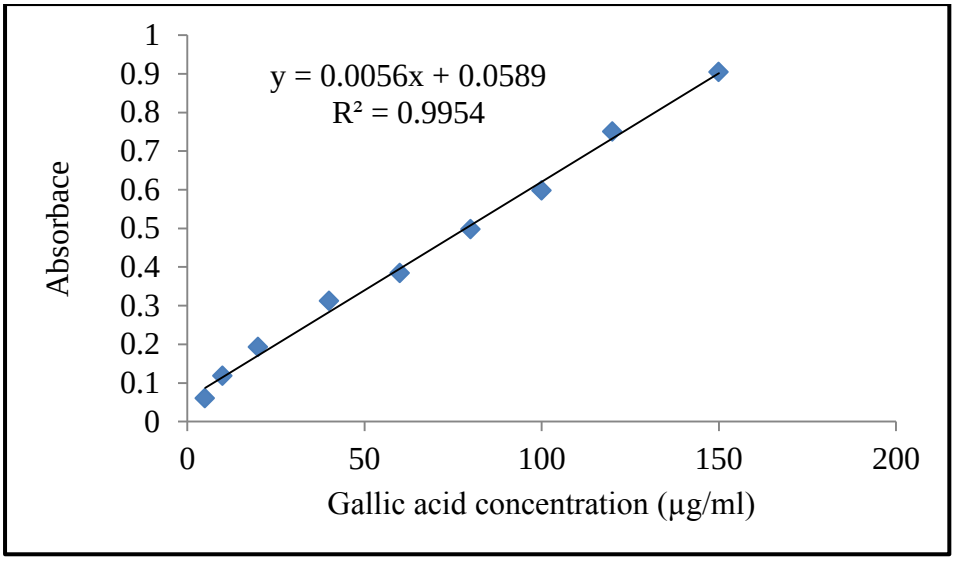

Figure: Gallic acid calibration curve for the determination of polyphenols.

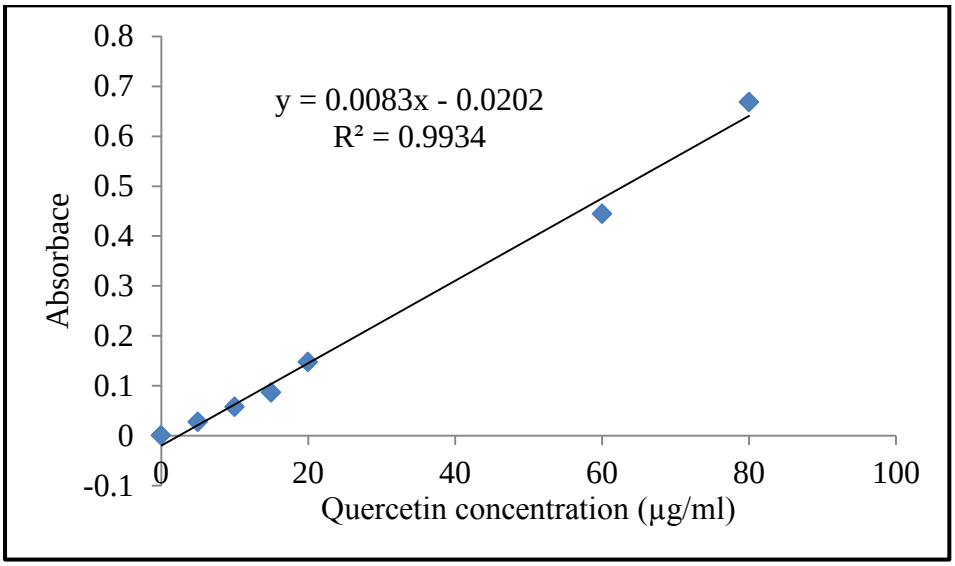

Figure: Quercetin calibration curve for flavonoid assays.

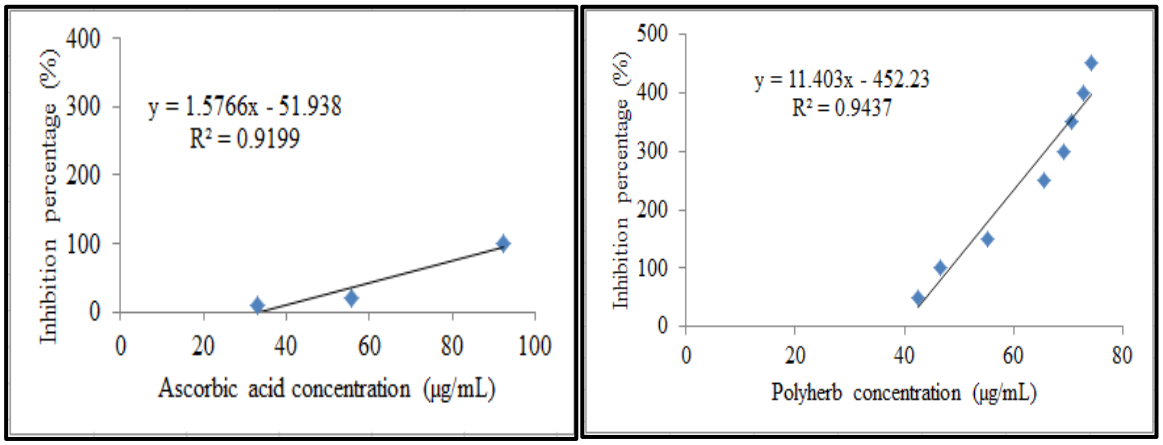

Figure: Inhibition percentage versus ascorbic acid and Polyherb concentrations for the determination of IC50 for FRAP activity.

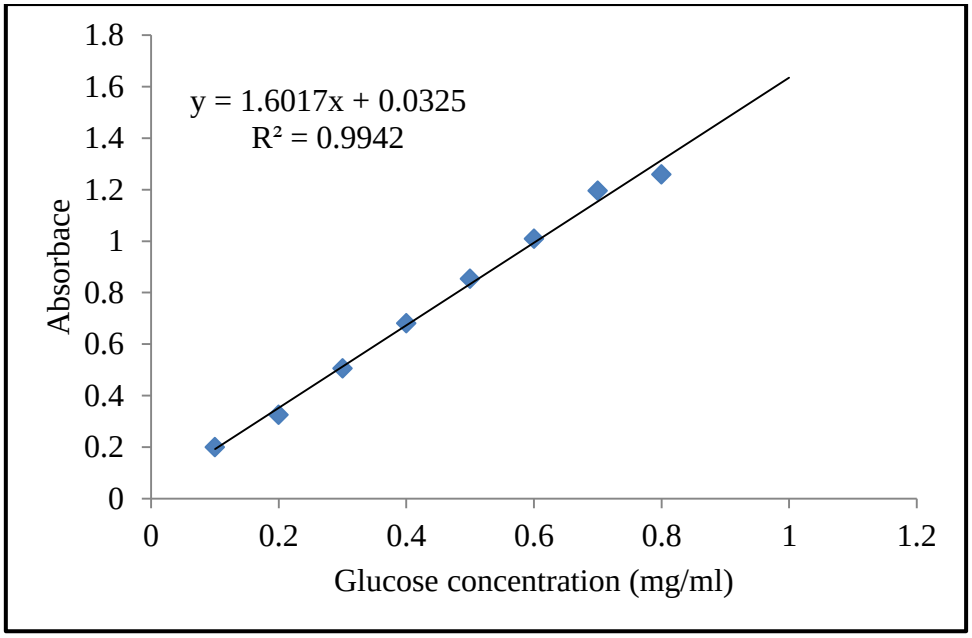

Figure: Glucose calibration curve for the determination of glycogen.