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Thème

الموضوع

Ackwledgment

"لَئِن شَكَرتُم لَأَزِيدَنَّكُم"

I thank Allah for all his blessings and grace upon me and for granting me success.

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Mr. Chaouch Rabeh.

Dedication:

I dedicate this humble work

To my dear parents

To all my family members

To all my friends

To everyone who cares about me

To everyone who helped and supported me

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List of Abbreviations

ALP	Alkaline phosphatase
ALT	Activities of plasma transaminases
AST	Activities of plasma transaminases
BHT	Butylate HydroxyToluene
CAT	Catalase
COX	Cyclooxygénase
Cu^{2+}	Copper ion
DNA	Desoxyribo Nucleotide Acid
DPPH	2,2'-diphenyl-1-picrylhydrazyl
Fe	Iron
Fe^{2+}	Iron ion
Fe^{3+}	Iron ion
G6PDH	Glucose-6-Phosphate Dehydrogenase
GPX	Glutathione Peroxidase
GR	Glutathione Reductase
GSSG	Oxidized Glutathione
H	Hydrogen atom
H^+	Hydrogen ion
H_2O_2	Hydrogen peroxide
HOCL	Hypochlorous acid
HPLC–ESI–QTOF-MS	High-performance liquid chromatography coupled to electrospray ionization quadrupole-time-of-fight mass spectrometry
IC_{50}	Concentration permettant d'inhiber 50 % du radical DPPH
IL-1	Interleukin-1
IL-10	Interleukin-10

IL-6	Interleukin-6
INOS	Oxyde nitrique synthase inductible
LDH	Lactate dehydrogenase
$LO^{\cdot}$	Pyroxil radical
$LOO^{\cdot}$	Pyroxil radical
mAbs	Monoclonal antibodies
Mg	Magnesium
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
$NADP^{+}$	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate
O_2^{-}	Superoxide radical
$OH^{\cdot}$	Hydroxyl radical
$R^{\cdot}$	Radical
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RSS	Reactive Sulfur Species
Se	Selenium
SOD	Superoxide Dismutase
STZ	Streptozotocin
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TNF	Tumorale Necrose Facteur
UV	Ultra Violet
WHO	World Health Organisation
Z. album	*Zygophyllum album*

Introduction

Introduction:

Chronic diseases are long-lasting health conditions that often progress slowly and can significantly impact the individual's quality of life. These diseases include diabetes, cardiovascular diseases, cancer, and strokes, and their development and progression is strongly related to oxidative.

Oxidative stress is a condition in which there is an imbalance between antioxidants and free radicals in the human body, leading to an excess of the latter which are highly reactive molecules that can cause considerable damage to cells, proteins, and DNA **(Durackova, 2008)**.

In cancer, oxidative stress can contribute to the development and progression of the disease by damaging DNA and promoting mutations. In diabetes, it damages the pancreatic cells and impairs insulin secretion. In cardiovascular disease, oxidative stress can contribute to the development of atherosclerosis and damage blood vessels.

While modern medicine has made great strides in managing chronic conditions, there is still a need for alternative therapies that can help prevent or treat these diseases. One alternative is the use of medicinal plants. Several studies have shown that natural compounds found in plants have the potential to prevent or treat chronic diseases due to their antioxidant, anti-inflammatory, and antidiabetic properties (**El-Attar et al., 2019)**. This has led to a renewed interest in plant-based therapies as a means of addressing chronic diseases.

These natural compounds called secondary metabolites are organic compounds that are produced by plants and other organisms for purposes like defense against predators, competition for resources, or attraction of pollinators. Some examples of natural compounds include alkaloids, terpenes, flavonoids, and phenolics.

Algeria is known for its rich flora, with over 4,500 plant species, making it one of the most biologically diverse countries in the Mediterranean region. The country's diverse geography, including mountain ranges, coastal plains, and desert landscapes, has contributed to the development of unique and diverse plant species. These plants have been used in traditional medicine for centuries due to their therapeutic properties, and are recently used in modern medicine as effective

alternatives. One of these plants is *Zygophyllum album*. Therefore this study we will Evaluate the oxidative stress effects on health, and define some types of diseases caused by oxidative stress, followed by an introduction of the *Z. album* characteristics as an endemic Algerian plant, and its antioxidant and biological activities.

Chapter 01

Oxidative stress and Antioxidant activity

1. Free radical and Oxidative stress:

A free radical can be defined as any species that contains one or more unpaired electrons **(Halliwell, 1988).** They are unstable and highly reactive and can abstract an electron from a stable compound transforming it into a free radical and proceeding as a chain reaction **(Lobo, 2010)**.

Free radicals are naturally produced in the body, as a derivative of metabolism (oxidation). They are essential to our well-being, having various regulatory roles in cells, and are divided into: Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and Reactive Sulfur Species (RSS) **(Finaud et al, 2006)**.

For example, ROS are produced during the process of respiratory burst and by immune cells (neutrophils and macrophages) to eliminate antigens **(Gomes, 2012)**. However, when free radical generation exceeds the capacity of antioxidant defenses, it results in oxidative stress **(Yoshikawa, 1993)**.

2. Reactive Oxygen Species:

Superoxide (O_2^-): In various ways, Superoxide is produced by adding a single electron to an oxygen molecule and it can be generated within a living organism, several molecules, including adrenaline, flavine nucleotides, thiol compounds, and glucose, can oxidize in the presence of oxygen to produce superoxide. The electron transport chain in the inner mitochondrial membrane reduces oxygen to water. Some of these radicals leak into the mitochondrial matrix, resulting in the formation of superoxide **(Young et al., 2000)**.

Hydroxyl radical ($OH^{\cdot}$): Hydroxyl radical is the most reactive radical known to chemistry. It can attack and damage almost every molecule found in living cells due to its high reactivity. $OH^{\cdot}$ only lasts for a few microseconds before it reacts with the molecule in its immediate vicinity, it can attack DNA causing chemical alteration of the bases (can lead to mutations). It also attacks the fatty acid sidechains of the membrane phospholipids when generated close to membranes, this reaction is known as Lipid peroxidation **(Halliwell, 1989)**.

Hydrogen peroxide(H_2O_2): Hydrogen peroxide is produced when Superoxide dismutase (SOD) removes O_2^-.This dismutation reaction is shown below:

$O_2^{-} + O_2^{-} + 2H \longrightarrow H_2O_2 + O_2$

Hydrogen peroxide is one of the most toxic oxygen species because the absence of charge makes it pass through cell membranes easily **(Halliwell, 1989)**.

The other free radical families that exist, such as reactive nitrogen species and reactive sulfur species are summarized in the table below:

Table 01: Classification and main effects of free radicals **(Finaud et al., 2006).**

Free Radical	contraction	Half-life	Main effects
Reactive oxygen species	ROS		
Super ion	O_2^{-}	10^{-5} sec	Lipid oxidation and peroxidation Protein oxidation DNA damage
Ozone	O^3	Stable	
Singlet oxygen	$_1O_2$	1 µsec	
Hydroxyl radical	OH•	10^{-9}sec	
Hydrogen peroxide	H2O2	Stable	
Hypochlorous acid	HOCl	Stable	
Alkoxyl radical	RO•	10^{-6}sec	
Peroxyl radical	ROO•	7 sec	
Hydroperoxyl radical	ROOH•		
Reactive nitrogen species	RNS		
Nitric oxide	NO•		Lipid peroxidation DNA damage Proteins oxidation
Nitric dioxide	NO_2•	1-10 sec	
Peroxynitrite	ONOO•$^{-}$	0.05-1 sec	
Reactive sulphur species	RSS		
Thyil radical	RS•		Protein oxidation DNA damage ROS production

3. Sources of Active Oxygen Species:

3.1. Internal sources:

Free radicals can be vital molecules within the human body and are needed in so many functions like:

a. **The immune system:** In the immune system, leukocytes like macrophages and neutrophils are in charge of destroying antigens and producing O_2^{-} with NADPH, this reaction is called oxidative burst and needs two O_2 molecules.

$$2\ O_2 + NADPH \longrightarrow 2\ O_2^{-} + NADP^{+} + H^{+}$$

O_2^{-} can be converted to H_2O_2 by SOD, the H_2O_2 can be transformed into Hypochlorous acid (HOCL) which is very active for antigen degradation **(Finaud et al., 2006)**.

b. The Mitochondria: Mitochondria is considered the main source of ROS in the body, it produces about 90 % of the ROS through cellular metabolism and the respiratory chain.

The “NADH-ubiquinone oxidoreductase” and “ubiquinone-cytreductase” are considered Mitochondria enzymes that produce O_2^{-} and H_2O_2.

4% of the O_2 in the mitochondria is turned into O_2^{-}, while the self-oxidation of ubisemiquinone is one of the main sources of O_2^{-} in the electron transport chain within the mitochondria by returning ubiquinone according to the following reaction **(Finaud et al., 2006)**:

$$\text{Ubiquinone} + e^{-}\ \text{Ubisemiquinone} + O_2 \longrightarrow \text{Ubiquinone} + O_2^{-}$$

3.2 External sources:

Free radicles can also be produced from environmental factors (external sources) like UV light, pollution, radiation, and heavy metals (mercury, lead…). The diet can also increase the production of free radicals, and so does the excessive consumption of alcohol and some medicines **(Martemucci, 2022)**.

4. The negative effect of ROS:

Despite some helpful effects, ROS have possible harmful effects because they can alter the size and the shape of the compounds they interact with;

On lipids: Cell membranes contain large amounts of lipoproteins and phospholipids, which are rich in unsaturated fatty acids, and are exposed to free radicals leading to lipid superoxidation. Lipid superoxidation changes the fluidity of cell membranes, reducing the capacity to maintain an equilibrated gradient of concentration, and increasing membrane permeability **(Finaud et al., 2006)**.

On proteins: Proteins such as enzymes or receptors, are molecules that are so sensitive to the action of oxygen free radicals that they lose their biological properties. Oxidized proteins became fat-soluble by removing ionized amine

groups or the central hydrophobic regions leading to the formation of abnormal lipid accumulations on membranes or around cells **(Finaud et al., 2006)**.

On DNA: ROS can also break DNA strands, damaging them which requires basic repairs. Although the DNA repair system is continuous, its capacity can be overreached or the repair processes can be altered. As a result, DNA oxidation can provoke mutagenesis which is a major contributor to human cancer and cell aging **(Finaud et al., 2006)**.

5. The antioxidants:

Antioxidants are endogenous or exogenous molecules, capable of preventing, delaying, and reducing oxidative destruction of biomolecules in low concentration and prohibit oxidizing chain reactions. This definition includes compounds of an enzymatic as well as a non-enzymatic nature **(Durackova. 2008, Belmimoun, 2016)**.

5.1. Enzymatic antioxydants:

All cells in eukaryotic organisms use powerful antioxidant enzymes to protect themselves against the generation of ROS. The three major classes of antioxidant enzymes or primary antioxidants are superoxide dismutases, catalases, and glutathione peroxidases(GSH) **(Durackova, 2008)**.

5.1.1 Primary antioxidants:

a. <u>Superoxide Dismutases (SOD):</u>

SOD is the first defense line against superoxide and oxidative stress. It removes O_2^- by converting it into hydrogen peroxide H_2O_2 and oxygen O_2 **(Halliwell, 1989).**

$$2\ O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$$

There are Different forms of SOD present in the body, Manganese (present in mitochondria), Copper, and Zinc (present in the cytosol) act as a cofactor **(Finaud et al., 2006)**.

b. <u>Catalase (CAT)</u>:

CAT is present in every cell, particularly in peroxysomes; cell structures that use oxygen to detoxify toxic substances and produce H_2O_2 **(Finaud et al., 2006)**.

It also transforms the hydrogen peroxide into water and molecular oxygen **(Belmimoun, 2016)**.

$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

c. Glutathione peroxidase (GPX):

GPX is the most efficient antioxidant for removing H_2O_2 since it is located in the same subcellular organelles as SOD. Distinctively, it is the only human enzyme known that requires the element selenium for its activity **(Halliwell, 1989)**.

GPX transforms H_2O_2 into water, this reaction uses GSH and transforms it into oxidized glutathione (GSSG).

Table 02: Localisation and actions of antioxidant enzymes (**Finaud et al., 2006).**

Antioxidants	Cofactors	Cellular localisation	Targets
Mn-SOD	Manganese	Mitochondria	Anion superoxide Peroxynitrite
Cu-Zn-SOD	Copper Zinc	Cytosol – mitochondria (membrane)	Anion superoxide Peroxynitrite
CAT	Iron	Peroxysome, cytosol and mitochondria	Hydrogen peroxide
GPX	Selenium	Cytosol and mitochondria	Hydrogen peroxide Peroxynitrite

CAT = catalase; **GPX** = glutathione peroxide; **SOD** = superoxide dismutase.

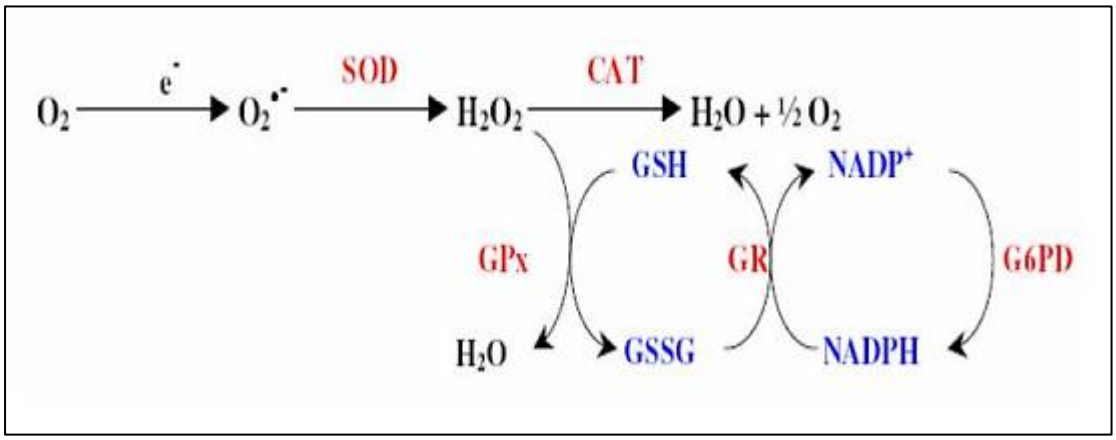


Figure 01: Total reactive mechanism summarizing detoxification by various antioxidant enzymes **(Kanoun, 2011)**

5.1.2 Secondary antioxidants:

Secondary antioxidants include glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PDH). The glutathione reductase (GR) renovates the GSH from the GSSG, this reaction needs NADH:

$$GSSG + NADPH+H^+ \longrightarrow 2GSH+ NADP^+$$

This reaction produces $NADP^+$, which is converted to NADPH by G6PDH **(Mamta et al., 2014)**.

5.2. Non-Enzymatic antioxidants:

5.2.1 Minerals:

Minerals are essential for the proper functioning of enzymes in the body's cells. They act as cofactors for enzymatic antioxidants and their absence can affect the metabolism of many macromolecules **(Mamta et al., 2014)**.

Some important minerals include iron, manganese, selenium, copper, and zinc.

Iron (Fe): Is the most abundant trace metal that binds with proteins in the biological system however the total of free iron is deficient. The low concentrations of iron-binding proteins promote ROS production, lipid peroxidation, and oxidative stress **(Mamta et al., 2014)**.

Magnesium (Mg): Is a cofactor for glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase. A magnesium deficiency reduces glutathione reductase (GR) activity therefore GSSG does not convert to GSH, causing oxidative damage to the cells **(Mamta et al., 2014)**.

Selenium (Se): Is also a very important component of enzymatic antioxidants. In the presence of selenium, glutathione peroxidase protects the cell membrane by stopping the oxidation of lipids and takes part in H_2O_2 and lipids hydroperoxide metabolism. Hence, Se behaves like vitamin E, possibly replacing it, and can be used to prevent the risk of cancer and cardiovascular diseases **(Mamta et al., 2014)**.

5.2.2 Vitamins:

Vitamin E: Vitamin E is a fat-soluble vitamin consisting of several isoforms known as tocopherols. This Vitamin is the most important chain-breaking antioxidant because of its ability to act directly on ROS and its abundance in cells and mitochondrial membranes. Vitamin E plays an important role in cell membranes as it stops lipid peroxidation, and interacts with numerous antioxidants such as vitamin C, and GSH, those antioxidants can regenerate vitamin E from its oxidized form **(Finaud et al., 2006)**.

Vitamin C: Vitamin C is a water-soluble vitamin and is an effective antioxidant in extracellular fluids and the cytosol. It is more abundant in tissues where there is a high production of ROS. In fluids, vitamin C can neutralize $OH^{\bullet}$, $O_2^{\bullet-}$, and fatty acid peroxyl radical ($LOO^{\bullet}$). Inside cells, vitamin C reinforces the action of vitamin E and GSH by regenerating their active form after reacting with ROS. It can also trap copper ions, which have a powerful oxidant action **(Finaud et al., 2006)**.

Vitamin A: Vitamin A is a fat-soluble vitamin present in many lipid substances. β-carotene, present in cell membranes, is converted into vitamin A when the body needs it. Although its mechanism *in vivo* is unclear it is less important than vitamin E in the antioxidant system. β-carotene is suggested to deactivate ROS and reduce lipid peroxidation **(Finaud et al., 2006)**

5.2.3 Polyphenols

Polyphenols are a class of phytochemicals that possess marked antioxidant activities. These activities depend on their chemical and physical properties which in turn regulate the metabolism depending on their molecular structures **(Mamta et al., 2014)**.

Flavonoids: Flavonoids are phenolic substances formed in plants from malonate, tyrosine, and amino acids phenylalanine. In *vitro*, flavonoids can inhibit pro-oxidant enzymes or form complexes with pro-oxidant ions such as Fe^{2+}, Fe^{3+}, or Cu^{2+}. Flavonoids also have direct trapping action upon some ROS by direct hydrogen atom donation **(Finaud et al., 2006)**.

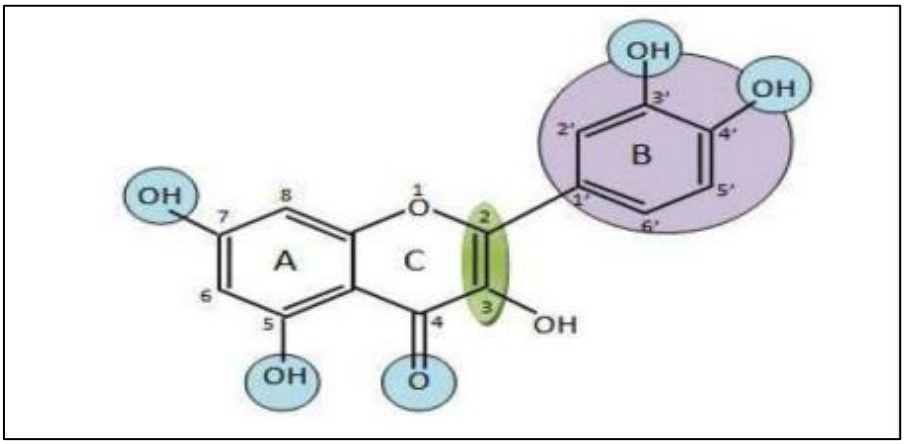


Figure 02: Active sites in the antioxidant activity of flavonoids (**Cazarolli et al., 2008)**

Flavonoids have a special structure that enables them to interact with root species and give them greater stability. As flavonoids return oxygen radicals ($R^{\cdot}$) such as $OH^{\cdot}$, O_2^{-}, $LOO^{\cdot}$, and $LO^{\cdot}$ by transporting hydrogen or electrons, the oxidizing products (flavonoid radicals) interact with each other to produce a stable quinine structure **(Pietta, 2000)**.

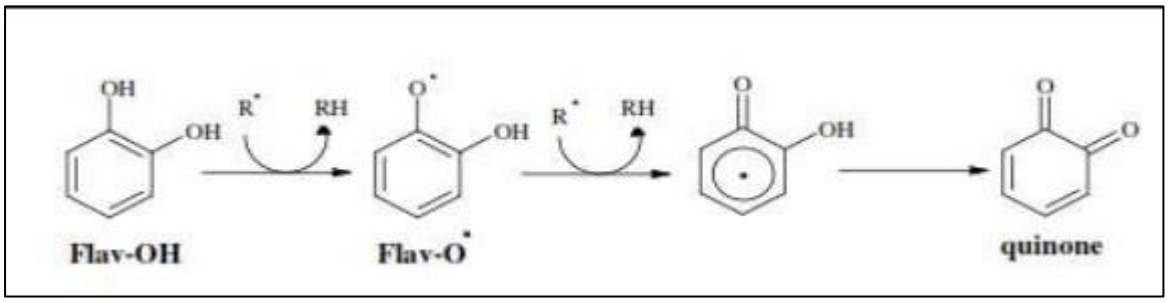


Figure 03: The interaction of flavonoids with each other **(Pietta, 2000)**.

Chapter 02

Diseases and Biological activities

I. Cancer:

1. Definition:

Cancer is a leading cause of death globally, accounting for approximately 10 million deaths worldwide. According to WHO one in every six deaths is caused by cancer **(Rehman et al., 2020)**.

Cancer is a disease of the genome, classically described as multiple successive clonal expansions driven by the accumulation of genomic changes or mutations that are preferentially selected by the tumor environment **(Yates et al., 2012)**. In other words, cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells **(Abbas, 2023)**.

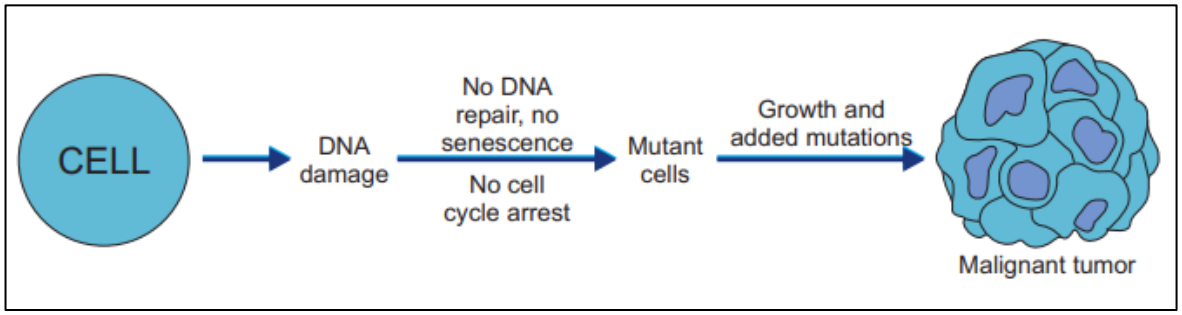


Figure 04: Simplified depiction of how a cell undergoes malignant change.

2. The causes of cancer:

The causes of cancer are diverse, complex, and partially understood, many things are known to increase the risk of cancer, including dietary factors, certain infections, lack of physical activity, obesity, and environmental pollutants, these factors may act together to initiate or promote carcinogenesis in the human body (**Didier et al., 2023**).

One key contributor to cancer development is oxidative stress. It has been implicated in carcinogenesis through several mechanisms, including lipid peroxidation, DNA damage, and its impact on both tumor suppressor genes and oncogenes. Tabaco, Asbestos, Arsenic, Radiation such as Gamma and X-rays, UV light, and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to these carcinogens, free radicals are formed,

damaging cells and affecting their ability to function normally and causing cancer. The mentioned disease can affect many organs like the lungs, liver, colorectal, stomach, breast, etc **(Didier et al., 2023)**.

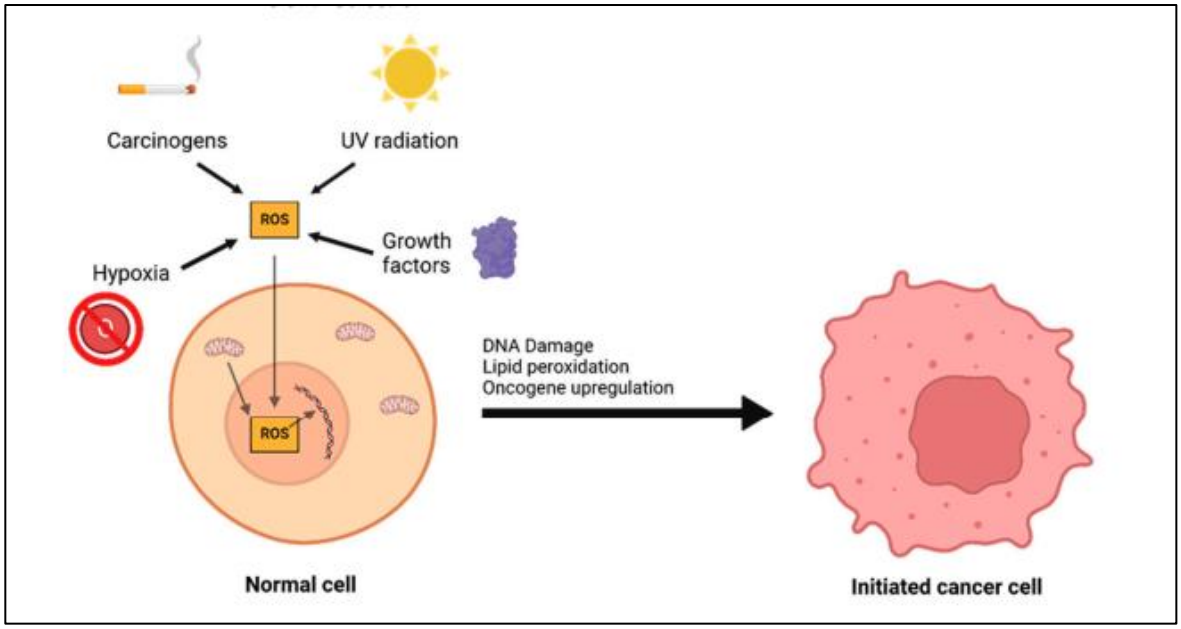


Figure 05: Some environmental and chemical factors that cause cancer

3. Cancer treatment:

3.1 Conventional treatment:

Surgery: Surgery can be used to diagnose, treat, or even help prevent cancer. Most people with cancer will have some kind of surgery. In cases where the cancer has not spread to other parts of the body, surgery can have a high chance of cure **(National Cancer Institution, 2015)**.

Chemotherapy: Chemotherapy is one of the most widely used strategies for cancer treatment, performed by using anticancer drugs that can specifically kill the cancerous cells without affecting the non-cancerous cells **(Rehman et al., 2020)**.

Radiation Therapy: Radiation therapy involves the use of ionizing radiation to treat cancer. It can be used as the primary treatment or as an additional therapy before or after surgery. Ionizing radiation works by forming free radicals that cause damage to DNA and lead to cell death. The radiation beam is carefully shaped to minimize damage to surrounding healthy tissues **(National Cancer Institution, 2019)**.

3.2. Modern treatments:

Stem Cell Transplant: Stem cells are undifferentiated cells present in the bone marrow (BM) with the ability to differentiate into any type of blood cells. Stem cell transplants are often used to treat people with cancers affecting their blood cells, such as leukemia and lymphoma. They do not usually work against cancer directly, Instead, they restore the body's ability to produce new blood cells after treatment with very high doses of chemotherapy or radiation therapy **(National Cancer Institution, 2023)**

Monoclonal antibodies: Monoclonal antibodies (mAbs) are one of the most effective strategies for treating patients suffering from hematological malignancies and solid tumors. These antibodies are man-made versions of immune system proteins administered intravenously to attack certain targets on cancer cells. Their mechanisms of action are recruiting host immune functions to attack the targeted cell, and binding to ligands or receptors thereby interrupting essential cancer cell processes **(Dejene, 2021)**.

4. Anti-cancer activity:

Cancer treatments such as chemotherapy and radiation often come with significant side effects that can be challenging for patients to endure. These side effects may include nausea, hair loss, and fatigue. While these treatments are effective in targeting cancer cells, it is important to continue researching and developing alternative therapies that can minimize these side effects while still effectively combating cancer **(Rehman et al., 2020)**.

Certain medicinal plants contain secondary metabolites such as alkaloids (vinblastine, vincristine, and camptothecin), terpenoids (lycopene and gamma-tocopherol), polyphenols (etoposide, resveratrol, curcumin, and epigallocatechin gallate), and flavonoids (apigenin, genistein, and kaempferol) that can help prevent cancer **(Wusirika et al., 2021)**.

These bioactive compounds can exert anticancer effects independently or in combination with other compounds by regulating metabolic and signaling pathways, inhibiting crucial enzymes for cancer progression, inducing apoptosis, and impacting angiogenesis and microtubule assembly. Additionally, they play a

critical role in regulating cell cycle arrest in the G2/M phase and are involved in DNA repair through the activation of ribonucleotide reductase **(Kojima et al., 2015)**.

Antioxidants: As mentioned oxidative stress is a major contributor to cancer, antioxidants such as vitamins, polyphenols, and plant-derived bioactive components can protect the body against the initial stages of cancer development. **(Didier et al., 2023)**.

Vitamins may also have a regulatory effect on certain components of the tumor microenvironment. For instance, vitamin E has been found to activate immune responses by dendritic cells and reduce the suppression of cytotoxic T-cell activation by myeloid-derived suppressor cells in leukemia **(Didier et al, 2023)**.

II. Diabetes:

1. Definition:

Diabetes, often referred to by doctors as diabetes mellitus, is a metabolic condition in which the person has consistently elevated amounts of glucose in the blood (blood sugar), either from a lack of insulin secretion, failure to respond well to it, or both **(Suresh, 2016)**.

According to WHO, 25.8 million people, 8.3% of the population have diabetes, approximately 18.8 million are diagnosed while 7 million remain undiagnosed.

2. Types of diabetes:

Diabetes can be broken down into two primary subtypes: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Type 1 diabetes can occur at any age, most often diagnosed in children, adolescents, or young adults **(Suresh, 2016)**. It occurs when the pancreatic Beta cells produce little to no insulin, causing the glucose to build up in the bloodstream, instead of going into the cells leading to hyperglycemia **(Dahlquist, 1998)**.

The exact cause of type 1 diabetes remains unknown, but it is believed to be an autoimmune disorder, possibly triggered by oxidative stress; the pancreatic β-cells

are attacked and destroyed by CD4+ and CD8+ cells as well as macrophages, leading to a deficiency in insulin production. Besides, pancreatic α-cells start to function abnormally and secrete an excessively large amount of glucagon, which further aggravates the metabolic disorders already caused by insulin deficiency **(Imam, 2015).** Patients with type 1 diabetes will need to take insulin injections for the rest of their lives **(Suresh, 2016)**.

Type 2 diabetes occurs when the fat, liver, and muscle cells do not respond correctly to insulin, this is called insulin resistance, and as a result, blood sugar accumulates in the bloodstream leading to hyperglycemia. Since increased fat makes it harder for the body to use insulin correctly, type 2 diabetes develops slowly over time and it is often diagnosed in overweight individuals. Low activity, poor diet, and excess body weight are common contributing factors to the development of the disease. Contrary to popular belief type 2 diabetes can also develop in thin people, this is more common in the elderly. Genetics and family history play a role in type 2 diabetes **(Victor et al, 2014)**.

Neuropathy, nephropathy, retinopathy, and kidney disease are secondary symptoms resulting from the oxidative stress damage caused by reactive oxygen species (ROS) which are generated due to hyperglycemia **(Victor et al, 2014)**.

Patients with diabetes (both types) typically experience; fatigue, hunger, increased thirst, and urination, blurry vision, and pain or numbness in the feet or hands **(Suresh, 2016)**.

3. Diabetes treatment:

Insulin therapy:

Insulin is the oldest treatment of the currently available medications, and therefore the treatment with which we have the most clinical experience. It is also the most effective at lowering glycemia. All patients with T1D need insulin treatment permanently and many patients with T2D will require insulin as their β-cell function declines over time. Insulin therapy should begin with diet, weight reduction, and exercise. Even though insulin is an effective diabetes treatment, it has some side effects like hypoglycemia, weight gain, and the risk of Malignancy **(Imam, 2015).**

Pancreas transplantation:

Pancreas transplantation continues to evolve as a strategy in the management of diabetes. In most cases, pancreas transplantation is performed on individuals with T1D with end-stage renal disease. The majority of pancreas transplantations are simultaneous pancreas-kidney transplantations. The prognosis after pancreas transplantation is excellent, with over 95% of patients still alive and 80-85% of the pancreas remaining functional one year post-transplant **(Imam, 2015).**

Islet Cell Transplantation:

Islet transplantation is the transplantation of isolated islets from a donor pancreas. It is an experimental treatment for T1D. Once transplanted, the islets begin to produce insulin, actively regulating the level of glucose in the blood. Islets are usually infused into the patient's liver. Since the body perceives islet tissues as foreign, the patient needs to undergo treatment with immunosuppressants **(Imam, 2015).**

4. Antidiabetic activity:

Despite having a good number of commercially available anti-diabetic drugs, the side effects delimit their unquestionable implications. In contrast, nutraceuticals and phytomedicines offer a low incidence of adverse effects that can be a fantastic alternative to regular drugs in combating diabetes and its related complications **(Saeid, 2017)**.

Polyphenols found in herbal products rich in flavonoids, and terpenoids, have been shown to have antidiabetic properties. These compounds are capable of reducing oxidative stress and inhibiting carbohydrate-hydrolyzing enzymes, thus helping to prevent hyperglycemia and reduce blood glucose levels **(Ruiz et al., 2013)**.

III. Inflammation:

1. Definition:

Inflammation is a vital part of the body's immune response. It is the body's way of signaling the immune system to heal and repair damaged tissue, as well as

defend itself against foreign invaders, such as viruses and bacteria. Without inflammation, wounds would fester, and infections could become deadly. **(Trabsa, 2015)**.

2. Types of inflammation:

Inflammation can be classified as either acute or chronic. Acute inflammation is the immediate response of the body to an aggressor agent. It is characterized by intense vasculoexudative phenomena, by a strong presence of polymorphonuclear at the level of the inflammatory focus **(Serhan et al., 2010)**.

Acute inflammations heal spontaneously or with treatment but can leave sequelae if tissue destruction is significant. The stages of this inflammatory response are always the same regardless of the inflammatory stimulus and the inflamed tissue, acute inflammation occurs in three phases: the vascular phase, the cell phase, and the resolution phase. Vascular changes characterized by pain, redness, heat, and swelling allow leukocytes to accumulate in the inflamed tissue and trigger the cell phase **(Trabsa, 2015)**.

Polynuclear cells are the first to migrate to the inflamed site, followed by monocytes and lymphocytes. Chemo-attractant substances guide them and help destroy the pathogen. Macrophages later cleanse the inflammatory focus and eliminate debris **(Wagner et al, 2000)**.

The repair phase is important and its intensity is related to the degree of cell destruction, macrophages complement the action of neutrophils and play a role as antigen presenters and repairers. Endothelial cells repair the endothelium using various molecules, macrophages and fibroblasts also participate in this process **(Gilroy et al, 2008)**.

However, inflammation can also be harmful when it becomes chronic, the persistence of the inflammatory reaction and the disruption of its physiological control lead to chronic inflammation. Excessive leukocyte infiltration and poor elimination of the causative agent contribute to its development. Chronic inflammation is also associated with certain autoimmune diseases and is characterized by a long duration, it has been linked to heart disease, diabetes, and arthritis. It can also play a role in cancer and other conditions **(Trabsa, 2015)**.

Many factors can contribute to chronic inflammation, including long-term exposure to environmental toxins, poor diet, stress, and autoimmune disorders **(Calder, 2016)**.

Mediators of inflammation:

The table below **(Table 03)** summarizes some inflammation mediators **(Trabsa, 2015).**

Mediators	Origins	Effects
Histamine	Mastocyts, basophils, eosinophils, and platelets	Ensures vasodilation, increases vascular permeability, and induces adhesion molecule expression on the vascular endothelium**.**
Serotonin	Mastocytes and platelets	Increases vascular permeability dilates capillaries and stimulates smooth muscle contraction**.**
Platelet activation factors	Platelets, neutrophils, monocytes, and endothelial cells	Vasodilation increases the stickiness of the vascular wall, stimulates platelet aggregation, induces ROS production, and releases lysosomal enzymes by neutrophils, eosinophils, and macrophages
Prostaglandin	Leucocytes	It acts on membrane receptors and can be pro-inflammatory (IL-1β, IL-6, or TNFα) or anti-inflammatory (IL-10). Involved in tissue repair.

3. Anti-inflammatory:

Anti-inflammatory therapy typically involves non-steroidal or steroidal drugs, which can have serious side effects on the renal and digestive systems **(Das, 2011).**

The anti-inflammatory effects of polyphenols depend on their specific structure and can affect macrophage functions and cytokine production, these compounds have been found to modulate humoral and cellular immunity as it happens with flavonoids which can modulate COX-2 and iNOS **(Trabsa, 2015)**.

Chapter 03:

Zygophyllum album

1. Plants in Algeria:

Introduction:

Plants are multicellular, eukaryotic organisms belonging to the kingdom of Plantae, characterized by their ability to perform photosynthesis; a process by which they convert sunlight into energy using chlorophyll pigments, they are also known for their ability to adapt to different environments to survive. Plants are integral components of the ecosystem and they play an important role in preserving the environment and diversity **(Abu Baker et al., 2014)**.

For ages, humans have relied on plants for their basic needs, for food as they directly supply 90% of human calorie intake and 80% of their protein intake, for shelter, clothing, and last but not least medicines. Plants have formed the basis of sophisticated traditional medicine systems that have existed for thousands of years **(Fakim, 2006, CHAWLA. 2009)**. Nearly all cultures from ancient times to the present day have used plants as a source of medicine **(Olayiwola, 1988)**.

The use of plants for medical purposes is not limited to traditional medicine, they are considered rich resources of ingredients that can be used in drug development, and most of the pills and capsules we take and use during our daily life come from plants **(Bassam, 2012)**, and one-quarter of all medical prescriptions formulations are based on substances derived from plants **(Fakim, 2006)**.

Plants synthesize secondary metabolites, including alkaloids, flavonoids, saponins, terpenoids, steroids, glycosides, and tannins, to defend themselves against exogenous biotic constraints and as a response to different forms of biotic stresses as well as to fulfill important physiological tasks, like attracting pollinators and establishing symbiosis **(Guerriero, 2018)**.

These components are produced in small quantities, there are more than 200000 of them divided into three main families **(Kanoun, 2011)**:

- Polyphenols
- Alkaloids
- Terpenes

Polyphenols:

Polyphenols are present in all vascular plants (fruit, vegetables, seeds, etc). They make up one of the most numerous groups of substances in the plant kingdom with more than 8000 phenolic structures **(Kanoun, 2011)**. The basic structural element is a benzoic nucleus to which one or more hydroxyl groups are linked **(Lebham, 2005)**.

Alkaloids:

They are complex nitrogenous bases of plant origin that contain nitrogen as an essential element, which gives them alkaline qualities **(Mauro, 2006)**.

The main source was flowering plants, but nowadays these compounds have been isolated from insects and marine microorganisms, but their quantity in flowering plants is much greater **(Mauro, 2006)**.

Alkaloids play a defensive role for the plant because they contain toxic substances for insects and herbivores and protect the plant from UV as reported **(Mauro, 2006**).

Terpenes:

Terpenes are a huge range of natural products with diverse carbon structures ranging from simple linear chains to carbon polycyclic structures. They are compounds resulting from the condensation of 5-carbon basic units of isoprene type **(Kanoun, 2011)**. More than 36,000 different structures have been identified, many of which have been isolated from flowers, stems, roots, and various parts of the plant as well as from insects **(Ayad, 2008)**.

These secondary metabolites have some therapeutic efficacy that gives the plants pharmacological roles such as antioxidant, antiviral, anticancer, antimicrobial, antifungal, antibacterial, antiparasitic, and anti-inflammatory activities (**Arvind, 2016)**.

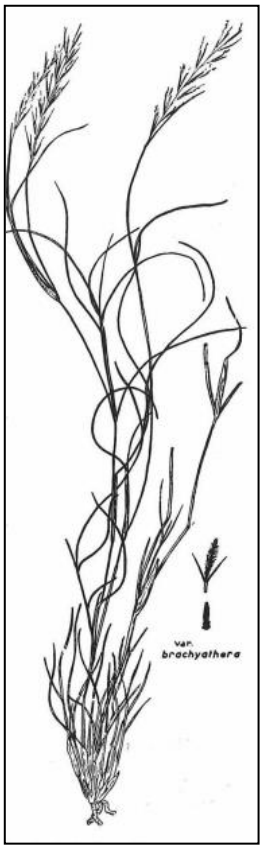
Algeria is one of the most biodiverse countries in North Africa because of its unique biogeography with a transition between tropical and temperate climates, and belonging to both the Mediterranean and Sahara-Arabian regions **(Meddour et al., 2021)**.

The Mediterranean region is rich in plants characterized by a variety of vegetation like pine and cork oak forests, this richness is due to the great topographic diversity of the environments of the region **(Zedam et al., 2016)**.

Moving to the Sahara region, the Sahara covers 84% of the surface area of Algeria. However, its flora seems to be very poor if compared to the small number of species that inhabit this space given the enormity of the surface it covers, however, it varies in its systematic composition **(Ozenda, 1991)**.

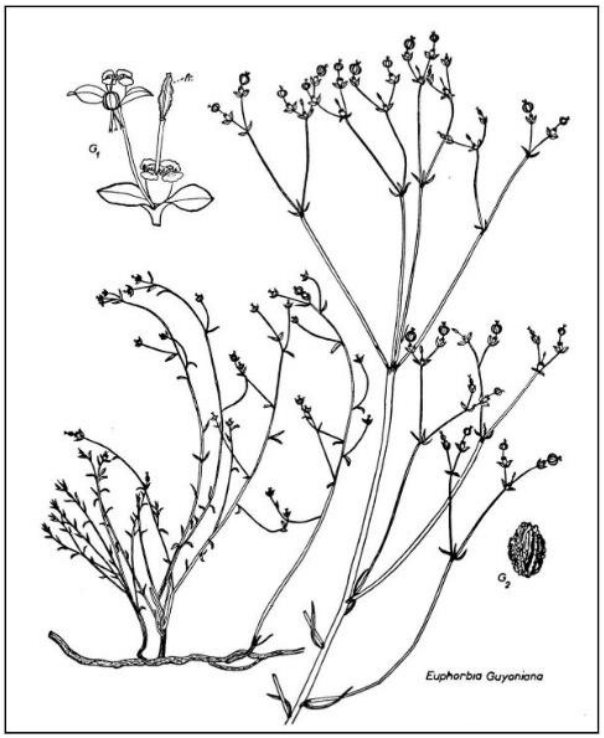
The Algerian Sahara has 650 species of which 162 species are endemic. Endemism represents approximately 25% of these species, like; *Urginea noctiflora, Aristida brachyathera, Anabasis oropediorum, Enarthrocarpusclavatus, Euphorbia Guyoniana, Helianthemum eriocephalum* **(Ozenda, 1991)**.

(a)

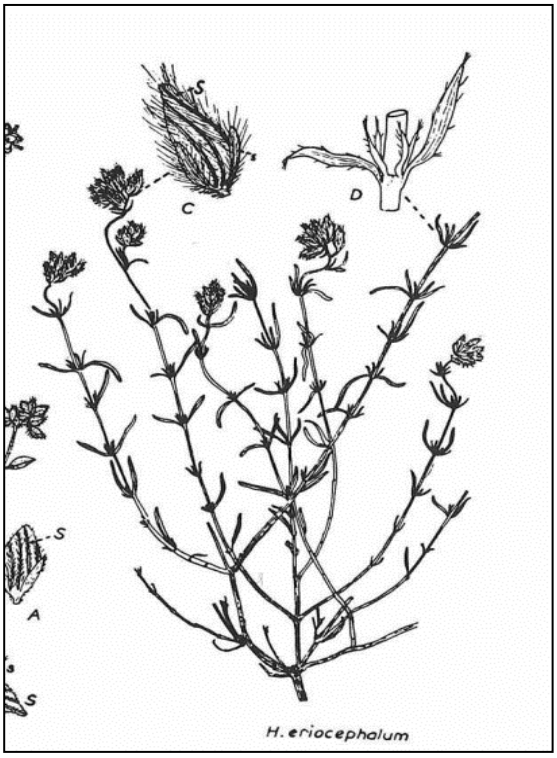


(b)

(c)



(d)



(e)

(f)

Figure 06: Some Algerian Sahara endemic species **(Ozenda,1988).**

(a)*Urginea noctiflora* **(b)** *Aristida brachyathera* **(c)** *Anabasis oropediorum* **(d)** *Enarthrocarpusclavatus* **(e)** *Euphorbia Guyoniana* **(f)** *Helianthemum eriocephalum*.

2. The Zygophyllaceae family:

The Zygophyllaceae family is the only example of a typical Saharan family since it barely exists in Europe, the Mediterranean, and Tropical Africa. This family includes about 25 genres and 500 species and can be found in all the continents but mainly in the arid regions. In the Sahara, 7 genres and 25 species are found and it forms 3% of the total desert flora **(Ozenda, 1991)**.

The three main genera of this family are:

- Fagonia
- Tribulus
- Zygophyllum

3. The Zygophyllum:

Zygophyllum is the most important genus of the family with hundreds of species **(Ozenda, 1991)**. In Africa, 20 species are recorded in the tropical zone, and around 20 species are also known in the South, and South-West **(Belguidoum, 2018)**. In North Africa, Zygophyllum simplex is easily recognizable by its simple leaves and its slender root, but with the rest of Zygophyllum, it is difficult to distinguish between them; they can only be distinguished by the shape of their fruit, one of these is the *Zygophyllum album* **(Ozenda, 1991)**.

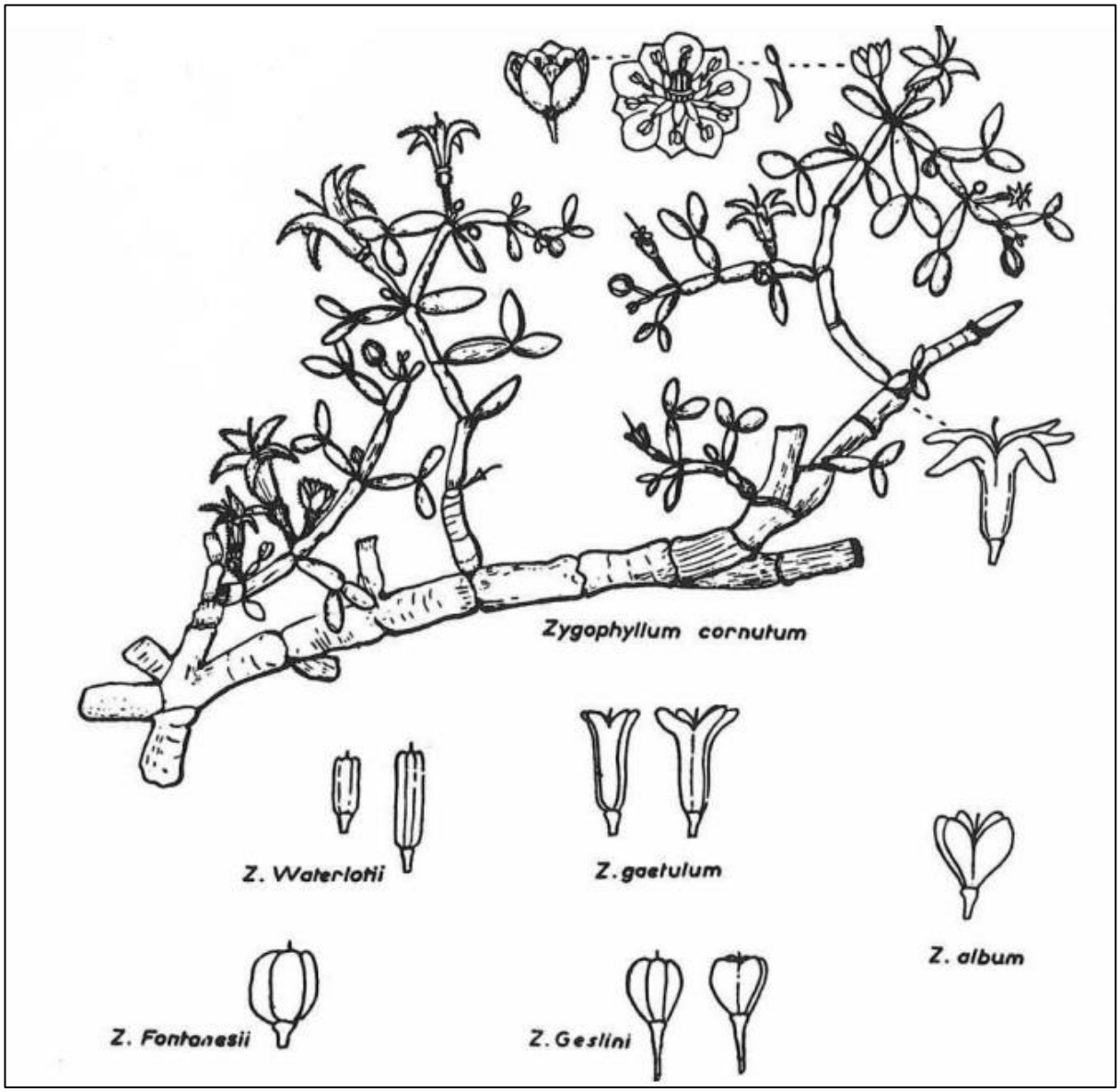


Figure 07: Represent the drawing of the Zygophyllum genus **(Ozenda, 1988)**

4. *Zygophyllum album*:

The *Z. album* is commonly known as ”Aggaya” in Algeria **(Bouhamou, 2012)**, or “Bougriba” in Tunisia **(Quezel et al, 1963)**. It is a desert plant that can withstand high salt levels, it typically grows in salty and gypsum lands in steppe form and is commonly found in the southern regions of Tunisia, however, it is quite rare in the southern parts of Algeria **(Ozenda, 1988)**.

4.1. Systematic of *Zygophyllum album*:

Kingdom: Plantae
Phylum: Spermatophyte
Class: Eudicots
Order: Sapindals
Family: Zygophyllaceous
Genus: Zygophyllum
Species: *Zygophyllum album*

Table 04: systematic of *Zygophyllum album*.

4.2. Botanical description of *Zygophyllum album*:

The plant is a small branched bush, the leaves have two light green chubby leaflets, covered with a thin layer of white hairs **(Ozenda, 1988)**, and the petioles are longer and plummier than the two leaflets, the leaves turn orange while drying **(Benhamou, 2012)**. The flowers are white, rarely yellow **(Ozenda, 1988),** and the fruit is not horned at the apex, dilated into 5 lobes well marked as long as the welded portion, while the fruit pedicles are shorter than the fruit **(Quezel et al, 1963)**.

Figure 08: The *Zygophyllum album* leaflets

Figure 09: The *Zygophyllum album* flowers

4.3. The chemical components:

The main components of the *Zygophyllum album* are:

Glycosides, Glucides, Sterides amino acids, Triterpenoid (*β*-amyrine, quinovic acid), Alkaloids (Harmine), Saponins, Sterol and Polyphenols like Tannins, Flavonoids (Kaempferol, Isorhamnetin, Quercetin-3-O-β-glucopyranoside) **(Belmimoun, 2017, Belguidoum, 2018)**.

4.4 The use of *Zygophyllum*:

The *Zygophyllum* has many therapeutic benefits, even though according to Ozenda the plant is considered lightly toxic. In Algeria, the leaves stems, and fruits of *Z. album* are used in traditional medicine in the form of an infusion to treat diabetes, spasms, rheumatism, and dermatoses, and also as a painkiller **(Ozenda, 1988, Souddi, 2023).** It can be used as an anti-inflammatory, antipyretic, and antiviral, to wash hair and clothes **(Belguidoum, 2018).**

Chapter 04:

General activities of *Zygophyllum album*

Biological Activities in Previous Research:

El Ghoul et al., 2011:

This work aimed to investigate the antihyperglycemic, antioxidant, and antihyperlipidemic effects of the aqueous extract of *Zygophyllum album* on streptozotocin (STZ) induced diabetic mice.

They prepared an aqueous extract of *Z. album*, and they studied the effect of the extract on blood glucose, lipids, cholesterol levels in plasma, and also on enzymatic and non-enzymatic antioxidants of defense systems such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme activities, and vitamin C, vitamin E and glutathione reductase (GSH) levels in liver and pancreas.

Z. album extracts reduced blood glucose in (STZ) diabetic mice. It also significantly abolished the increased GPx, SOD, and CAT activities in both liver and pancreas. The levels of GSH and vitamin C were significantly augmented in *Z. album treated* diabetic mice.

Feriani et al., 2020:

The present study investigated the bioactive compounds in methanol extract of Z. album (MEZA) using HPLC–DAD–ESI–QTOF-MS/MS and explored its possible antioxidative, anti-inflammatory, anti-apoptotic, and hepatoprotective effects. The current study has concentrated on male Wistar rats.

The results:

Twelve phenolic compounds were identified; isorhamnetin-3-O-rutinoside was the main one and it was the main composite (144.6 mg/100 g dm).

Results showed that MEZA reduced significantly the biochemical markers (AST, ALT, LDH, and ALP), and the hepatic oxidative stress indicators (MDA, PC, SOD, CAT, and GPx) in deltamethrin (DLM)-treated rats.

Moreover, MEZA limited the inflammatory responses through the downregulation of the NF-κB gene, which suppressed the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6).

Mnafgui et al., 2015:

This study investigates the antidiabetic, antidiarrheal, and antihypertensive activities of the essential oil extracted from fresh leaves of *Zygophyllum album* (OZA) in alloxan-induced diabetic rats.

As a result:

The OZA significantly decreased the activity of α-amylase in the pancreas and serum of the diabetic rats by 43% and 38%, respectively, which led to reduce the serum glucose level by 60% and a lower glycated hemoglobin (HbA1c) rate of 17% compared with untreated diabetic animals. OZA showed a good effect in the management of diabetes mellitus.

El-Attar et al., 2019:

This study aims to explore the anticancer activity of Zygophyllum album extracts. They prepared three extracts by soaking Shoot powders in several solvents with increasing polarity (Dichloromethane, Methanol, and hot water, respectively).

For measuring the cytotoxic activity they used an MTT assay.

As a result:

The cytotoxicity of each extract was assessed against Human lung carcinoma (A-549) cell lines. The result showed that the dichloromethane extracts were significantly active against human lung carcinoma with IC_{50} values of 70.48 µg/ml.

The anticancer activity of *Z. album* dichloromethane extracts was tested on HepG2 (Liver cancer cell) and THLE2 (normal cell) cell lines and was examined by MTT assay. *Z. album* crude extract inhibited the proliferation of human hepatocellular carcinoma (HepG2) which recorded an IC_{50} value of 27.74µg/ml, but low cytotoxic activity was observed against normal liver (THLE2) cells (IC_{50} = 1485 µg/ml).

Kchaou et al., 2016:

The study was to explore the anti-acetylcholinesterase activity and antioxidant effect as well as the content of phenolic compounds of various extracts from *Zygophyllum album.*

They prepared an 80% aqueous methanol maceration, and then extracted fractions using solvents; Hexane, dichloromethane, ethyl acetate, and n-butanol from the aerial parts of the plant and then tested its antioxidant activities using the DPPH assay.

As a result:

The dichloromethane extract gives the highest antioxidant capacity (0.2mg/mL). Although the IC_{50} of various extracts were significantly lower than those of BHT and vitamin E.

It was evident that the extracts show proton-donating ability and could serve as free radical inhibitors or scavengers, acting possibly as primary antioxidants.

M. Kchaou et al. 2016:

The study aimed to investigate the chemical composition of essential oil of *Zygophyllum album* leaves and their activities; antioxidant, anti-diabetic, antiobesity, and anti-bacterial activities. Essential oil was obtained from freshly harvested leaves.

The *in vitro* α-amylase inhibition activity for essential oil was determined based on the spectrophotometric assay using acarbose as the reference compound and the antioxidant activities were tested using the DPPH assay.

As a result:

The essential oil of *Z. album* exhibits moderated free radical-scavenging activity with an IC_{50} value of 400 µg mL-1 when compared to BHT (IC_{50}= 17 µg mL-1) and vitamin E (IC_{50}= 26 µg mL-1).

The essential oil of *Z. album* is an interesting pancreatic α-amylase inhibitor with an IC_{50} value of 43.17 µg mL-1. The detected α-amylase inhibitory activity is comparable to that of Acarbose (IC_{50}= 14.88 µg mL-1).

Conclusion

Conclusion:

In conclusion, oxidative stress plays a significant role in the development and progression of various chronic diseases like:

cancer; an abnormal and uncontrolled growth of cells, diabetes; a metabolic disorder due to insufficient insulin production or the body’s inability to effectively use insulin, and inflammation, which affects an individual's quality of life.

The usual treatment is effective against these diseases, but it often comes with dangerous side effects.

Medicinal plants are great alternatives to the common treatment thanks to bioactive compounds and are considerably safer, cheaper, and more obtainable.

Z. album is a desert plant used in usual medicine as a painkiller and also to treat spasms, rheumatism, and dermatoses. In daily life, we use it to wash our hair and clothes.

Z. album is rich in bioactive compounds, giving it therapeutic benefits.

The researchers find that *Z. album* can be used as an antioxidant, anticancer, antidiabetic, anti-inflammation, antipyretic, and antiviral to prevent diseases.

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Abstract

The biological activities are studied and confirmed by many research, which are linked to secondary metabolites contained in plants. This bibliographic study aimed to study some biological activities of the *Zygophyllum album (Z. album)* and its effects on reducing oxidative stress.

We mentioned that free radicals and oxidative stress are the main causes of problems and chronic diseases, like diabetes, cancer, cardiovascular diseases, inflammation, and others. We discussed some chronic diseases related to excess radicals on the body molecules, treatments, alternatives, and uses of antioxidants.

In this study, the *Zygophyllum album* was chosed as an endemic plant from Algeria, to evaluate its properties, its endemic environment, its botanical description, and some of its traditional uses.

As described and published by authors, we conclude that *Z. album* extracts are very rich in biological activities and must used as a source in pharmaceutical approaches.

The keywords: *Zygophyllum album,* Antioxidants, Oxidative stress, Diseases, and Biological activities.

الملخص

تناولت العديد من الأبحاث موضوع الوضائف البيولوجية المرتبطة بالمواد الأيضية الثانوية الموجودة في النباتات.

هذه الدراسة تهدف لدراسة الوضائف البيولوجية لنبات *Zygophyllum album* و أثره في تقليل الجذور الحرة.

ذكرنا أن الجذور الحرة و الجهد التأكسدي هي الأسباب الرئيسية للمشاكل الصحية و الأمراض المزمنة، كداء السكري، السرطان، أمراض القلب و الأوعية الدموية و الإلتهابات و غيرها. و توسعنا في بعض هذه الأمراض و علاجاتها الحالية و بعض البدائل و مدى فعالية مضادات الأكسدة في علاجها.

إخترنا لهذه الدراسة نبات *Zygophyllum album* و هو من النباتات المستوطنة في الجزائر، تطرقنا لخصائصه، أوصافه المورفولوجية، بيئته و بعض الإستعمالات التقليدية له.

ختاما، كما نشر و وصف الكتاب في مقالاتهم، فإن مختلف مستخلصات الـ *Z. album* غنية جدا بالمواد الفعالة و لابد من استغلالها في إنتاج الأدوية.

الكلمات المفتاحية: *Zygophyllum album* ، مضادات الأكسدة، مضادات السرطان، مضادات السكري، مضادات الإلتهاب.