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Phytochemical profile and inhibition of carbohydrates digestive enzymes activity of date nuts

Submitted by:

Bessahraoui Aicha

Bouchemal Chaima

Bouchemal Chaima

Saim Aicha

President	**Dr .ZAIME Sihem**	**M.C.A**	**El-Oued University**
Examiner	**Dr .LAIB Ibtissam**	**M.A.A**	**El-Oued University**
Supervisor	**Dr. Mahboub Nasma**	**M.C.A**	**El-Oued University**

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Thanks to God, so praise be to God for the beginning and the end

I extend my full thanks to myself for completing this work hard and being here today

I dedicate my success to the source of strength, my support "dear father"

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Thank God, I would not have done this without God's grace.

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Abstract

Diabetes is a chronic condition characterized by high blood sugar levels. This can be a huge challenge for many, which is why many researchers are looking for natural and alternative treatments that may help manage the disease.

Studying and analyzing date seeds as an alternative to natural treatment could be an important step towards providing effective and safe solutions for diabetics. We studied the seeds of dates Ghars grown in Oued Souf, with the aim of exploring the nutritional value, estimating the quantitative chemical content of the date seeds, and estimating its effectiveness as an antioxidant and antimicrobial. With the aim of utilizing, it as a natural ingredient for treating diabetics type 2. We reached the following results:

The yield of date seed extract from the Ghars variety was estimated at 12.25%.

The results obtained by estimating primary metabolites showed that the date seed contains a high percentage of proteins compared to carbohydrates and lipids. The highest value was recorded for secondary metabolites of polyphenols, flavonoids, and tannins.

Qualitative analysis of date pit extract using HPLC showed the presence of 14 phenolic compounds. Antioxidant activity results based on the FRAP test showed that the Ghars date seed extract had strong antioxidant activity, as the IC50 of the extract reached 323.21 ± 0.025 mg/ml, and that of ascorbic acid was 4.57 ± 0.025 mg/ml. The results of antimicrobial activity showed that *Escherichia coli* bacteria are more sensitive to the extract compared to *Pseudomonas aeruginosa* bacteria, *Staphylococcus aureus* bacteria, and *Bacillus subtilis* bacteria.

The results of antidiabetic activity have been proven through two methods:

The first method is to use yeast: date pit extract increases glucose absorption. This confirms that these seeds also improve glucose absorption by human cells and thus help reduce blood sugar. The second method is using the alpha-amylase enzyme: the extract inhibits the action of the alpha-amylase enzyme, thus preventing the hydrolysis of starch into glucose. The IC50 was estimated at 0.229 mg/ml.

From the results obtained, we can say that date pits have great effectiveness in maintaining blood sugar levels, making them an ideal choice for diabetics type 2.

Keywords : Phytochemical profile, date seeds, Ghars, HPLC analysis, antimicrobial, antidiabetics.

Résumé

Le diabète est une maladie chronique caractérisée par une glycémie élevée. Cela peut représenter un défi de taille pour beaucoup, c'est pourquoi de nombreux chercheurs recherchent des traitements naturels et alternatifs qui pourraient aider à gérer la maladie.

L'étude et l'analyse des graines de dattes comme alternative au traitement naturel pourraient constituer une étape importante vers la fourniture de solutions efficaces et sûres pour les diabétiques. Nous avons étudié les graines de dattes Ghars cultivées à Oued Souf, dans le but d'explorer la valeur nutritionnelle, d'estimer le contenu chimique quantitatif des graines de dattes et d'estimer leur efficacité en tant qu'antioxydant et antimicrobien. Dans le but de l'utiliser comme ingrédient naturel pour le traitement des diabétiques de type 2. Nous avons obtenu les résultats suivants :

Le rendement en extrait de graines de datte de la variété Ghars a été estimé à 12,25%.

Les résultats obtenus en estimant les métabolites primaires ont montré que la graine de datte contient un pourcentage élevé de protéines par rapport aux glucides et aux lipides. La valeur la plus élevée a été enregistrée pour les métabolites secondaires des polyphénols, des flavonoïdes et des tanins.

L'analyse qualitative de l'extrait de noyau de datte par HPLC a montré la présence de 14 composés phénoliques. Les résultats de l'activité antioxydante basés sur le test FRAP ont montré que l'extrait de graines de datte Ghars avait une forte activité antioxydante, puisque la CI50 de l'extrait atteignait 323,21 ± 0,025 mg/ml et celle de l'acide ascorbique était de 4,57 ± 0,025 mg/ml. Les résultats de l'activité antimicrobienne ont montré que les bactéries *Escherichia coli* sont plus sensibles à l'extrait que les bactéries *Pseudomonas aeruginosa*, *Staphylococcus aureus* et *Bacillus subtilis.*

Les résultats de l'activité antidiabétique ont été prouvés par deux méthodes :

La première méthode consiste à utiliser de la levure : l'extrait de noyau de datte augmente l'absorption du glucose. Cela confirme que ces graines améliorent également l'absorption du glucose par les cellules humaines et contribuent ainsi à réduire la glycémie. La deuxième méthode utilise l'enzyme alpha-amylase : l'extrait inhibe l'action de l'enzyme alpha-amylase, empêchant ainsi l'hydrolyse de l'amidon en glucose. La CI50 a été estimée à 0,229 mg/ml.

D'après les résultats obtenus, nous pouvons dire que les noyaux de dattes ont une grande efficacité dans le maintien du taux de sucre dans le sang, ce qui en fait un choix idéal pour les diabétiques de type 2.

Mots clés : profil phytochimique graines de dattes, Ghars, analyse HPLC, antimicrobien, antidiabétiques.

ملخص

مرض السكري هو حالة مزمنة تتميز بارتفاع مستويات السكر في الدم. يمكن أن يشكل هذا تحديًا كبيرًا للكثيرين، ولهذا السبب يبحث العديد من الباحثين عن علاجات طبيعية وبديلة قد تساعد في إدارة المرض.

إن دراسة وتحليل نواة التمر كبديل للعلاج الطبيعي يمكن أن تكون خطوة مهمة نحو تقديم حلول فعالة وآمنة لمرضى السكر. قمنا بدراسة نواة التمر صنف الغرس في واد سوف، بهدف استكشاف القيمة الغذائية، وتقدير المحتوى الكيميائي الكمي لنواة التمر، وتقدير فعاليته كمضاد للأكسدة ومضاد للميكروبات، بهدف الاستفادة منه كمكون طبيعي لعلاج مرضى السكر من النوع الثاني. حيث توصلنا إلى النتائج التالية:

قدر محصول مستخلص نواة التمر من صنف غرس بـ 12.25%.

أظهرت النتائج التي تم الحصول عليها من خلال تقدير نواتج الايض الاولي أن نواة التمر تحتوي على نسبة عالية من البروتينات مقارنة بالكربوهيدرات والدهون، أما نواتج الايض الثانوي من البوليفينول والفلافينويدات والتانينات فقد سجلت أعلى قيمة لها.

أظهر التحليل النوعي لمستخلص نواة التمر باستخدام HPLC وجود 14 مركب فينولي. وأظهرت نتائج نشاط مضادات الأكسدة بناءً على اختبار FRAP أن مستخلص نواة تمر الغرس له نشاط مضاد للأكسدة قوي، حيث بلغ IC50 للمستخلص 323.21±0.025 ملجم/مل، وحمض الأسكوربيك 4.57±0.025 ملجم/مل. أظهرت نتائج النشاط المضاد للميكروبات أن بكتيريا الاشريكية القولونية أكثر حساسية للمستخلص مقارنة ببكتيريا الزائفة الزنجارية، بكتيريا المكورات العنقودية الذهبية وبكتيريا العصوية الرقيقة.

تم إثبات نتائج النشاط المضاد لمرض السكر من خلال طريقتين:

الطريقة الأولى هي استخدام الخميرة: حيث يعمل مستخلص نوى التمر على زيادة امتصاص الجلوكوز. وهذا يؤكد أن هذه البذور تعمل أيضًا على تحسين امتصاص الغلوكوز بواسطة الخلايا البشرية وبالتالي تساعد على تقليل نسبة السكر في الدم. الطريقة الثانية هي باستخدام إنزيم ألفا اميلاز: حيث أن المستخلص يثبط عمل إنزيم ألفا أميلاز، وبالتالي يمنع تحلل النشا إلى غلوكوز، وتم تقدير IC50 بـ 0.229 ملغم / مل.

ومن النتائج التي تم الحصول عليها يمكننا القول إن نواة التمر لها فعالية كبيرة في الحفاظ على مستويات السكر في الدم، مما يجعلها خيارا مثاليا لمرضى السكري من النوع الثاني.

الكلمات المفتاحية: الملف الكيميائي النباتي، نواة التمر، غرس، تحليل HPLC، مضاد الميكروبات، مضاد لمرض السكر.

Summary

Chapter III: Material and Methods

Chapter IV: Results and Discussion

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List of Abbreviations

- %: Porcentage.
- Sc: *Saccharomyce cervisiae*.
- DP: Date pits.
- RP: Reducing power.
- IC50: Inhibitory concentration 50.
- CN: Gentamycin.
- DMSO: Dimethyl sulfoxide.
- Abs: Absorbance.
- PH: Potential hydrogen.
- NI: No inhibition.
- HPLC: High performance liquid chromatography.
- ANOVA: Analysis of variances.

General Introduction

Diabetes is known as a global epidemic and represents a public health problem in developing countries (**HAWLEY. 2015).** It is a chronic disease characterized by high blood sugar and dysfunction of the pancreas **(American Diabetes Association. 2019)**, either due to insulin deficiency and/or insulin resistance. High blood sugar can be severe, causing thirst and urination and can lead to It can cause the patient to enter a coma, and it may be a mild case of high blood sugar. Diabetics in this case do not show any symptoms and the disease is called the "silent killer." (**SETHUK. 2020).**

High blood sugar is accompanied by serious and disabling complications, such as microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (coronary artery disease, cerebrovascular disease, and peripheral arterial disease), and the severity of the disease increases when it affects the rest of the body's organs, such as failure Renal (**PAPATHEODORON. 2016).**

Diabetes today is a great obstacle and burden on medium-sanctaval and poor health systems in terms of facilities and costs, many nutrition experts suggest date seeds as a magical natural remedy to adjust and control blood sugar levels and classify them as the ideal choice for treatment. This is why we studied the physical and chemical properties of date seeds and tried to know the nutritional value of date seeds and how they affect lowering blood sugar levels.

Algeria enjoys a great wealth and diversity of date palms, with more than 13 million palm trees and 940 varieties registered, with a total date production of 440,000 tons annually. (**HANNACHI. 1998) (MA/ DSAEE. 2001).**

Dates are a small, pure, sweet and delicious fruit that many people prefer and want to eat from time to time, but they do not pay attention to the benefits of the date kernel and they get used to throwing it away without knowing that its benefits and nutritional value are no less than the value of the fruit itself **(BOUAZIZ. 2015)**. It is used to feed animals or to make caffeine-free coffee **(HABIB. 2009)**. Also, in the treatment of liver diseases and digestive system disorders, as well as the treatment of diabetes, which we will discuss in our topic (**Kchaou. 2016)**, as date seeds can be considered a valuable source of functional and medicinal components, as it was found that they consist of a high amount of fiber (75-80%), fats (10-13%), and proteins (5-16%). %) (**BEBES. 2004) (AL-FARSI. 2007) (ALFARSI. 2008).**

The aim of our research is to study the physical and chemical properties and nutritional value of date seeds of the Ghars variety, and to find out how to inhibit the activity of carbohydrate-digesting enzymes in date fruits to reduce sugar level in blood.

In this research, we will discuss two parts:

- Bibliographic part consisting of two chapters:

  - Chapter One: Diabetes mellitus.
  - Chapter Two: Date seeds.
- An experimental part consisting of two chapters:
  - Chapter One: Materials and methods.
  - Chapter Two: Results and discussion.

Chapter I: Diabetes Mellitus

1.History of diabetes

Diabetes is a chronic disease that is widespread throughout the world, according to the World Health Organization (WHO) **(RAIS. 2022)**. It was discovered in the twentieth century by ancient Egyptian doctors 3,500 years ago **(LASKER. 2010).** The term diabetes mellitus was derived from the Greek word diabainein, which means to draw or pass, and it is called siphon. It was the first to coin it by Araetus of Cappodocia, and in 1675 AD, Thomas Willis added the Latin word mellitus, which means hone **(ALAM. 2017).** Ibn Sina described the complications and clinical manifestations of diabetes and emphasized the idea of the sweet taste of urine. The disease was also classified into two categories according to Johann Peter Frank: diabetes insipidus (tasteless urine) and true diabetes (sweet urine). Matthew Dobson confirmed the presence of sugar in both the blood and urine of diabetic patients**(UMURZAKOVA. 2023).** In 1857, Lord Bernard discovered the function of glycogen in the liver, and Joseph von Mering and Oscar Minkowski were considered discoverers of the role of the pancreas, as they showed that dogs developed diabetes when the pancreas was removed. Here, Laguesse concluded that the islets of Langerhans produce an internal secretion, and Edward Sharpy-Shafer named it insulin, which regulates the process of carbohydrate metabolism **(AHMED. 2002).**

2.Definition of diabetes

Diabetes mellitus is a group of meta-diseases bolic hyperglycemia that results from a defect in insulin secretion or the action of insulin or both abnormalities associated **(L'ADA. 1999),** The basis of these abnormalities in the metabolism of carbohydrates, fats, and proteins in diabetes is due to the lack of insulin action on the target tissues **(AMERICAN. 2014**), Several pathogenetic processes are involved in the development of diabetes, these include processes which destroy the beta cellsβ of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action **(CONSULTATION. 1999),** its high level is also associated with damage, dysfunction and failure of peripheral organs, including the retina, kidneys, nervous system and cardiovascular system **(ALAM. 2014),** the classification identifies the first type, autoimmune and non-immune, with destruction of beta cells (β), type 2 with varying degrees of insulin resistance and decreased insulin secretion **(ALBERTI. 1998).** Gestational diabetes is a carbohydrate intolerance caused by they appear for the first-time during pregnancy **(BIRSON. 2016).**

3.Physiological balance

3.1. Pancreas

The pancreas is a flattened and elongated organ located on the back surface of the stomach, they weigh between 60 and 80 grams and are 12 to 15 cm long and 2 to 4 cm wide **(BESSAGUET. 2021)**. The pancreas is divided into 4 parts: a head, neck, body and tail. The head and tail mark the right and left extremities of the gland, respectively. The head and neck of the pancreas lie slightly to the right of the midline while the tail is to the left of the midline **(MAHADEVAN. 2019).** It is located transversely in the upper abdomen between the duodenum on the right and the spleen on the left. The head of the pancreas is the enlarged part of the gland surrounded by the C-shaped curve of the duodenum. The body of the pancreas continues from the neck and passes over the aorta and L2 vertebra. The tail of the pancreas lies anterior to the left kidney, closely related to the splenic hilum and the left colic flexure **(TALATHI. 2023).**

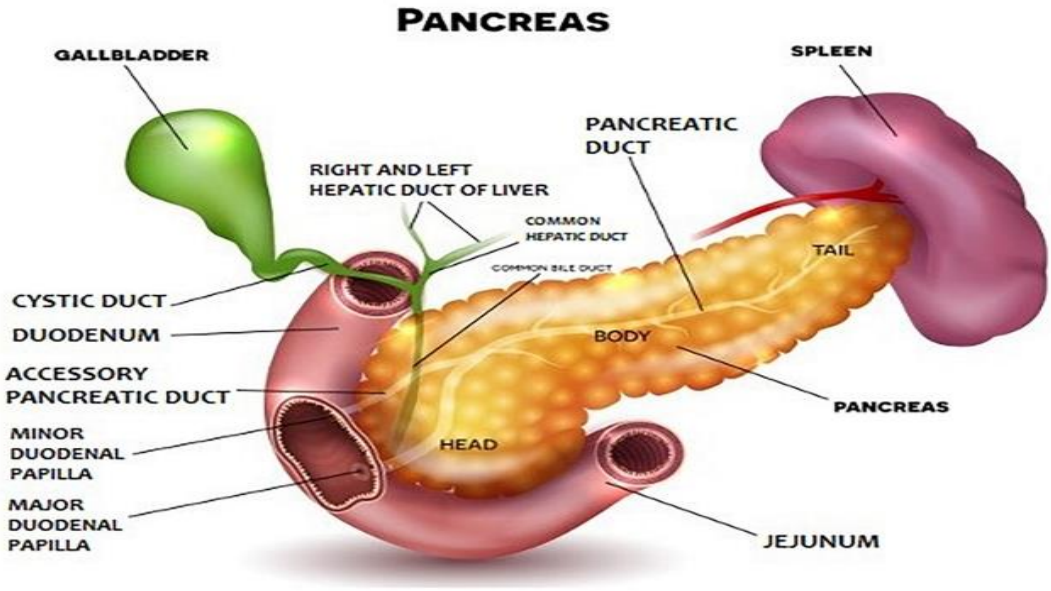


Figure 01: Anatomy of the human pancreas **(KARPINSKA. 2022).**

3.1.1. Functions

The pancreas consists of two organs in one:

- Exocrine gland: secretes enzymes into the digestive tract.
- Endocrine glands: secretes hormones into the bloodstream.

The endocrine cells are mainly grouped into the pancreatic islets (of Langerhans), including five types of cells: the alpha cells (α) are responsible for producing glucagon, the beta

cells (β) produce insulin, the delta cells(δ) produce somatostatin, the epsilon cells (ε) produce ghrelin, and the PP cells produce the pancreatic polypeptide **(FRANTZ. 2012).**

As exocrine gland, the acini secrets pancreatic juice including digestive enzymes to facilitate absorption and digestion of nutrient molecules in the duodenum. As an endocrine gland, the islets of Langerhans of pancreas secrete insulin and glucagon into the bloodstream directly involved in metabolism **(QAID. 2016).** The secretory units of the exocrine part of the pancreas are groups of cells, called acini, surrounding the ends of small ducts, that feed into a centrally located pancreatic duct and drains into the hepatic duct and then the duodenum. The acinar cells secrete a fluid rich in digestive enzymes, which can digest proteins, carbohydrates, nucleic acids and fat. In general, these digestive enzymes are secreted as proenzymes **(TAN. 2014).**

3.2. Insulin

Definition: insulin is; a polypeptide hormone, composed two amino acid chains (A chain: 21 amino acids; B chain 30 amino acids). The chains are connected to each other by disulfide linkage; those chains contain 51 amino acids with a molecular weight of 6,000 **(QAID. 2016)**. It is secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by faciliting cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects **(WILCOX. 2005)**.

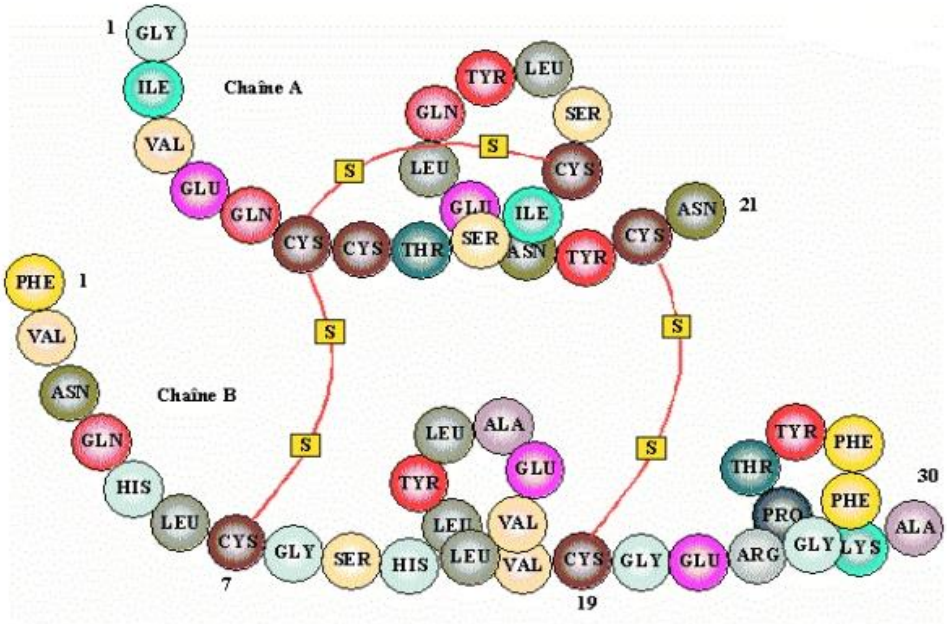


Figure 02: Diagram of the insulin molecule **(MALARDÉ. 2012).**

3.2.1. Secretion

The secretory response in pancreatic β cells results from the concerted action of nutrients (glucose and acids) together with the effects of hormones and of neurotransmitters acting on G-protein coupled receptors **(LANG. 1999).**

- Glucose enters theβcell thanks to the Glut 2.
- In order to stimulate insulin secretion, glucose must be metabolized in the β cell.
- Phosphorylation of glucose by glucokinase. Actuely, glucose metabolism increases ATP, which closes the K^+/ATP_ dependent channel and opens voltage _ dependent calcium channels (VDCC).
- Entry of Ca^{2+} into the β cell (signal necessary for exocytosis).
- Translocation and exocytosis of insulin containing vesicles with assistance from cytoskeletal filaments **(MOSBAH. 2012).**

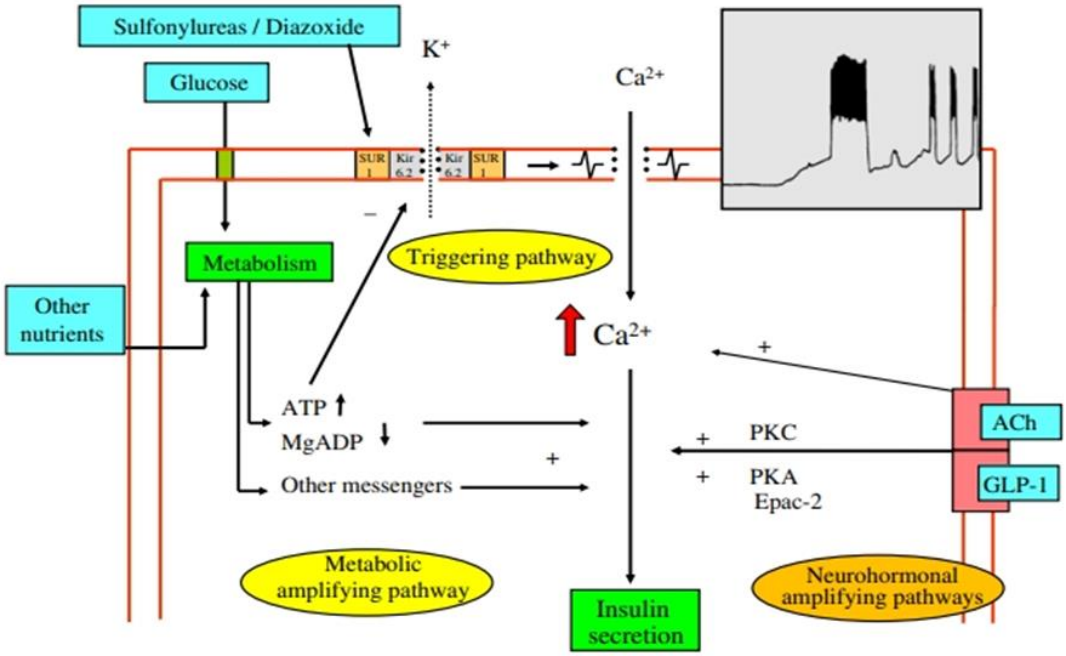


Figure 03: Schematic representation metabolic amplifying pathways mediating the stimulation of insulin secretion by glucose **(HENQUIN. 2009).**

Important second massagers modulating insulin release are the inositol phosphate and diacylglycerol. Hydrolysis of phosphatidyl inositol4,5-bisphosphate (PIP2) by activation the phospholipase C in inositol triphosphate (IP3) and diacylglycerol (DAG).

IP3 mobilize Ca^{2+} from endoplasmic reticulum, whereas diacylglycerol (DAG) can act on exocytosis of insulin **(LAYCHOK. 1990)**.

3.2.2. Receptor

The insulin receptor is glycoprotein integral membrane composed of two major subunits α and β subunits which bond with disulfide bridges **(HEDO. 1983)**, which is an insulin_ stimulated, tyrosine_ specific protein kinase. the α and β subunits of the receptor are synthesized in the form of a polypeptide chain which is cleaved and carbohydrate side chains are added. the protein sequence of the receptor as follows:

subunit α which binds to insulin, and subunit β has a kinase activity allowing its autophosphorylation **(CARPENTIER. 1988)**, activation of this kinase is believed to generate a signal that eventually results in insulin's action on glucose, lipid, and protein metabolism (**KAHN. 1985)**.

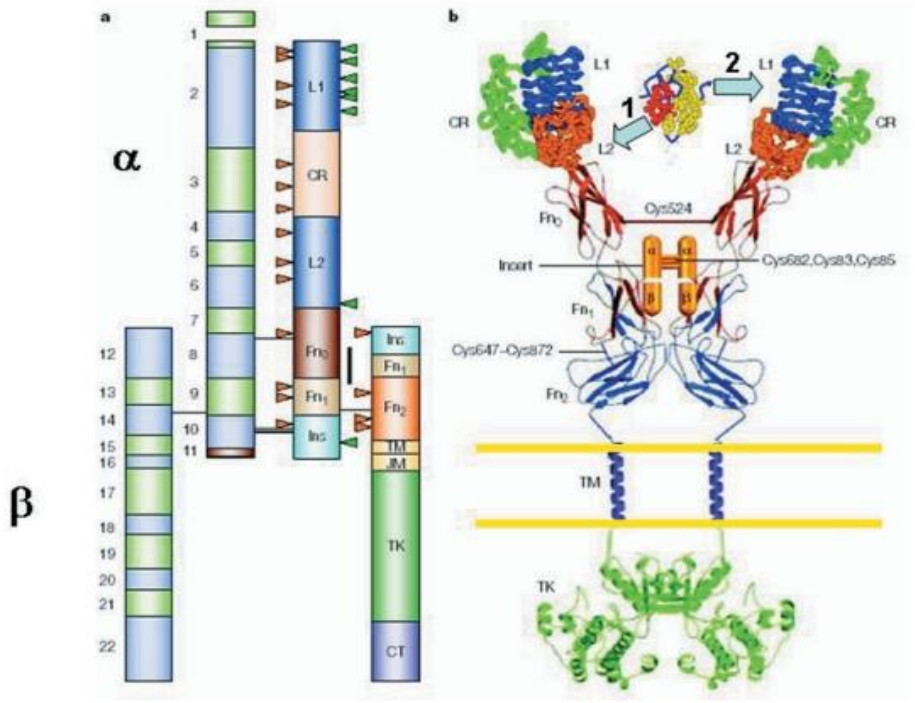


Figure 04: Structure of the insulin receptor **(DE MEYTS. 2005).**

3.2.3. Insulin function

- One of the major effects of insulin is the inhibition of hepatic glucose production, which acts rapidly by inhibiting glycogenolysis and gluconeogenesis.
- Metabolism of fatty acids, in their storage in the form of triglycerides in adipose tissues and inhibits lipolysis.
- Inhibits intrahepatic fatty acid oxidation.
- Increases the use of ketone bodies by skeletal muscles.
- Regulation of protein metabolism by inhibiting protein catabolism.

– (proteolysis) **(GIRARD. 2008)**.

3.2.4. Mechanisms of action

Insulin after its fixation on its receptor induces activation of the receptor and the transmission of the intracellular message **(CAPEAU. 1996)**.

The first event is the activation of the B subunit by the phosphorylation of tyrosine kinases. After this step; the transmission of the hormonal message done by a cascade of phosphorylation/dephosphorylation **(CAPEAU. 1992)**.

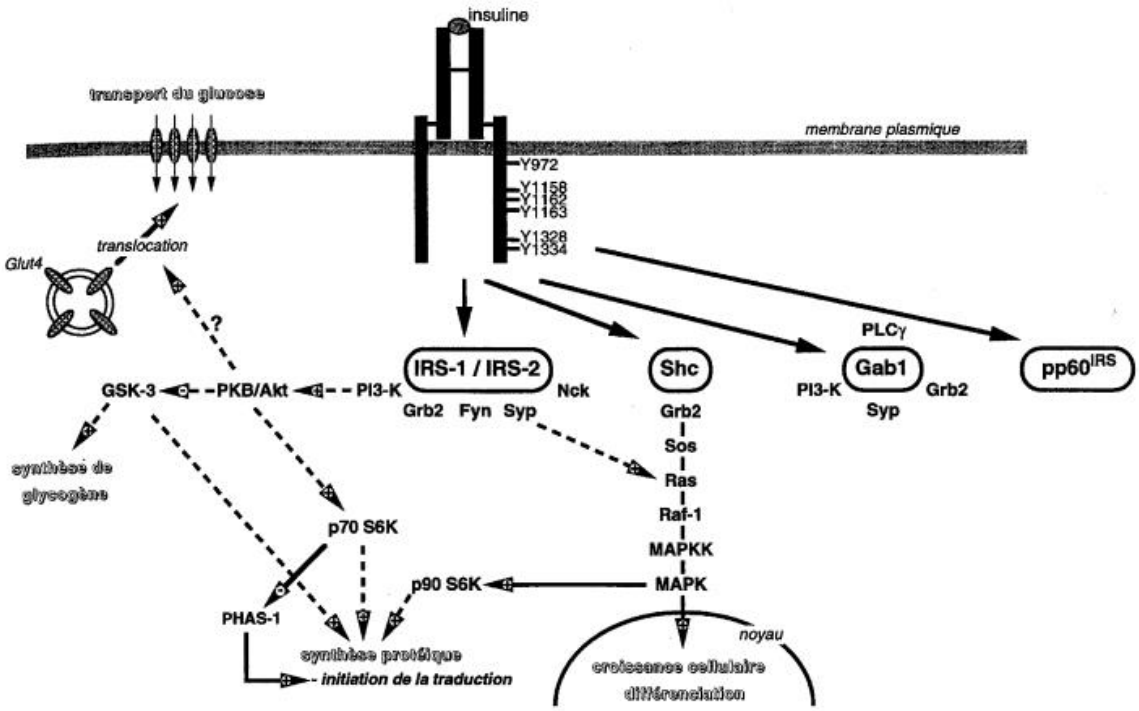


Figure 05: Simplified diagram of signaling pathways initiated by insulin **(CAPEAU. 1996).**

4.Classification of diabetes

The world health organization (WHO) expert committee on diabetes in 1980 and later, the WHO study group on diabetes mellitus endorsed the substantive recommendation of the NDDG. These groups recognized two major forms of diabetes, which they termed insulin – dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin –dependent diabetes mellitus (NIDDM, type 2 diabetes) **(ON THE DIAGNOSIS. 2003)**.

Both the 1980 and 1985 reports included two other classes of diabetes: "gestational diabetes mellitus" (GDM) and "other types" **(WORLD HEALTH ORGANIZATION. 2019)**.

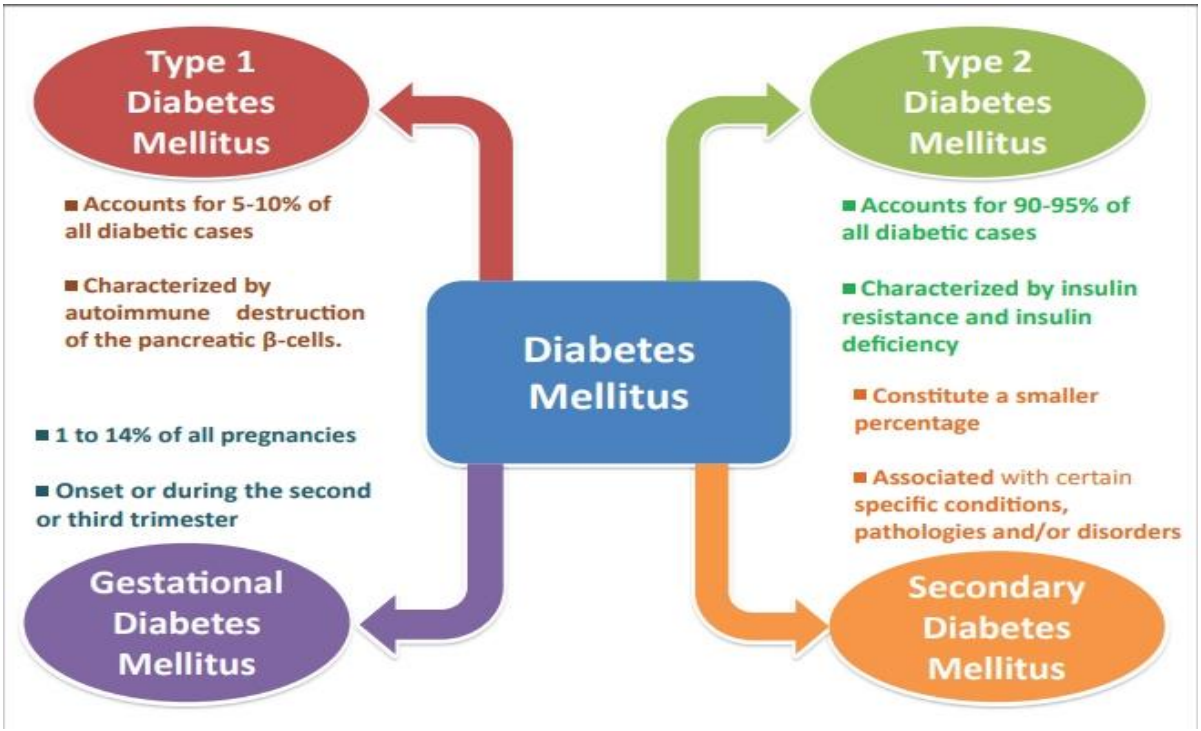


Figure 06: Types of diabetes mellitus **(BANDAY. 2020).**

4.1. Type 1 diabetes mellitus

Type1 diabetes mellitus (T1DM) is a chronic Auto-Immune disease, which are due to the insulin deficiency that occurs as the consequence of the loss of the pancreatic islet ß cells, characterized by increased blood glucose levels (hyperglycemia) **(KATSAROU. 2017)**.

T1DM usually develops in children or young adults, but it can appear at any age, it is most common during childhood (ages 1 to 14 years) **(ILONEN. 2019).**

4.1.1. Pathophysiology

Type 1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets. Several features characterize type 1 diabetes mellitus as an autoimmune disease **(BAYNES. 2015)**.

Studies on the natural history of T1D suggest that autoimmunity against multiple antigens of islet β-cells, driven by T-cells, is more likely to be triggered by environmental factors in genetically susceptible individuals, the susceptibility of islet β-cells leads to cell stress and the formation of neoantigens that are attacked by the immune system **(DEL CHIERICO. 2022)**.

The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion, there is excessive secretion of glucagon in IDDM patients. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma **(OZOUGZU. 2013)**.

The β-cell destruction which can lead to diabetic ketoacidosis (DKA) in some other cases, β-cells may retain some degree of function to secrete only that quantity of insulin, which is only sufficient to prevent ketoacidosis for many years **(BANDAY. 2020)**.

4.1.2. Etiology

So far, the causes leading to diabetes have been categorized as 3 types, namely: genetic predisposition/hereditary factors, viral infections and environmental factors **(ACHARJEE. 2013).** The risk of diabetes cor-relates with the inheritance of the human leukocyte antigen (HLA) alleles located on chromosome 6 in the major histocompatibility complex (MHC), which contains a series of genes that may contribute to diabetes susceptibility **(EISENBARTH. 1993)**. Many factors cause T1DM, are autoimmunity, lifestyle, diet. Even viruses like enterovirus, rotavirus, and rubella contribute to T1DM **(DESAI. 2019)**.

4.2. Type 2 diabetes mellitus

Type 2 diabetes mellitus(T2DM) represents 90%-95% of those affected, and it was previously referred to as non-insulin dependent diabetes, as it affects adults **(AMMERICAN. 2010)** It is a common disorder whose prevalence is increasing throughout the world, Type 2 diabetes is associated with many metabolic disorders, such as central obesity and a high incidence of cardiovascular disease and mortality, its main cause in diabetes consists of excessive hepatic glucose production, peripheral insulin resistance, and defective beta cell secretory function **(EDELMAN. 1998)**.

4.2.1. Pathophysiology

Type 2diabetes is a heterogeneous syndrome characterized by a defect in carbohydrate and fat metabolism, its causes are multifactorial and include genetic elements and the environment that affect the function of beta cells(β) and the sensitivity of tissues **(**muscles, pancreas, liver, adipose tissue**)** to insulin **(SCHEEN. 2003)**.

Many studies have demonstrated that diabetes and pre-diabetes do not develop until the beta cell(ß) fails to adequately compensate for the surrounding state of insulin resistance. They have also indicated that beta cell(β) dysfunction also depends on a pre-existing risk, perhaps genetically determined, as well as the ability of the beta cells(β) to secrete a sufficient amount of insulin due to beta cell(ß) mass and secretory capacity **(DADAMO. 2011)**.

Diabetes mellitus II combines defects in insulin secretion and insulin action, and these defects are in different proportions depending on the type of patient and the stage of the disease, as recommendations for diet and physical activity are the basis of treatment **(SCHEEN. 1996),** they also found that impaired insulin secretion is a decrease in glucose response, which is

observed before the clinical manifestation of the disease, and from this, impaired glucose tolerance occurs due to decreased insulin secretion in the early stage that responds to glucose, Also, decreased net insulin secretion after meals leads to high blood sugar after eating **(KOHEI. 2010),** Including obesity in the abdominal area is the strongest factor leading to type 2 diabetes, as evidenced by 80% of the disease suffering from overweight, and the effect of obesity resulting from diabetes is linked to its ability to stimulate or worsen insulin resistance **(FERY. 2005)**.

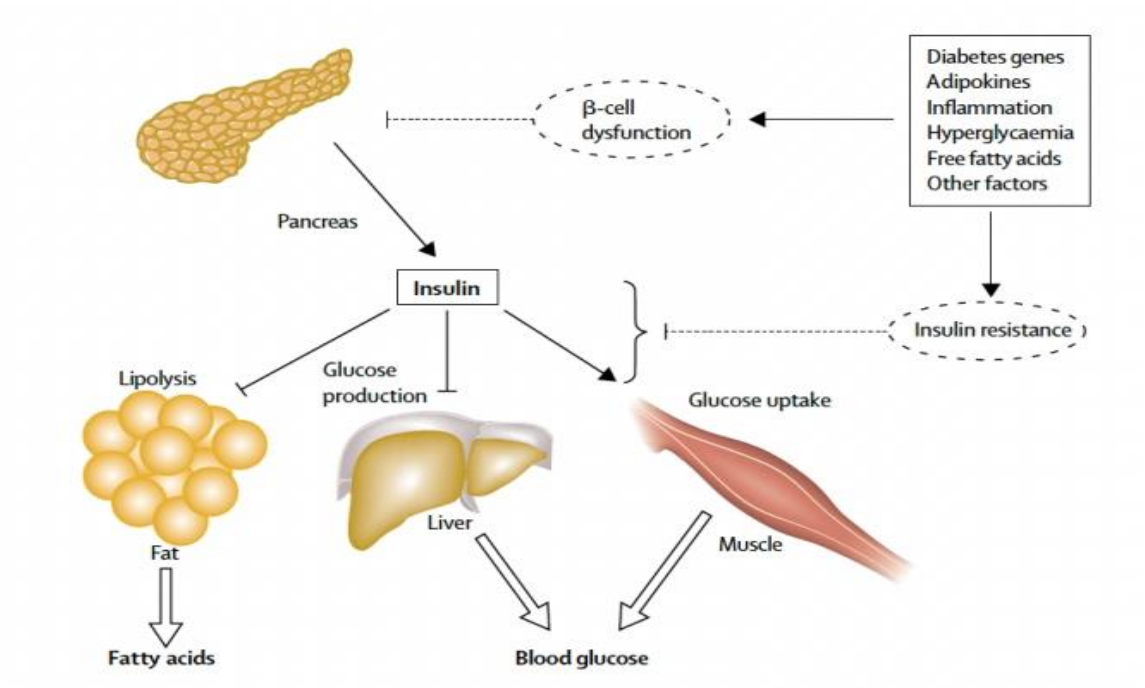


Figure 07: Pathophysiology of hyperglycemia in type2 diabetes **(STUMVOLL. 2005).**

4.2.2. Etiology

Type 2 diabetes mellitus is a major cause of morbidity and mortality worldwide, it is expected that its prevalence will increase significantly in the future, so the metabolic pathways that cause type 2 diabetes must be understood for the purpose of health care **(BETERSEN. 2006)**.

Type 2 diabetes is widely known to be multigenetic and heterogeneous in its origins, but it has two features: First, insulin resistance can be defined as an impairment of the ability of hormones to suppress hepatic glucose production and enhance peripheral glucose disposal **(MCGARRY. 2002)**.

Insulin has a basic function, which is to store fatty and glycosidic substrates, as its effects result from the binding of insulin to a specific membrane receptor **(CAPEAU. 2003),** which

causes insulin resistance in the target organs (muscle, adipose tissue, or liver), a common pathophysiological feature of type 2 diabetes **(KALIN. 2017)**.

Insulin resistance in skeletal muscle manifests itself primarily as a decrease in insulin-stimulated glycogen synthesis due to decreased glucose transport **(SESTI. 2006),** Muscle glucose is transported via insulin-independent GLUT4, where resting GLUT4 molecules are incorporated into true vesicles within the cell is protruded when insulin is signaled to the surface of the cell, compared to the condition of type 2 diabetes, the transfer of GLUT4 from inside the cell to outside the cell is slowed, leading to type 2 diabetes **(SPINAS. 2001)**.

Secondly, the function of pancreatic beta cells(ß) is at risk through insufficient insulin secretion to the point of insulin resistance **(MCGARRY. 2002),** To maintain energy balance, insulin must be secreted from the pancreatic beta cells(ß) by sensitizing the beta cells to the presence of increased levels of glucose in the blood after meals and responding to it, Also, a disturbance in the response of the beta cells(ß) to a deficiency or excess of sugar leads to diabetes **(MACDONALD. 2005**), Physiology Insulin secretion passes through two stages: First, rapid secretion after 5 to 10 minutes after glucose stimulation. Second, insulin secretion remains slow and gradual, which remains a glucose stimulus, However, in the case of type 2 diabetes, the first stage, which is rapid secretion, is skipped, leading to an increase in the blood sugar level after meals **(SPINAS. 2001)**.

The causes of diabetes 2 are complex and are still partly unknown, but its causes remain genetic and environmental factors **(FERY. 2005)**, including obesity, according to the World Health Organization, obesity has been classified as an epidemic that causes type 2 diabetes and the development of its complications. From the beginning, the increasing rate of new onset of diabetes 2 researchers has been linked to resistance Surrounding insulin **(CHOBOT. 2018)**, including obesity in the abdominal area, is the strongest factor leading to type 2 diabetes, as evidenced by 80% of patients suffering from over weight **(FERY. 2005).** Obesity causes fat cells to release increased amounts of fatty acids, glycerol, hormones, inflammatory cytokines and other factors involved in the development of insulin resistance **(DESBRES. 2012**). As well as age, the majority of patients range in age between 55-75years, after which the prevalence rate decreases due to deaths due to the disease **(RIGALLEAU. 2007),** Manystudies have proven a linkbetween type 2 diabetes, and other causative factor sex ‹Genetic factors‹Physical activity‹Smoking and alcohol‹Thyroiditis and diabetes **(BADACHE. 2019),** the spread is also wide spread in developing countries, where the ages of people range between 40 - 60 years, meaning the working age is greater compared to developed countries. It affects people who are more than 60 years old, and this change is related to lifestyle **(OZOUGWU. 2013)**.

4.3. Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy **(MPONDO. 2015),** this condition is associated with fetal stillbirth, metabolic disorders in newborns, and related problems **(COUSTAN. 2013),** it is accompanied by an increase in intrauterine complications **(BOUGHERARA. 2017).**

Gestational diabetes (GDM) is the result of exaggerated insulin resistance and decreased insulin secretion, and it poses a great danger to the mother and child due to its complications **(BAMMOU. 2022),** It is considered a phenomenon of imbalance in a woman's body during pregnancy, and the imbalance begins in the 6-month due to the hormones she secretes Placenta with the possibility of a woman with gestational diabetes returning to her normal state after pregnancy, as well as the possibility of developing type 2 diabetes in the future **(MOHAMED. 2022)**.

4.3.1. Pathophysiology (GDM)

Gestational diabetes mellitus (GDM) is considered to be a typical condition of glucose intolerance in which a woman previously undiagnosed with diabetes exhibits high levels of blood glucose during the third trimester of pregnancy **(CHEN. 2015).** Insulin resistance and impaired beta cell(β) function, both contribute to GDM, Pregnancy is a diabetogenic state characterized by impaired insulin sensitivity **(SINGH. 2008).** It appears at the beginning of the second chapter It increases gradually during the third trimester of pregnancy It can result from a combination of an increase in Maternal fat mass and its "anti-insulin" effect **(BOUGHERARA. 2017),** the major contributors are the placental hormones namely, human placental lactogen, progesterone, cortisol, growth hormone and prolactin. These hormones cause decreased phosphorylation of insulin receptor substrate -1 and thus profound insulin resistance **(SINGH. 2008),** It ensures that adequate nutrition reaches the fetus resulting from changes in carbohydrate and fat metabolism in the mother. Glucose is delivered to the fetus through the placenta through a 30% increase in the mother's essential endogenous hepatic glucose production. The pathophysiology of gestational diabetes and type 2 diabetes is also similar. Gestational diabetes could be a reflection of an early stage of type 2 diabetes that occurs in the course of pregnancy **(PIRSON. 2016)**.

4.3.2. Etiology

Gestational diabetes (GDM) has serious long-term consequences for the mother and the unborn child: the mother is at very high risk of developing type 2 diabetes (T2D) while the children carry risk factors, of cardio metabolic diseases from the age of 7 - 10 years **(MAYMONE. 2013)**, among the classic risk factors are a personal history of gestational diabetes, maternal age and obesity, and among the non-classical risk factors are either physiological **(**low birth weight, small maternal size**),** or pathological **(**insulin resistance, polycystic ovary syndrome**) (PIRSON. 2016)**.

Gestational diabetes causes an increase in the rate of caesarean sections and severe perinatal complications, due to mechanical problems at the moment of birth: shoulder dysplasia (which is more dangerous for (GDM), clavicle fractures or of another nature, brachial plexus lesions **(BOUGHERARA. 2017)**.

Most women with gestational diabetes suffer from beta cell(β) dysfunction that manifests as insulin resistance, Defects in beta cell(β) function may also be due to autoimmune destruction of pancreatic beta cells(β) typical of type 1 diabetes or due to monogenic mutations **(KAAJA. 2008),** Hormonal, inflammatory, and immune factors also contribute to insulin production, secretion, and action, leading to insulin resistance, including the development of gestational diabetes, Lifestyle fluctuations **(**diet, decreased physical activity**)** also contribute to its development **(KINTIRAKI. 2023)**.

5. Diagnosis of diabetes

Diabetes causes many health problems and complications (frequent urination, increased hunger, increased thirst...), and as the disease progresses, the patient suffers tissue or blood vessel damage, leading to the development of a more severe case of diabetes, which results in complications (retinopathy, neuropathy...), and diabetes may lead to death.

Early diagnosis is one of the most important steps necessary for this condition **(EI-SAPPAGH. 2016) (BALAJI. 2019) (SALIM. 2005),** the tests needed to reach a diagnosis of diabetes are:

- **plasma glucose**

Percentage of a plasma glucose test in a normal person (<140 mg/dL) or (<7.8 mmol/l) **(COLAGIURI. 2002)**, compared to the percentage of people with diabetes (≥200 mg/dL) or (≥11. 1mmol/l) **(EMANCIPATOR. 1999)**.

❖ **Fasting plasma glucose**

The rate of the Fasting plasma glucose test in a person in a normal state (<100 mg/dL) or (<5.6 mmol/l) **(PETERSMANN. 2018),** compared to the percentage of people with diabetes (≥126 mg/dL) or (≥7.0 mmol/l) **(ALBERTI. 2010)**.

❖ **Oral glucose tolerance test**

The HbA1C test rate in a normal person (<5.7%) or (<39 mmol/mol) **(PETERSMANN. 2018),** Compared to the percentage of people with diabetes (≥6.5%) or (≥48 mmol/mol) **(KARNCHANASORN. 2016)**.

6.Complications of diabetes

6.1. Acute complications

High blood sugar leads to initial symptoms such as: increased thirst, increased urination, fatigue, and blurred vision **(GROTZKE. 2013).** Diabetic ketoacidosis (DKA), hyperosmolar non-ketotic coma (HNC), lactic acidosis (LA), are among the most important acute metabolic complications of diabetes **(FISHBEIN. 1995)**.

6.1.1. Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis most often occurs in people with type 1 diabetes as a result of imbalances in insulin levels, which results in an increase in the ketone hormone in the blood or urine. Urinary tract infections and gastroenteritis are the most important causes of diabetic ketoacidosis that can occur in patients with type 2 diabetes **(DHATARIYA. 2020)**.

6.1.2. Hyperosmolar non-ketotic coma (HNC)

It is characterized by the absence of ketoacidosis, severe hyperglycemia, and hyperosmolarity. It is one of the most common acute complications in patients with non-insulin-dependent diabetes, which can be treated by controlling diet or oral blood sugar-lowering agents. One of the most common causes of the disease is infection, especially gram-negative pneumonia **(CIAMMAICHELLA).**

6.1.3. Lactic acidosis (LA)

It is a wide anion gap metabolic acidosis **(ENGLISH. 2004)**. It is known as a significant decrease in bicarbonate levels and arterial blood pH and a further increase in lactic acid levels **(KRZYMIEN. 2013).** Imbalance in the circulatory or respiratory system results in tissue hypoxia and thus excessive production of lactic acid. Shock is the most important causes associated with lactic acidosis **(OLIVA. 1970)**.

6.2. Chronic complications

Chronic complications of diabetes are classified into: micro-vascular and macro-vascular complications **(YAMAZAKI. 2018)**.

6.2.1. Micro-vascular complication

6.2.1.1. Diabetic retinopathy

The risk of diabetic retinopathy leads to vision loss as a result of prolonged diabetes **(IGHODARO. 2018).** one of the most important reasons for the development of diabetic retinopathy is the presence of small blood vessel aneurysms in the capillaries of the retina **(BAILES. 2002).** High blood pressure and uncontrolled high blood sugar affect the development of retinopathy. Retinopathy is classified into two categories: Proliferative retinopathy is the most dangerous compared to non-proliferative retinopathy, which is caused by bleeding and dilatation of blood vessels **(HSUEH. 1992)**.

6.2.1.2. Diabetic nephropathy

Nephropathy affects both type 1 and type 2 diabetics. Its characteristics include increased urinary albumin excretion or decreased renal glomerular filtration rate **(MEZIL. 2021).** In addition; end-stage kidney disease is the main factor in nephropathy **(TRIPATHI. 2006).** the duration of diabetes, high blood pressure, blood sugar control, and dyslipidemia are among the most serious causes of nephropathy **(REDDY. 2020)**.

6.2.1.3. Diabetic neuropathy

Diabetic neuropathy is one of the severe complications in diabetics, characterized by imbalances in the skull, nerves, thoracic nerves, or extremities **(BANSAL. 2006).** Lack of response of nerve receptors to mechanical stimuli and heat is the main cause of neuropathy. The most important initial symptoms of neuropathy are burning feet and a pins and needles sensation **(SAID. 2007).** the severity of symptoms also varies depending on the type of fiber involved **(EDWARDS. 2008)**.

6.2.2. Macro-vascular complications

6.2.2.1. Peripheral artery disease

A disease caused by atherosclerosis, specifically in the lower extremities. Diabetes is associated with an increased risk of peripheral artery disease, as inflammation of the blood vessels leads to disorders in the vessel wall and thus causes atherosclerosis **(THIRUVOIPATI. 2015)**.

6.2.2.2. Coronary artery disease

Coronary artery disease as a result of hardening of the coronary arteries, which leads to death. Among the risk factors for coronary artery disease is diabetes, as high blood sugar and insulin resistance lead to endothelial cell and platelet dysfunction and thus the ability to clot blood **(AL-NOZHA. 2016)**.

6.2.2.3. Cerebrovascular disease

Cerebrovascular diseases are a group of diseases that are caused by a defect in the blood vessels in the brain, for example: a stroke in which an artery that feeds the brain is blocked or torn **(PORTEGIES. 2016).** High blood sugar in patients with type 2 diabetes leads to damage to blood vessels and disorders of sugar or fat metabolism **(ZHOU. 2014)**.

7.Treatment

Traditional medicine is a combination of knowledge and practice, used to diagnose and eliminate physical or mental illness, and is based on ancient experience and observations passed down from generation to generation **(ABAYOMI. 2010).**

In the majority of areas of pathology, plants have been used for therapeutic purposes, can be used also to treat chronic diseases such as diabetes mellitus which is based on use plant extract and natural active ingredients **(SCHLIENGER. 2014).** Several plants are recognized for their anti-diabetic properties, Due to its large reservoir of active ingredients. The constituents include glycans, proteins, and mucilages. Other than that, the compounds that have been identified include flavonoids, steroids, triterpenoids and Alkaloids. The majority of anti-diabetic recipes are prepared through decoction and maceration of various components of medicinal plants **(BENKHNIGUE. 2014)**, as Recent studies have shown that certain extracts have a hypoglycemic effect, while others have an anti-hyperglycemic effect **(HOLALY. 2017)**.

Chapter II: Date nuts

1.Date palm

1.1. Generality of date palm (*phoenix dactylifera*)

Date palm has long been one of the most important fruits crops in the region of the Arabian Peninsula, north Africa and the middle east **(NEUTON. 2013)**. There are more than 100 million date palm trees cover approximately 1.3 million ha of the earth surface **(GHANIM. 2023)**.

The term *Phoenix* comes from phoenix, name of the date palm among the ancient Greeks who considered it as the tree of the Phoenicians, and *Dactylifera* (Dactylus in Latin) becomes finger shaped as a result of the shape of the fruits and fero (which bears) en Latin.

The palm tree is a monocotyl arborescent of the Arecaeae family (palmae), genus *phoenix* distributed in the tropical region of the world which included 14 species **(GROS. 2013)**.

1.2. Systematic date palm *Phoenix Dactylifera*

- **Group**: *spadiciflora*
- **Order**: *palmea*
- **Family**: *palmaceae*
- **Sub-family**: *coryphoideae*
- **Tribe**: *phoeniceae*
- **Genus**: *phoenix*
- **Specis**: *Dactylifera L* **(ZAID. 2002)**

1.3. Morphology of date palm

The date palm is a tree whose diameter varies from 0.4 to 1 m and the hight of 30 to 40 m, characterized by:

- Fasciculate root system without a pivot.
- Vegetative system composed: the trunk, palm and dates (**CHOUCH. 2014)**.

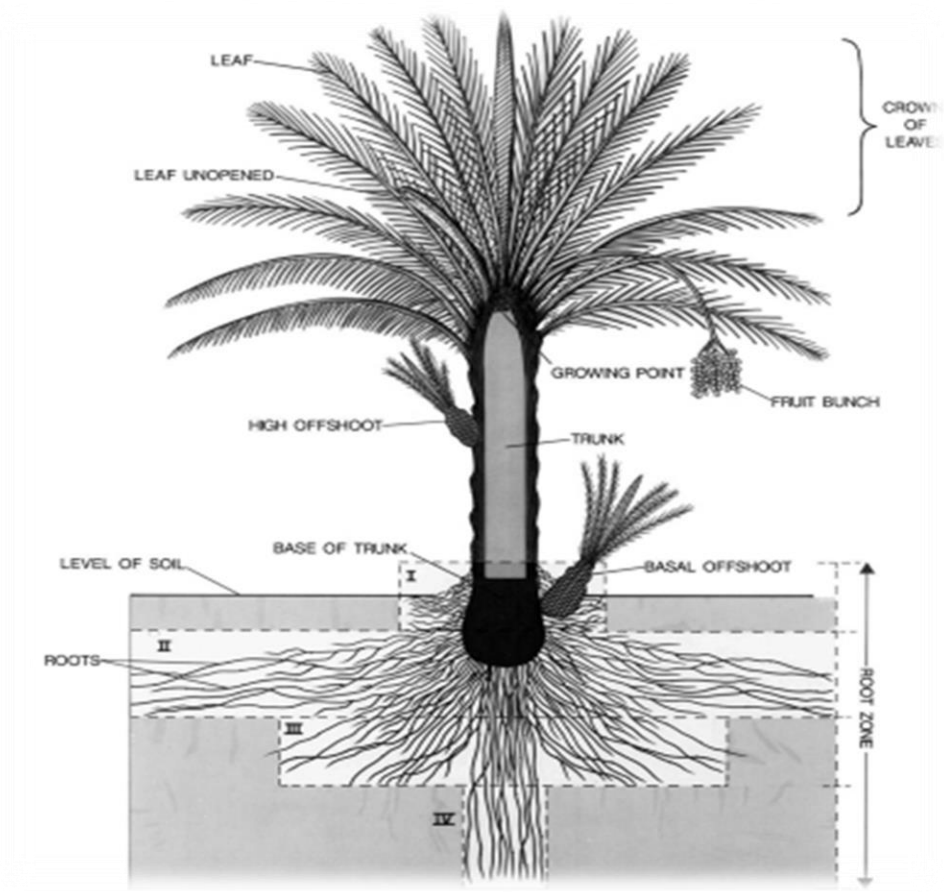


Figure 08: Diagrammatic representation of date palm structure **(CHAO. 2007).**

1.4. Geographical distribution of date palm in Algeria

The palm grove is essentially concentrated in the South-East, its importance decreasing towards the West and the South. The Algerian orchard is located as follows: in the South-East of Algeria the Oued, Ouargla, and Biskra, and the South-West there are Adrar and Bechar, and in the extreme South Ghardaia, tamanrasset, Tindouf and Illizi **(MESSAR. 1996)**.

Statistics reveal that there are more than 18 million palm trees occupying an area exceeding 160 thousand hectares **(NOURANI. 2023)**. The Deglet Nour variety represents 36.75% of palm trees, the Ghars variety represents 18.80%, and Deglet el Bayda and its counter parts represent 44.44% **(SAKER. 2007)**.

The yield per date palm is estimated at 67.7 kg. the yield of Degla Beida, dry dates, el Ghars amounts to 51.6 kg and 58.2 kg per date palm, compared to production of 86.3 kg per date palm for " Deglet Nour" **(ALGÉRIE PRESSE SERVICE. 2018)**.

Figure 09: Map of the distribution of observation zones and phoenicol in Algeria **(ESPIARD. 2002).**

2.Dates

2.1. Definition and description of Dates

The fruit of the palm tree is a berry, which is generally rectangular or circular in shape, and consists of solid materials surrounded by flesh or pulp, which is the edible part.

- **Epicarp:** It consists of a soft cellulose layer called the skin.
- **Mesocarp: that** varies depending on its sugar content and deep color.
- **Endocarp:** Light-color with a fibrous texture.

Date dimensions vary greatly, with weight ranging from 2 to 8 grams and length from 2 to 8 cm depending on the variety. The colors of dates vary from yellowish white to black, red or dark brown. **(ATALLAOUI. 2015)**.

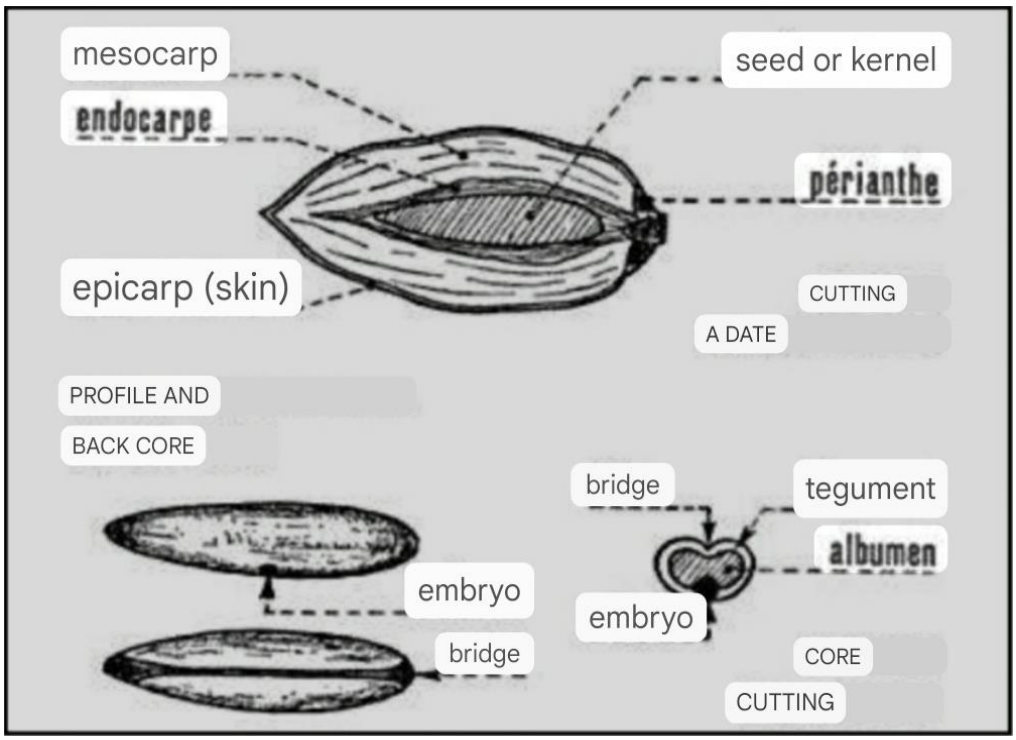


Figure 10: Date palm fruit and seed (CHACHA. 2017).

2.2. Classification of dates

2.2.1. Soft dates

It is characterized by its watery flesh (more than 30%), which is why it requires transformations to reduce the quantity of water to preserve it, like Ghars. It also contains a high percentage of invert sugars (fructose, glucose) **(BOUSDIRA. 2007)**.

2.2.2. Semi-soft dates

the amount of water they contain is less than the previous category (from 20 to 30%), but their freshness is constant, like Deglet Nour **(BOUSDIRA. 2007)**.

2.2.3. Dried dates

Have a naturally dry pulp, containing less than 20% water, like white dakkla **(BOUSDIRA. 2007)**.

2.3. Ripening and formation of dates

During its maturity, the palm fruit passes through several stages of growth and development that include several changes in size, weight, color, texture and taste until the fruit becomes fit for consumption. The time it takes during its growth phase is affected by a number of factors, including genetic factors, climate factors... etc. It can be divided the stages of growth

and development of palm fruits are divided into five stages: (LouLou, Kimri, Khalal, Routab, and Tmar) **(SHABANA. 2006)**.

2.3.1. Stade LouLou

This is the stage that occurs immediately after fertilization or pollination and lasts about five weeks. During this stage, the dates are spherical, green in color, and very small in size, the size of a pea, weighing approximately 1 gram. The stage ends with the two carpels falling unfertilized **(BABAHANI. 2012) (BELAROUSSI. 2019)**.

2.3.2. Stade Kimri

This stage lasts from nine to 14 weeks. The dates are green and are characterized by rapid enlargement of the fruit, a slight increase in sugars and dry matter, and an increase in the concentration of tannins and starch **(AMELLAL. 2008)**.

2.3.3. Stade Khalal

This stage lasts from three to five weeks, as the fruits begin to turn from green to yellow or red, depending on the variety. This stage is characterized by a slow increase in the weight of the fruits, a loss of moisture, and a significant increase in the formation of sucrose and the deposition of tannins, which results in the fruits becoming softer in season Texture **(ZABER. 2012) (EL AREM. 2011)**.

2.3.4. Stade Routab

This is the stage when the dates are clearly ripened, as they become soft and transparent. This period is characterized by the loss of water and the dates becoming softer and taking on a color between brown and black. Dry dates do not pass through this stage **(ZOUIOUECHE. 2011)**.

2.3.5. Stade Tmar

This is the stage when the dates are fully ripe, so that they become harvestable. The stage is characterized by the loss of water and the adhesion of the skin to the pulp **(ZOUIOUECHE. 2011)**.

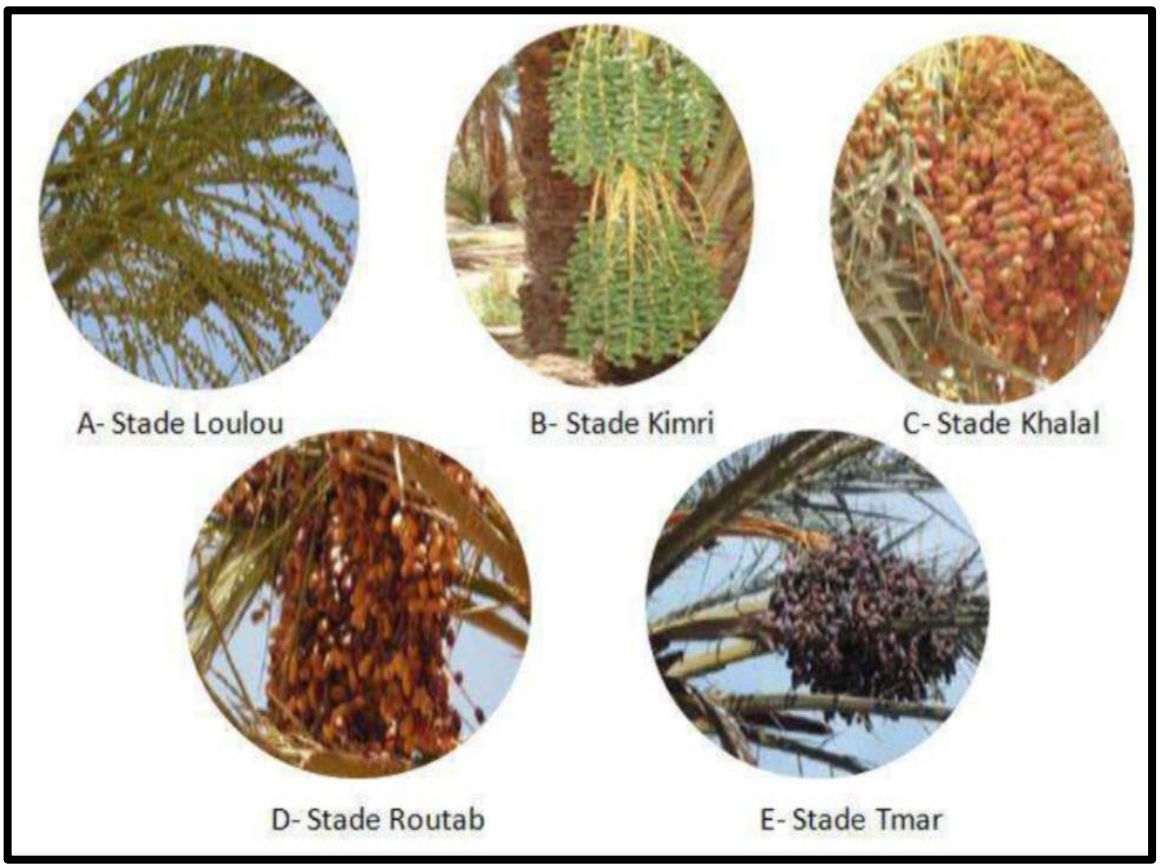


Figure 11: (A, B, C, D, E). - Stages of date evolution **(SAYAH. 2018).**

3. Ghars date

3.1. Definition

Ghars A very rustic variety, found in most Algerian palm orchards. The ripe fruits of Al-Ghars are characterized by a soft texture and an irregular rectangular shape. Their ripening continues from August until September. They are eaten fresh or preserved **(TALHAOUI. 2015) (SAYAH. 2018)**.

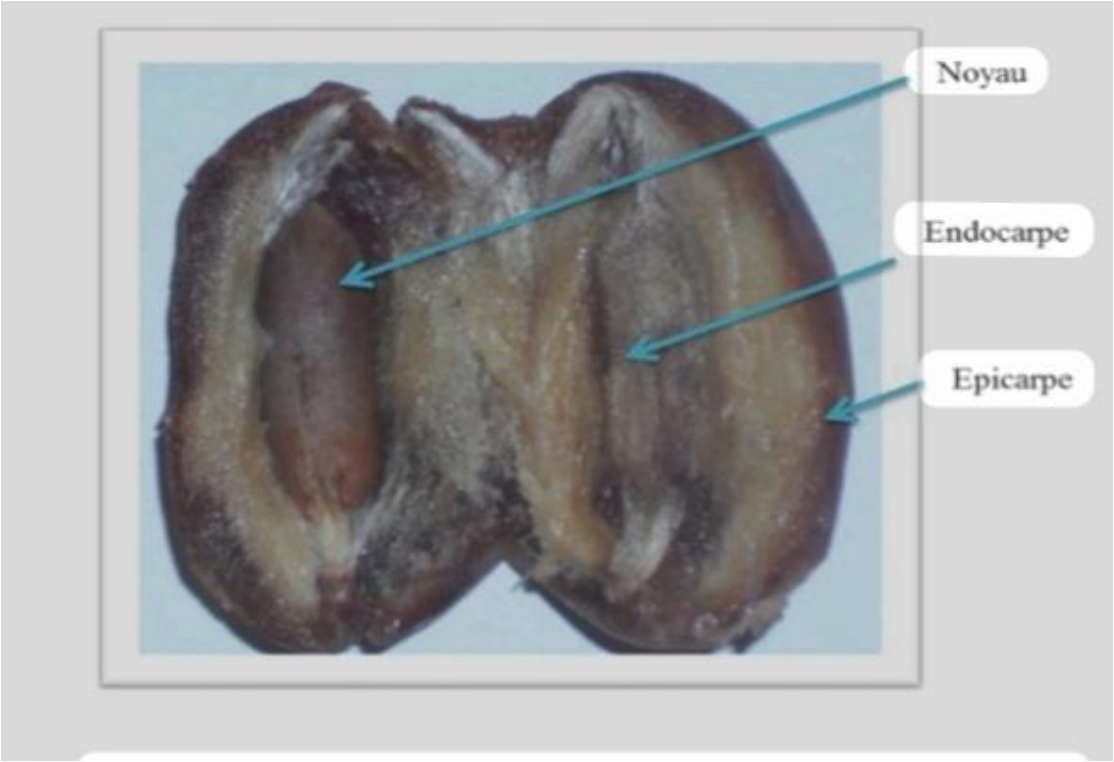


Figure 12: The parts of the date palm fruit (Ghars variety) **(ZOUIUECHE. 2011)**.

3.2. Morphological characteristics of Ghars dates

Ghars dates are soft dates with a straight shape, yellow in color at the ripening stage and brown in the date stage. The Mesocarp contains fibrous tissue **(SAYAH. 2018)**.

Table 01: Characteristics of Ghars dates **(SAYAH. 2010)**.

Fruit caractère	Ghars
Date shape	Ovoid
Color at the Tmar stadium	Dark brawn
Consistency	Soft to semi-soft
plasticity	Tender
texture	Fibrous
Taste	Fragrant
Core shape(g)	Ovoid
Core color (g)	Brown
Date weight(g)	8,81
Pulp weight(g)	7,28
Core weight(g)	1,13
Date size(cm)	4,47
Core size(cm)	2,73
Stone/ date (%)	12,87

4. Date kernel or seed

4.1. Definition and description

It is a rectangular nucleus and varies in size. Its size ranges from 8 to 16% of the date weight, i.e. from 0.5 grams to 4 grams, its length ranges from 1.2 to 3.6 grams, and its width ranges from 0.6 to 1.3 cm. Its color is between gray the brown color consists of horny albumen with a solid consistency surrounded by a layer or membrane of cellulose. The pulp of dates contains a higher percentage of fat than that found in meat. It contains the main fibers in cellulose and hemicellulose **(AL-FARSI. 2011)**.

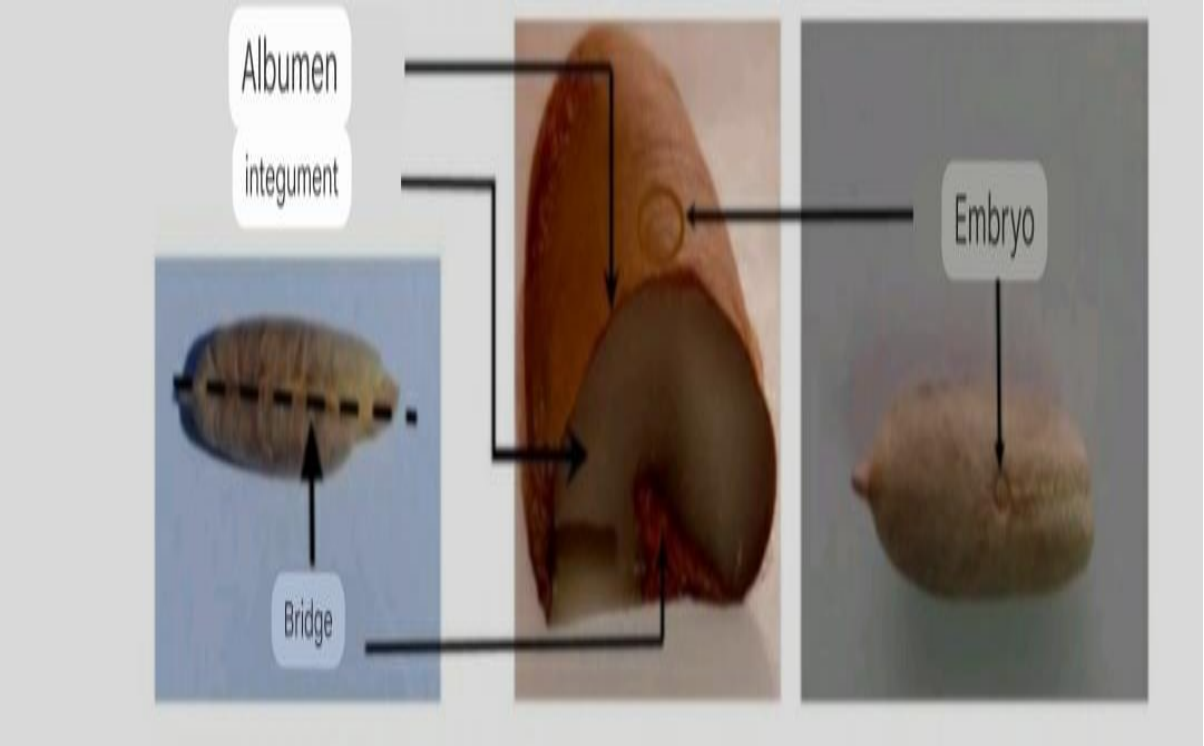


Figure 13: Date pit **(BENMAHDI. 2019)**.

4.2. Biochemical composition of the date seed

The date kernel contains proteins, carbohydrates, fats, and minerals (K, P, Ca, Na, Fe, Mn, Zn, Cu). In addition to the presence of proteins and fatty acids such as oleic, palmitic, lauric, linoleic, and palmitic acids **(BENMEHDI. 2019)**.

Table 02: Composition of date seeds of Ghars on g/100 gDw **(ACHOUR. 2022)**.

date	Moistur	PH	Ash	Protein	carbohydrate	Grude cellulose	Energy valus
Ghars	10,92± 0,01	6,18± 0,04	1,10± 0,03	6,40± 0,2	71,11± 0,84	14,18± 0,05	422,11 (Kcal/100g)

4.3. Physical proprieties of date seeds Ghars

- shape: sub cylindrical.
- weight (g): 0.99± 0.33
- length: 2.26± 0.06**(ACHOUR. 2022)**.

4.4. Mineral proprieties of date seeds Ghars

Table 03: Mineral concentrations (mg/Kg dry Weight) of date seeds **(ACHOUR. 2022)**.

Mineral	concentration (mg/Kg dry weight) of date seeds
K: 3900	
Na:2000	
Fe:47.4	
Zn:15.9	
Mg:7.42	
Cr:3.94	
Cu :0.30	
Ni<0.4	
Se<0.04	
As<0.75	
Cd<0.05	

4.5. Application of date seeds

4.5.1. Food

date seeds are an interesting source of hight-added value bioactive compound, regarding their potential use in food industries **(OUAHIOUNE. 2020)**. It is taken as a substitute for coffee that its looks taste, smells, coulour, odour and flavor like a coffee (**VENKATACHALAM. 2016)**, the absence of caffeine and the high level of total phenolic compounds in date seed can serve as a strong motivation factor who want to characteristic flavor of coffee without raising daily caffeine intake **(GHNIMI. 2015)**.

Another study found that it can be as an excellent source of dietary fiber that's why they application in some bakery products like bread and muffins **(AHFAITER. 2018)**.

4.5.2. Medecine

The functional ingredient of date seeds has used in traditional medicine to relieve toothaches and lower the risk of cardiovascular disorders **(ALHARBI. 2021)**, and have an

effect on sexual hormones **(ALDHAHERI. 2004)**. Date pits was also applied in diet based therapie due to its rich photochemistry **(NIAZI. 2017)**.

4.5.3. Cosmetic composition:

Current research is carried out with the non-therapeutic use of an effective amount of date seed extract in soaps **(JULIA. 1987)**. It also used to treat the skin manifestations of aging, or to reduce wrinkles and soften the skin **(JAUVE. 2006)**.

Chapter III: Material and Methods

1.Materials

1.1. Plant material

The dates were collected from the Ghars variety in the fall season of 2023 from El Oued (Debila) Province, where they were washed and dried in a special place.

preparation of samples (cores)

preparation of cores includes the following steps:

- **coring**: separation of the cores from the dates (the separation process is very simple; we separate them manually.
- **washing**: the seeds are washed several times with tap water, to remove all the impurities that stick to the date seed.
- **drying**: the date seeds were dried according to the traditional method, the date pulps were spread on a clean and ventilated bed, in the shade and protected from humidity, for approximately two weeks.
- **Crushing**: crushed using a grinder.

1.2. Products

Products	Chimic formula	Degree of purity
Hydrochloric acid	Hcl	36 %
Magnesium	Mg	99.99 %
Ferric chloride	$Fecl_3$	98 %
Methanol	CH_3OH	99.85 %
Ethanol	C_2H_5OH	60 – 90 %
Folin ciocalteau	C_6H_6O	99.5 %
Sodium carbonate	$Na_éCO_3$	99 %
Aluminum chloride	$Alcl_3$	99 %
Vanillin	$C_8H_8O_3$	99 %
Trichloroacetic acid	$C_2Hcl_3O_2$	99 %
Ether	$C_4H_{10}O$	99 %
Chloroform	$CHcl_3$	99 %
Sodium hydroxide	NaOH	80 %
Glucose	$C_6H_{12}O_6$	99 %
Sulfuric acid	H_2SO_4	98 %
Copper sulfate	$CuSO_4$	98 %

Sodium potasium titrate	$KNaC_4H_4O_6$	99 %
Bovine serum albumin	$C_8H_{21}NOSi_2$	98 – 99 %
Phosphoric acid	H_3PO_4	25 %
Ascorbic acid	$C_6H_8O_6$	99 %
Potassium ferricyamide	$C_6N_6FeK_3$	98 %
Amidon	$C_6H_7N_30$	99 %
Disodium phosphate	Na_2HPO_4	99 %
Sodium chloride	Nacl	99 %
Dintrosalicylic	$C7H4N_2O7$	98 %
Hexane	C_6H_{14}	95 %
Petroleum ether	C_6H_{14}	80 – 100 %
Ethyl acetate	$C_4H_8O_2$	99.5 %
Butanol	C_4H_9OH	99 %

2.Methods of analysis

2.1. Phytochemical test

Preparation of the aqueous extract

5g of date kernel powder was mixed with 100ml distilled water, and then placed in a water bath device at 40 degrees for 30 minutes, and then we filtered it to obtain the extract **(KANERIA. 2012).**

2.1.1. Detection of flavonoids

5ml extract + 5ml alcochloride (4ml ethanol + 1ml concentrated HCL) + 0.5g of magnesium,

The appearance of a yellowish-orange color indicates the presence of flavonoids **(LOCK. 2006).**

2.1.2. Detection of tannin

1ml extract + 1ml water + 2 drops of Fecl3 (5%).

The appearance of a bright green color indicates the presence of tannin.

2.1.3. Detection of polyphenols

2ml extract + a few drops of Fecl3 (2%)، The appearance of green color indicates the presence of polyphenols **(N'GUSESSAN. 2009).**

2.1.4. Detection of alkaloid

1ml extract +1ml water +3 drops of dragendorff reagent,

The appearance of brown color is evidence of the presence of alkaloid.

2.1.5. Detection of saponins

2ml extract + 2ml distilled water

Shake for 15 seconds, and then rest for 15 minutes.

The appearance of 2cm foam is evidence of the presence of saponin **(RIZK. 1982).**

2.2. Extract preparation

- 20g powder +70/30 Alco-hydraulic (70 ml methanol, 30 ml distilled water).
- Soak the mixture for 24 hours then we repeated the filtration process 3 times.
- The solvent was evaporated in a rotary evaporator at 50°C to remove methanol.
- The phase aqueous was evaporating at 50°C in oven After 24 hours, we get the extract.

2.3. Estimating the yield

The yield is a division between the mass of the plant extract and the mass of the dry matter used in the extraction (the mass of the dry starting material).

Yield % = (M / M_0) * 100

M = Extract mass.

M_0 = Mass of primary dry plant matter.

3.Determination of total phenolic contents in crude extracts

The total phenolic contents of the crude extracts were determined according to the Folin-Ciocalteu's phenol reagent method of **(CHOUIKH. 2020)** we mixed 0.2 ml of the extract with 1 ml of Folin-Ciocalteu reagent (10%), and then we added 0.8 ml of sodium carbonate solution (7.5%). After stirring the test tubes, we let them rest for 30min, the absorbance was measured at 765 nm using the spectrophotometer UV. The total phenolic content was expressed as (mg of Gallic acid equivalents in gram of extract).

4.Determination of flavonoids contents in crude extracts

According to **(CHOUIKH. 2020)** we blended 1 ml of the extract with 1 ml of $AlCl_3$ solution (2%). After stirring the test tubes, we let them rest for 60 min at room temperature

based on the measured absorbance 430 nm, and then the content of flavonoids in the extract was expressed in (mg /g of extract).

5.Determination of total condensed tannins contains (HTC)

According to **(LAIB. 2023)** the condensed tannins contain (HTC) were calculated. 2mg of extract powder was mixed with 2ml of distilled water, where we prepared concentrations (10 mg/ml-100 mg/ml) of extract. We take 125 µL of sample in each tube; Added 750 µL of freshly made vanillin reagent (4%vanillin in methanol) and 375 µL of strong hydrochloric acid were pipetted into an aluminum foil-wrapped tube with the sample. The mixture was thoroughly mixed before the hydrochloric acid was added. The reaction's absorbance against water was evaluated at 500 nm after 15 minutes at 20 to 2°C.Catechin was utilized to create the calibration curve.

6.Preparing extracts for estimation of primary metabolites (proteins, carbohydrates and lipids)

The extracts were prepared for the determination of primary metabolites according to the method of **(CHOUIKH. 2020)** from powdered plant samples follow the following steps:

- Take 0.5 g of date pits and put them in a bowl.
- Add 5 ml of trichloroacetic acid (20 %), then mix with a magnetic shaker for 5 minutes, and then put it in glass tubes.
- Separate the mixture in a centrifuge for 10 minutes at a speed of 3000 rpm and obtain the supernatant 1 with which we estimate the carbohydrates.
- As for precipitate 1, we add 2 ml of ether/chloroform solution (1V/ 1V).
- The mixture was separated again by centrifuge for 10 minutes at a speed of 3000 rpm to obtain the supernatant 2 from which we estimated the lipids.
- As for sediment 2, we add 5 ml of 0.1 sodium hydroxide solution, shake the mixture, and then estimate the protein using it.

6.1. Carbohydrate quantification

Preparation of glucose standard solution

Dissolve 5 mg of glucose in 5 ml of sulfuric acid (1N) to obtain a solution with a concentration of 1000 µg/ml, from which a series of standard solutions with concentrations 25, 100, and 200 µg/ml were prepared.

Practical steps for estimation

- Place 1 ml of the prepared standard solution as well as the sample extract (supernatant 1) in glass test tubes.
- Add 1 ml of phenol (5%) then 5 ml of concentrated sulfuric acid.
- Shake and leave the samples for 15 minutes.
- Reading the optical absorbance at a wavelength of 490 nm using a spectrophotometer.
- Draw the standard curve by taking advantage of the results of reading standard solutions that determine the concentration of carbohydrates in each sample in mg/ml.

6.2. Protein quantification

Preparation of solutions

- Solution (A): It is prepared by mixing 50 ml of sodium carbonate Na_2CO_3 (2%) with 50 ml of sodium hydroxide NaOH (0.1N).
- Solution (B): Prepared by mixing 10 ml of copper sulphate solution (CuSO4) (0.5%) with 10 ml of sodium-potassium titrate solution $kNaC_4H_4.O64H_2O$ (0.1%).
- Solution (C): It is prepared by hydrating a concentrated Folin-Ciocalteau solution at a ratio of (1V/1V).
- Solution (D): Prepare basic copper sulphate reagent by mixing 50 ml of solution (A) with 1 ml of solution (B).
- **Preparation of protein standard solution**
- Dissolve 3 mg of bovine serum albumin (BSA) protein in 3 ml of sodium hydroxide NaOH (0.5 N) to obtain a solution with a concentration of 1000, from which a series of standard solutions with concentrations of 100, 400, 600, 800 and 1000 µg/ml were prepared.

Practical steps for estimation

- Place 0.2 ml of the prepared standard solution along with the protein extract from the samples in glass test tubes.
- Add 2 ml of solution D.
- Add 2 ml of solution C.
- Leave in the dark for 30 minutes at laboratory temperature.
- Reading the optical absorbance at a wavelength of 750 nm using a spectrophotometer.

- Draw the standard curve using the reading results of the standard solutions which determine the protein concentration in each sample in mg/g of dry matter.

6.3. Lipid quantification

Prepare the lipid standard solution

Dissolve 2.5 mg of oil (100 % soda) in 1 ml of solution ether/chloroform (1V/V1) to obtain a solution with concentrations of 1000, 1500, 2000 and 2500 µg/ml.

Prepare the Sulfophosphvanillinic reagent solution

Dissolve 75 mg of vanillin in 11 ml of distilled water, then add 39 ml of phosphoric acid H_3PO (85%) to obtain a volume of 50 ml.

Practical steps for estimation

- Place 0.1 ml of the prepared standard solution as well as the sample extract (supernatant 2) in glass test tubes.
- Add 0.1 ml of concentrated sulfuric acid.
- Shake the tubes and leave them for 10 minutes in a water bath at 100°C.
- After the tubes cool, we take 0.15 ml from them and put them in other tubes.
- Add 1.5 ml of the prepared reagent (Sulfophosphvanillinic).
- Mix the tubes in the dark for 30 minutes.
- Reading the optical absorbance at a wavelength of 530 nm using a spectrophotometer.
- Draw the standard curve by taking advantage of the results of reading standard solutions that determine the concentration of fat in each sample in mg/g of dry matter.
- In the presence of fats, the color of the solution turns pink.

7.Extraction

- Maceration 100g of date kernel powder in 300 ml hydro alcoholic (70 ml methanol, 30 ml distilled water) for 24 hours.
- Filter the mixture three times until the color of the filtrate weakens, that is, extract the largest possible amount, and then put it in a device rotary evaporator to remove methanol.

- Then we performed a selective liquid/liquid separation, starting with hexane at a ratio of 1/3 of the volume of the dissolved extract and repeating the process 3 times.
- After separating the organic phase, we treated the remaining aqueous phase with a trace of petroleum once.
- Then we separated the organic phase and treated the new aqueous phase with chloroform at a rate of 1/3 of the volume of the extract, and the process was repeated 3 times.
- Then we separated the organic phase and treated the new aqueous phase with ethyl acetate once.
- Then we separated the organic phase and treated the new aqueous phase with butanol more than once.

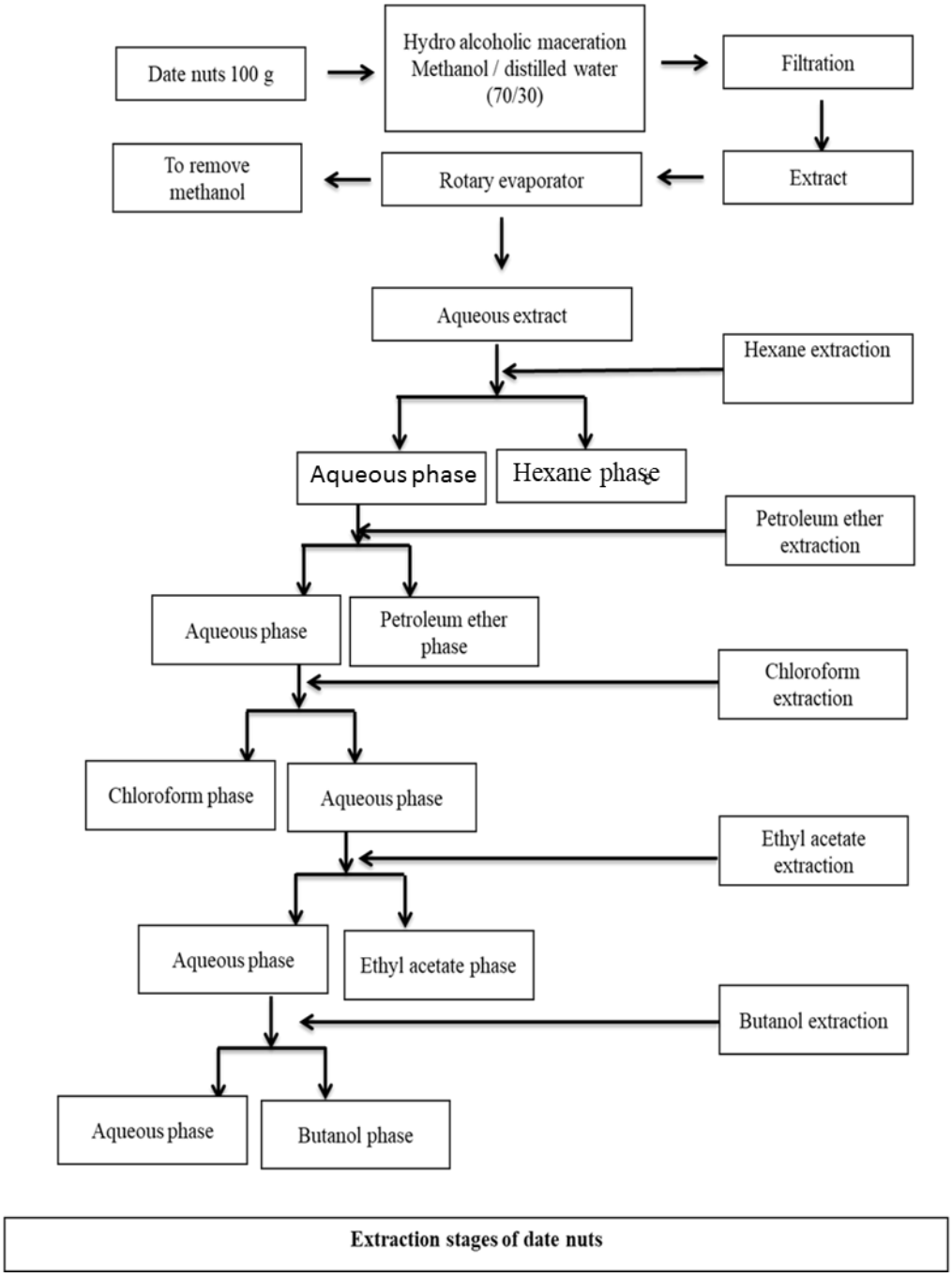


Figure 14: Extraction stages of date nuts

8.Antioxidant test (FRAP)

FRAP Test (Ferric Reducing Antioxidant Power Assay)

In our study, we used ascorbic acid (V.C) as a reference basis for capturing free radicals, where we prepared extended concentrations of (V.C) (10 mg/ml -100 mg/ml).

- volume of each sample with different concentration is made to 250ul using the same solvent employed for extraction of the sample.

- in all the test tubes 625 ul of PBS is added.
- Thoroughly mix the contents in each tube.
- Then, 625 ul of 1% potassium ferricyanide solution is added in all different conc samples.
- After this, each reaction mixture is vortexed well using a vortex shaker.
- The samples are incubated at 50°C for around 20 minutes.
- Once the incubation time is over, 625 ul of 10% TCA is added in each sample.
- The test tubes are centrifuged at 3,000 rpm for 10 minutes.
- from these centrifuged samples, 625 ul from supernatant is collected in separate test tubes.
- Then, to these new separate test tubes having 625 ul supernatent, we add 625 ul of deionized water.
- After this, in the same new separate test tubes, we add 125 ul of ferric chloride.
- This would give us bluish color formation.
- And then take measurement at 700nm.

The antioxidant activity linked to the reducing power of the extracts is expressed in Reducing Power (RP) using the following formula **(DIENG. 2017)**:

$RP = 100 (A_a - A_b)/ A_a$

A_a: extract absorbance.

A_b: absorbance of white.

9.Anti-microbial test

This is the basic technique used to study the antimicrobial effect of a substance. Petri dishes containing Sabouraud dextrose agar supplemented with 2% glucose (for yeasts) and Mueller-Hinton agar (for bacteria) are aseptically inoculated with a suspension of 10^6 cells/mL obtained from a young culture of yeasts or bacteria, respectively. Inoculation is done by swabbing. After the dishes have dried, the agar is perforated at the center using the upper part of a Pasteur pipette. The resulting cavities are filled with the aqueous solution of the extract at concentrations of 100, 50, 25, and 12.5 mg/mL (approximately 50 µL per well). The dishes are incubated in an incubator at 37°C for 48 hours for yeasts and 24 hours for bacteria. Inhibitory action is indicated by the formation of a zone of inhibition around the wells. The results are read by measuring the diameters of the inhibition zones. A product is considered active if the diameter of the inhibition zone is greater than 6mm **(KIEHLBAUCH. 2000) (BONEV. 2008).**

10.Anti-diabetic activity

10.1. Using a yeast cell

This protocol involves studying the ability of plant extracts to improve glucose absorption by yeast cells. Here are the main steps:

1. Washing Yeast: Commercial yeast (*Saccharomyces cerevisiae*) is washed by centrifuging it several times in distilled water. This helps remove impurities and prepare a 10% yeast suspension in distilled water.

2. Preparation of extract solutions: Different concentrations of herbal extracts are prepared, ranging from 160 mg/mL to 20 mg/ml.

3. Mixing with glucose solution: Each extract solution is mixed with 2 ml glucose solution at a concentration of 25 mM.

4. Incubation: The mixture of plant extract and glucose is incubated at 37°C for 10 minutes.

5. Adding the yeast suspension: After incubation, 200 µL a yeast suspension is added to the mixture, followed by vortexing to ensure good mixing. Everything is then incubated at 37°C for specific times: 15, 30, 60 and 120 minutes.

6. Centrifugation: After incubation, the tubes are centrifuged to separate the yeast cells from the reaction medium.

7. Measurement of glucose concentration: In the supernatant obtained after centrifugation, the glucose concentration is measured using a spectrophotometer at a wavelength of 540 nm according to the method of **(CIRILLO. 1962) (BURGER. 1959).**

Increase in glucose uptake % = [(Abs control – Abs sample) / Abs control] * 100

10.2. Enzymatic method

❖ **preparation of solutions**

- mixture of 1g Amidon with 100ml tampon: pH=6.9 (0.1324 g H_2NaSO_4, 0.2788 g Na_2HPO_4 and 0.039 g NaCl).
- α amylase prepare by 0.0253 g of α amylase in 100ml distilled water.
- DNS: mixture of 12g potassium sodium tetrahydrate and 8 ml NaOH (2M) and 20 ml Dintrosalicylic (96 mM).

❖ **preparation of extract solutions**

- Different concentrations of plant extracts are prepared ranging 0,25_0,5_1_2 mg/ml, from a stock solution (0.01 g extracted with 5ml distilled water).

- incubation: 100 µL of plant extract and 900 µL α amylase is incubated at 37°C for 10min.
- after incubation, 500 µL Amidon added to the mixture, all incubated at 37°C for 10 min.
- after the second incubation, 500 µL DNS and meters were added in a tide bath with a temperature of 120°C for 5min and cooling.
- after cooling added 3ml distilled water and measured using a spectrophotometer at a wave length of 540 nm.

11.Statistical analysis

The results Standard Deviation, average, reducing power %, IC50, Significance ($p \geq 0.05$) and ANOVA were obtained and represented in curves and graphs using the Excel program.

Chapter IV: Results and Discussion

1.Phytochemical study of date seeds type "Ghars "

Through a phytochemical survey, it was found that date pits are rich in secondary metabolic products.

❖ **Flavonoids test:**

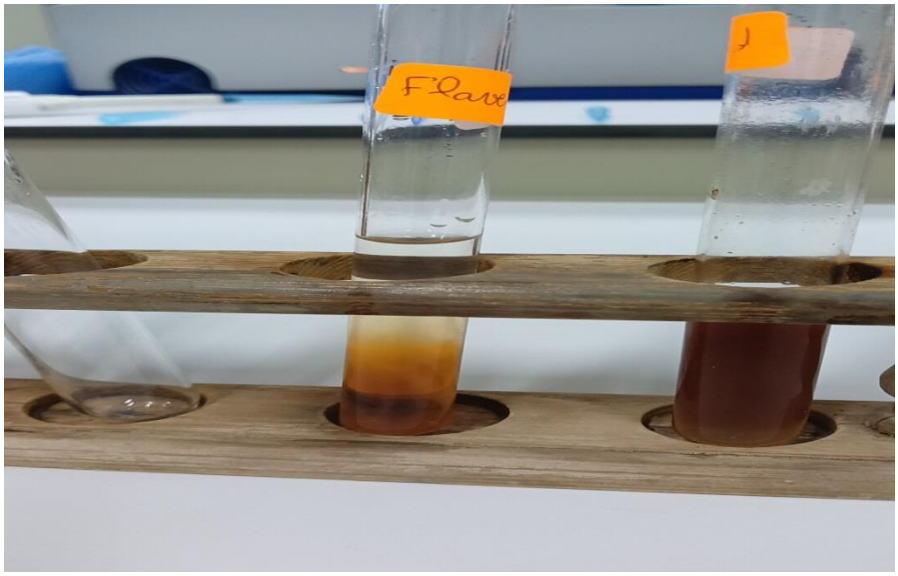


Figure15 : Flavonoids test results.

Changing the color of the extract to orange is evidence of the presence of flavonoids.

❖ **Tannin test:**

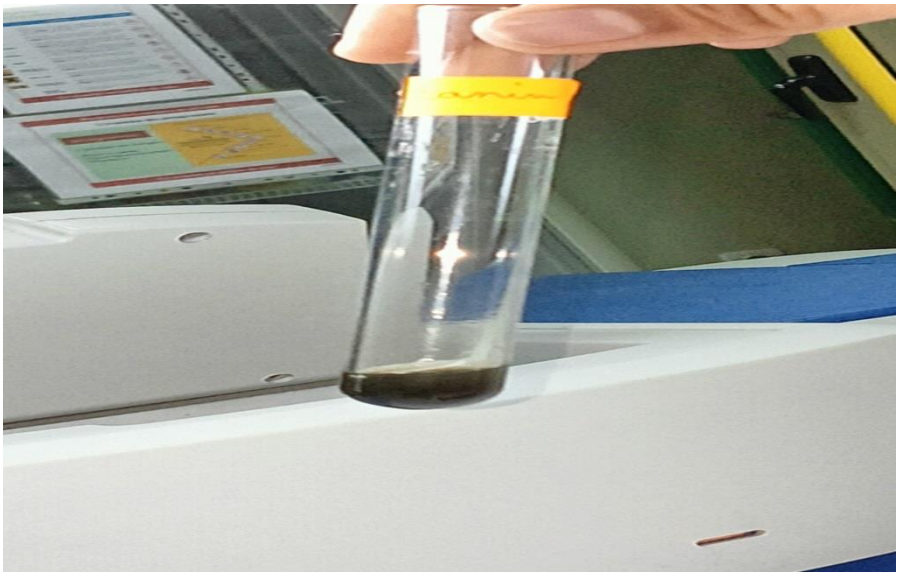


Figure 16: Tannin test results.

The appearance of a dark green color is due to the presence of tannins.

❖ **Polyphenols test:**

Figure 17: Polyphenols test results.

The color of the extract changes to green due to the presence of polyphenols.

❖ **Alcaloid test:**

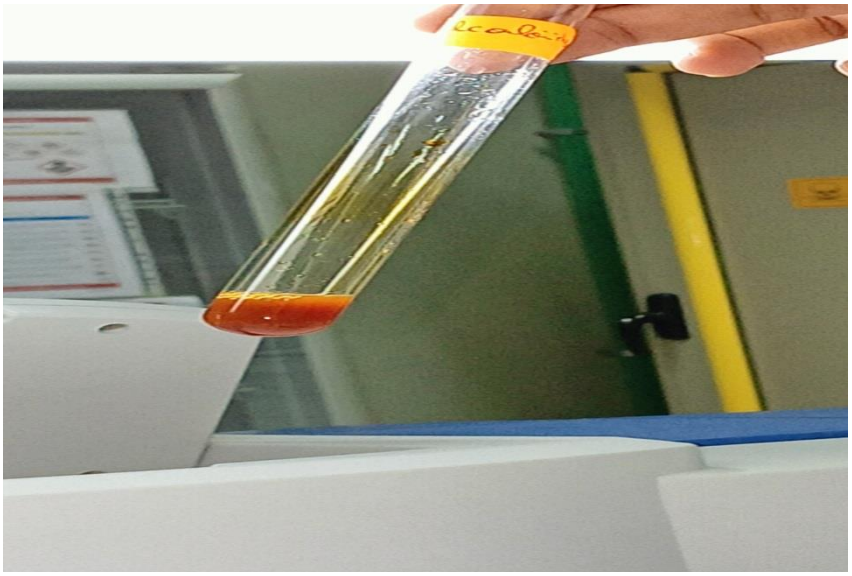


Figure 18: Alcaloid test results.

The appearance of brown color indicates the presence of alkaloids in the extract.

❖ **Saponin test:**

Figure 19: Saponin test results.

A 2cm thick foam forms, indicating the presence of saponin.

2.Estimating the yield

Yield = (2.45 g / 20 g) * 100 = 12.25 %

After the hydromethanolic extraction process (70/30), the yield was estimated according to the aforementioned relationship at 12.25%.

The yield of hydromethanolic extracts for Ghars seeds at **(BOUNOUA. 2023)** was estimated at 13.5%, which was close to our results. It was found that the yield of the hydromethanolic extract of Deglet Nour seeds was 10.7% according to **(MESSAOUDI. 2021**), while the results were much lower for **(BARA. 2020),** which relied on aqueous extraction, which was estimated at 4.6%.

The results obtained showed a significant extraction yield estimated for the hydromethanolic extract unlike the aqueous extract.

3.Determination of total phenolic contents in crude extracts

The results for polyphenol content are shown in the following figure:

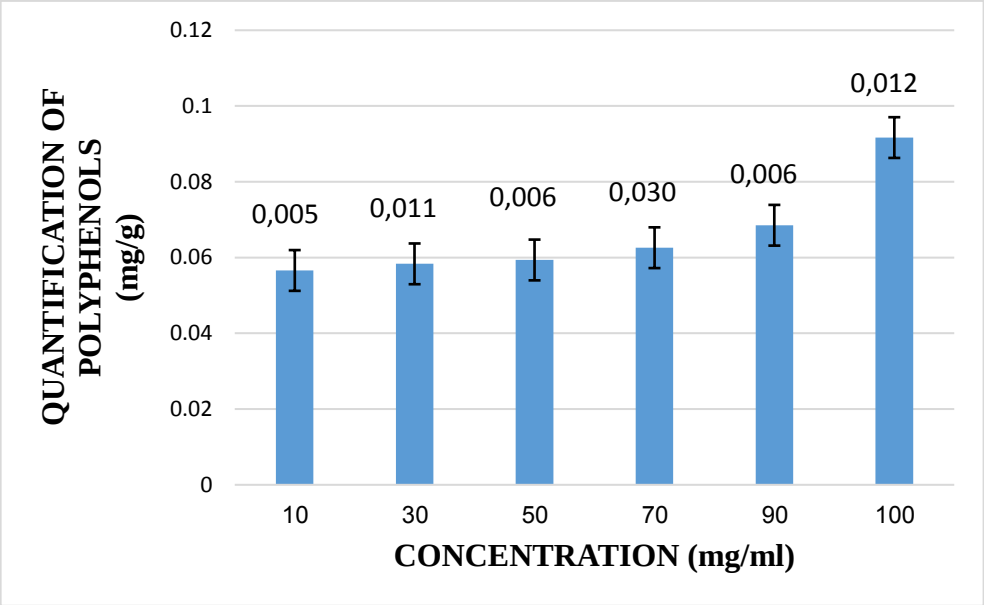


Figure 20: Polyphenols contents (mg/g) in date nuts extracts.

We note from the results obtained that the polyphenol content estimated at (mg/g) increases with increasing concentrations of the extract 10, 30, 50, 70, 90 and 100 mg/ml, where the highest percentage was estimated at 0.0916 ± 0.012 mg/g at a concentration of 100 mg/ml and the lowest percentage 10 mg/ml was estimated at 0.056 ± 0.005 mg/g.

According to the study of **(ANNOUN. 2013)** for the Mesh Degla pits types, values close to our results were obtained, which were found to be 0.117 mg/g, in comparison, a higher percentage was recorded according to **(YOUSFI. 2022)** study of date kernels in the Adrar region, which reached 2.52 mg/g.

Polyphenol is secondary plant metabolite which has influence antioxidant, anti-inflammatory and antimicrobial **(ZILLICH. 2015)** and are compounds that prevent the harmful effects of metals such as lead and mercury **(CHAHRAZED. 2021).**

Differences in polyphenol concentrations from one date seeds to another are due to several factors, which are the growing conditions (climate, soil....) in addition to the method of storage and ripening. It has also been shown that the grinding process leads to losses in polyphenol content **(BOHN. 2014)**.

The Folin-Ciocalteu reagent acts with sugars and amino acids (has low specificity) which leads to a disturbance in the results of polyphenols **(GÓMEZ- CARVACA. 2006)**.

4.Determination of flavonoids contents in crude extracts

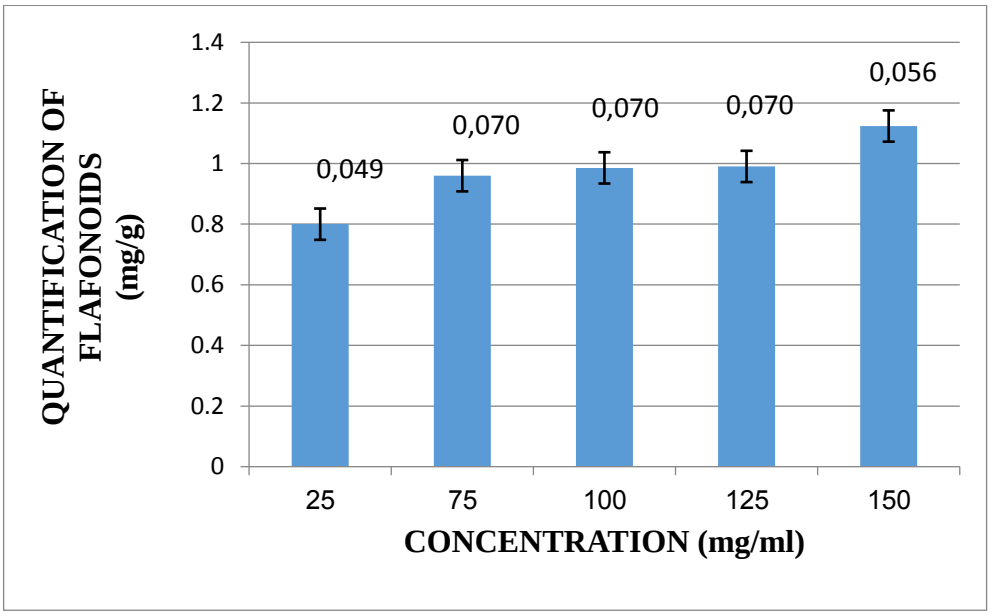


Figure 21: Flavonoids contents (mg/g) in date nuts extracts.

The figure displays the flavonoids contents determined in the five different concentrations 25, 75, 100, 125, and 150 mg/ml. The analysis shows a difference in concentration of flavonoids, the highest flavonoids content was obtained at the concentration 150 mg/ml with a value 1.12 ± 0.056 mg/g, on the other hand the lowest concentration 25 mg/ml with a value 0.8 ± 0.049 mg/g.

Compared to the flavonoids content in the Ghars variety recorded in the **(IMANE. 2023)**study, it is lower than our study with a value of 0.00399 mg/g. On the other hand, high values were also observed on the pits of dates from Batinah (Oman region) with a value of 159.3 mg/g (**AL FARSI. 2008**).

The study shown by **(MOUHOUB. 2017)**, on the seeds of touggourt dates presented a flavonoid content lower than that obtained from our study with a value of 0.5 mg/g.

From the results, it is noted that the flavonoid content depends on the variety of date seeds, the extraction conditions and the nature of the extraction matrix **(BENYAHIA. 2022).**

5.Determination of total condensed tannins contains (HTC)

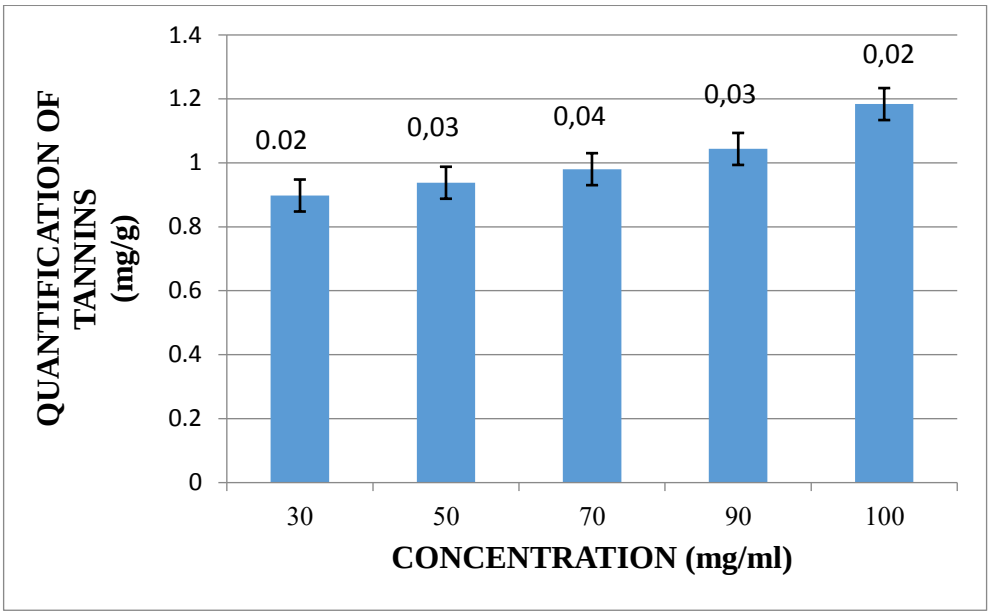


Figure 22: Tannins contents (mg/g) in date nuts extracts.

According to the results obtained in the figure "22" which represents the tannin content of "Ghars" date seeds as a function of different concentrations 30, 50, 70, 90 and 100 mg/ml.

A significant quantity of these compounds is observed varying between 0.897 ± 0.02 mg/g and 1.183 ± 0.02 mg/g at the concentration 30 and 100 respectively. These values are higher than those reported by **(YOUSFI. 2022)** 0.130 ± 0.036 mg/g on date seeds from the Adrar region and lower compared to **(BELBACHIR. 2021)** 3.605 mg/g of Ajwa variety.

6.Estimated nutritional value

Carbohydrates, protein, and lipids were estimated using linear equations for the following standard curves.

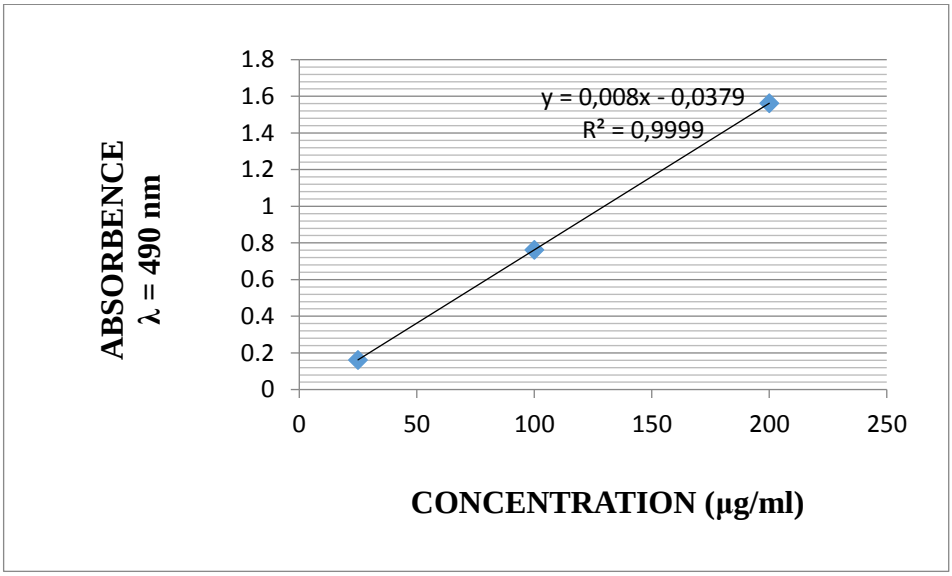


Figure 23: Glucose standard curve.

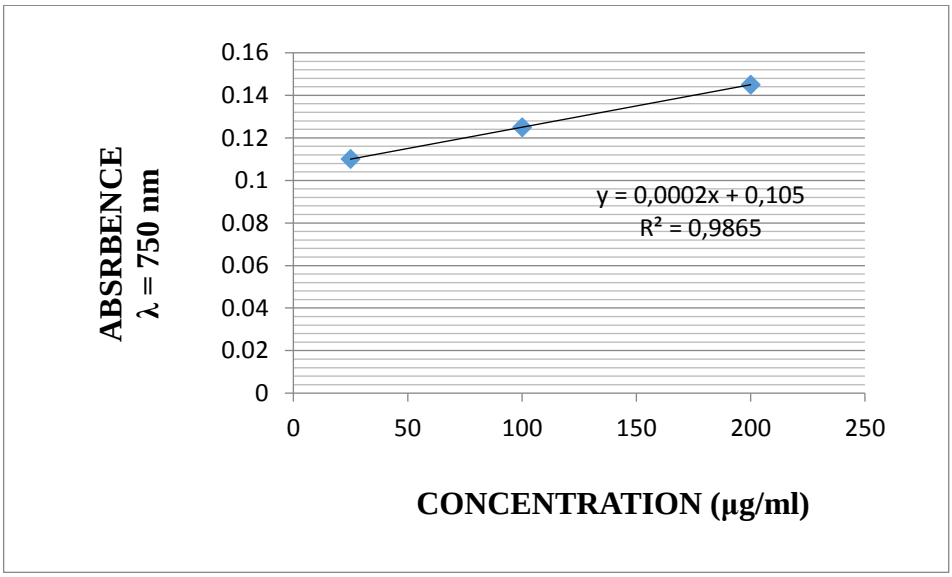


Figure 24: Protein standard curve.

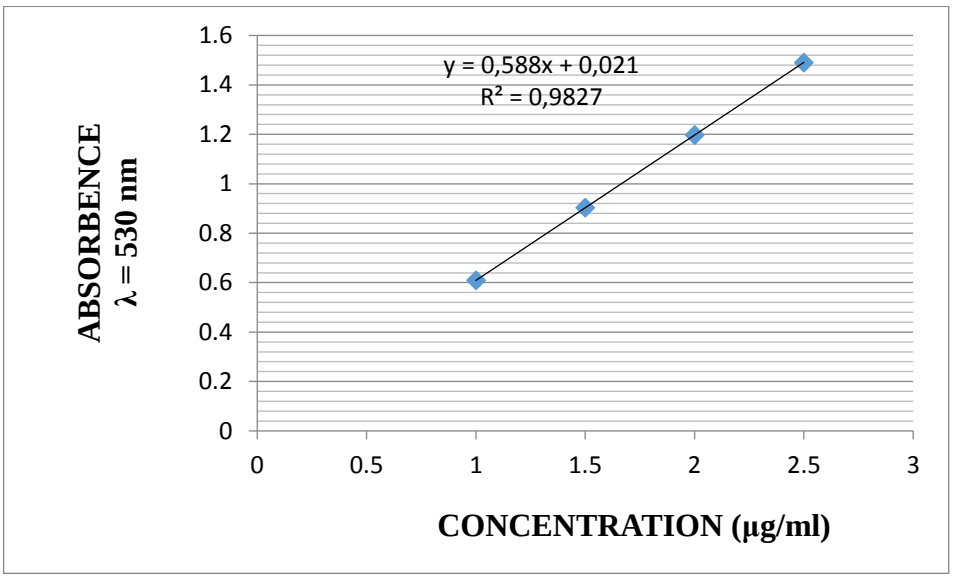


Figure 25: Standard curve for lipids.

The results of nutritional values for carbohydrates, protein and lipid are represented in the following figure.

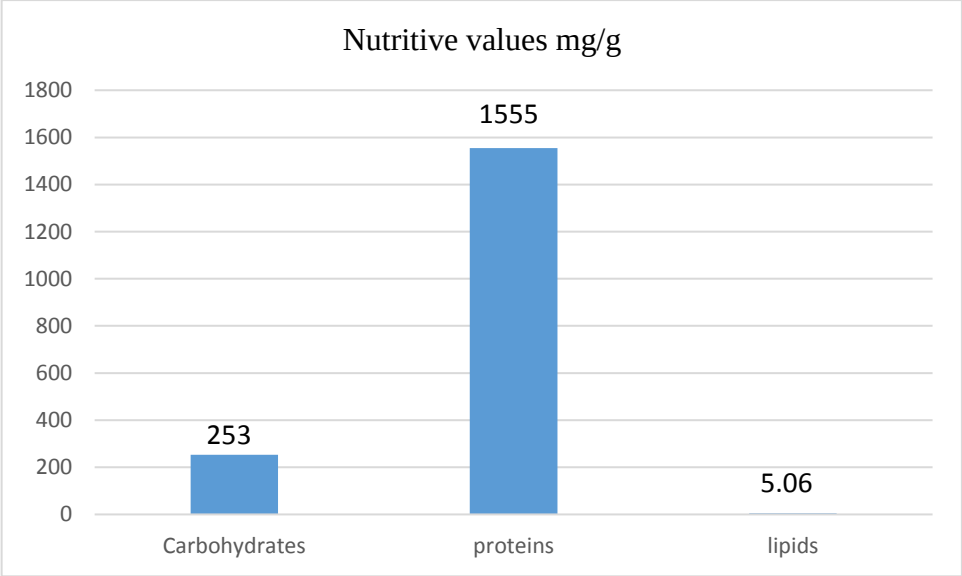


Figure 26: Nutritive values of date seeds variety Ghars.

Nutritional values results showed that date seeds extract is rich in proteins 1555 mg/g and a medium percentage of carbohydrates 253 mg/g, and lacks lipids 5.06 mg/g.

(LEILA. 2018) study recorded the percentage of proteins at 8.25% and the percentage of lipids at 6.58%.

When studying **(BESBES. 2004)** for variety Deglet Nour the percentage of proteins is 9.56 %, the percentage of carbohydrates is 83.1 %, and the percentage of lipids is 10.19 %.

When studying **(SAWAYA. 1984)** for variety Sifri, the percentage of proteins was 6.5 %, carbohydrates were 60 %, and the percentage of lipids was 10.4 %.

7.Antioxidant test

FRAP Test (Ferric Reducing Antioxidant Power Assay)

The reducing power of the date seeds extract of the different concentration and ascorbic acid was calculated in percentage and is presented in the figure 27.

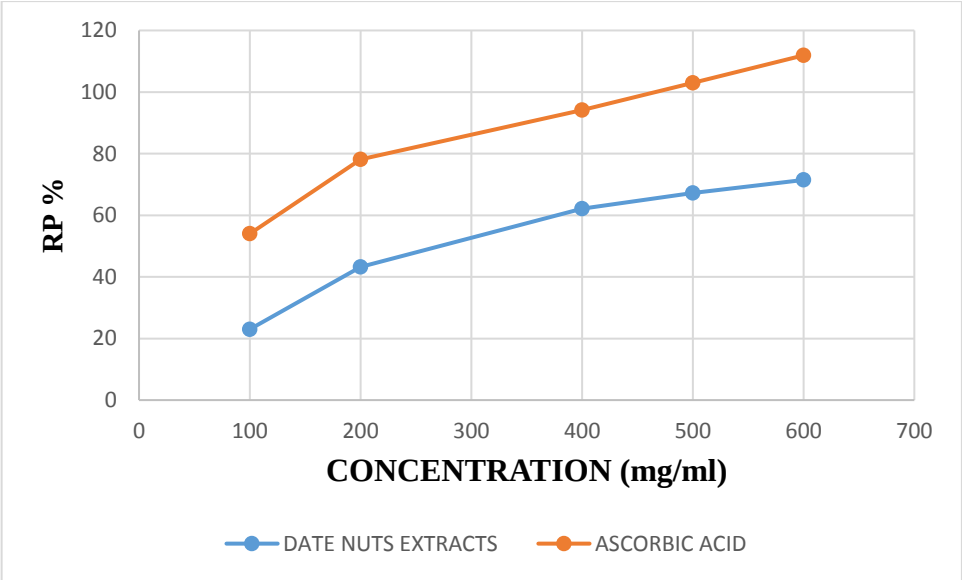


Figure 27: Reducing power of date nuts extract as well as that of ascorbic acid.

According to the results obtained, we found date seeds extract to have antioxidant activity based on the reference ascorbic acid. the ANOVA test indicates a significant difference between the percentages of FRAP inhibition of date seeds extract and ascorbic acid ($p \geq 0.01$).

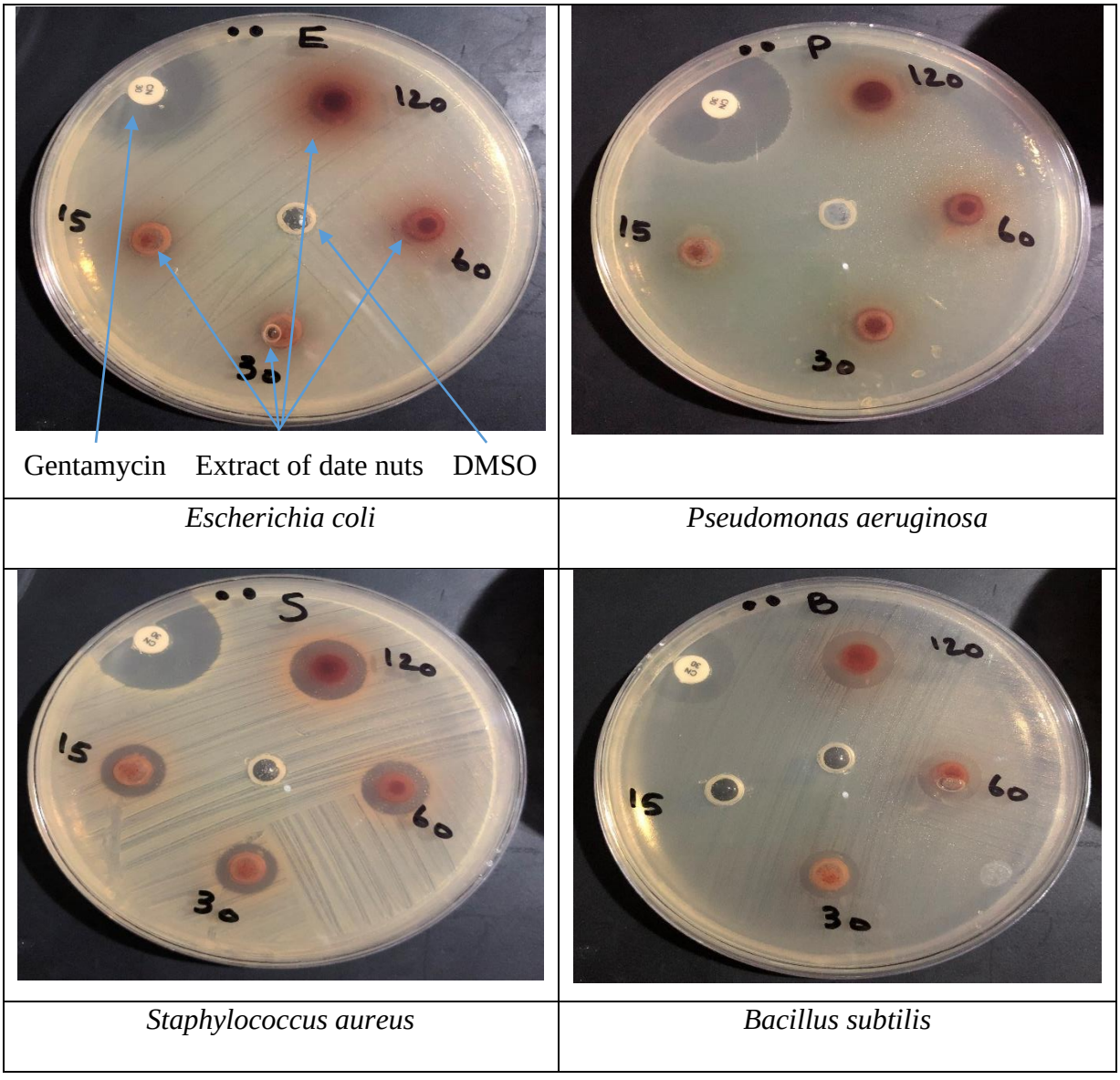
The highest percentage of reducing power for the extract was 71.4701 ± 0.025 % compared to 111.92 ± 0.025 % for ascorbic acid at a concentration of 600 mg/ml, and at a concentration of 100 mg/ml the difference was large, as the results were 23 ± 0.025 % and 54 ± 0.025 % for the extract and ascorbic acid, respectively. The difference in oxidative activity is highlighted using this parameter of inhibition concentration 50 (IC50), Our results for the IC50 323.21 ± 0.025 mg/ml were compared to the IC50 for ascorbic acid 4.57 ± 0.025 mg/ml.

According to **(THOURI. 2017)** in her study on several Korkobi date seeds extracts depending on the solvent. The IC50 percentage for the methanol extracts was better than the acetone extract, as the results for the methanol extract were estimated at 0.27 ± 0.01 mg/ml compared to the acetone extract 0.73 ± 0.045 mg/ml, which concluded that extraction with solvents leads to increased dissolution of selected compounds (polyphenol compounds...),

which give the extract antioxidant properties such as free radical scavengers, hydrogen donors, and reducing agents.

8.Anti-microbial test

Our investigation consists of showing the presence or absence of the antimicrobial activity of the hydromethanolic extract of date seeds of the "Ghars" variety against four bacterial strains Gram (+): *Staphylococcus aureus*, *Bacillus subtilis* and Gram (-): *Escherichia coli*, *Pseudomonas aeruginosa*, and then compare it to that of the standard antibiotic Gentamycin (positive control).



Escherichia coli | *Pseudomonas aeruginosa*

Staphylococcus aureus | *Bacillus subtilis*

Figure 28: Antibacterial activity of Gentamycin (positive control) and hydroalcoholic extract of date nuts on four bacterial strains.

Table 04: Results of antibacterial tests.

Strains used	120 mg/ml	60 mg/ml	30 mg/ml	15 mg/ml	CN
Escherichia coli	10	8	16	NI	24
Pseudomonas aeruginosa	8	NI	NI	NI	25
Staphylococcus aureus	15	14	12	10	23
Bacillus subtilis	13	12	10	NI	15

NI = No inhibition

CN = Gentamycin.

The results and table 04 show the results of the antibacterial activity. the ANOVA test indicates a significant ($p = 0.01$).

Through the results obtained, we notice in the zone of inhibition from one bacteria to another, where the antibacterial activity of *Escherichia coli* is more sensitive to the extract, the zone of inhibition is 16 mm at a concentration compared to *Staphylococcus aureus*, the zone of inhibition is 15 mm at a concentration of 120 mg/ml, which represents a close ratio to *Escherichia coli*. They also found a lower sensitivity to *Bacillus subtilis*, the zone of inhibition is 13 mm at a concentration of 120 mg/ml.

The *pseudomonas aeruginosa* inhibition zone is only 8 mm in the presence of the extract concentration 120 mg/ml.

According to **(GHANIA. 2015)**, in his study of an antibacterial test for date seeds of the Ghars variety, in which he used two extracts, PNDA4 (polysaccharide alkali soluble) and PNDH (polysaccharide), of three types of bacteria, *Staphylococcus aureus*, *Escherichia coli*, and *pseudomonas aeruginosa*, and the results were as follows: In *Escherichia coli*, the sensitivity of the bacteria was greater to the PNDH extract with a length of the inhibition zone of 5mm and to PNDA4 with a value of 3.5mm. As for the PNDA4 extract, the activity was greater with *Staphylococcus aureus* than with PNDH with a value of 6.5mm and 1mm, respectively. In *pseudomonas aeruginosa* bacteria, the results were similar for both extracts, with PNDH and PNDA4 with a value of 4.5 mm and 3.5 mm.

(BOUNOUA. 2023) study showed that date seed extract of the plant species was more effective in *Staphylococcus aureus* 16 mm and *Bacillus subtilis* 10 mm, while *Escherichia coli* 9 mm.

9.Anti-diabetic activity

9.1. Using a yeast cell

Saccharomyces cerevisiae, a single-celled organism with the ability to divide in a specific medium, was used to determine the effect of date seeds extract to increase glucose uptake.

The increase in glucose uptake by yeast cells (not containing the extract) and yeast cells containing date nuts extract was estimated and is represented in the following figure.

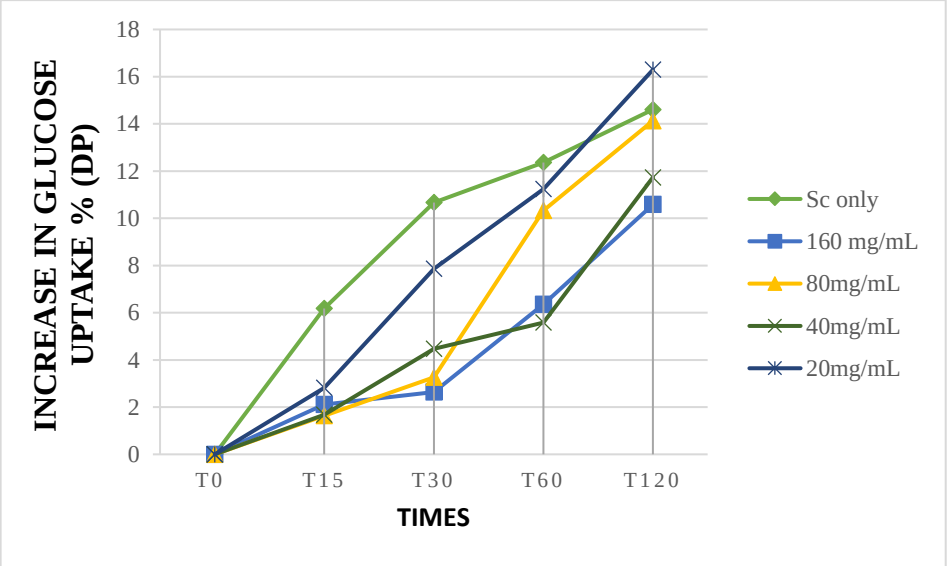


Figure 29: In vitro antidiabetic activity of extracts DP using a yeast cell model represented % glucose uptake by yeast cells mediated by different (DP) extract concentration.

ANOVA test indicates no difference ($p \geq 0.05$)

Sc = *Saccharomyces cervisiae*.

The results of increased glucose uptake in yeast cells that did not contain the extract showed that after T120, the percentage of increased glucose uptake was 14,606%. In the presence of date seeds extract, at a concentration of 20 mg/ml, the rate of increased glucose uptake was 16.292%, meaning that the rate of glucose uptake increased compared to concentrations (40, 80, 120) mg/ml, which reduced the glucose uptake of yeast cells, which was the rate of glucose uptake (11,731. 14,130. 10,582) %, respectively.

We demonstrate that date seed extract at a concentration of 20 mg/ml increases the ability of yeast to absorb glucose (14.606 to 16.292), this suggests that they could also improve glucose uptake by human cells. one that helps maintain lower blood glucose levels in diabetic patients.

9.2. Inhibitory effect of date seeds extracts on α-amylase

α amylase is an enzyme found in human saliva that digests starch and converts it into simple sugars, which is the main source of carbohydrates **(BUTTERWORTH. 2011).**

the percentages of inhibition (%) of the enzymatic activity of α amylase in the presence of the extract of date seed variety Ghars indicated in the figure 30.

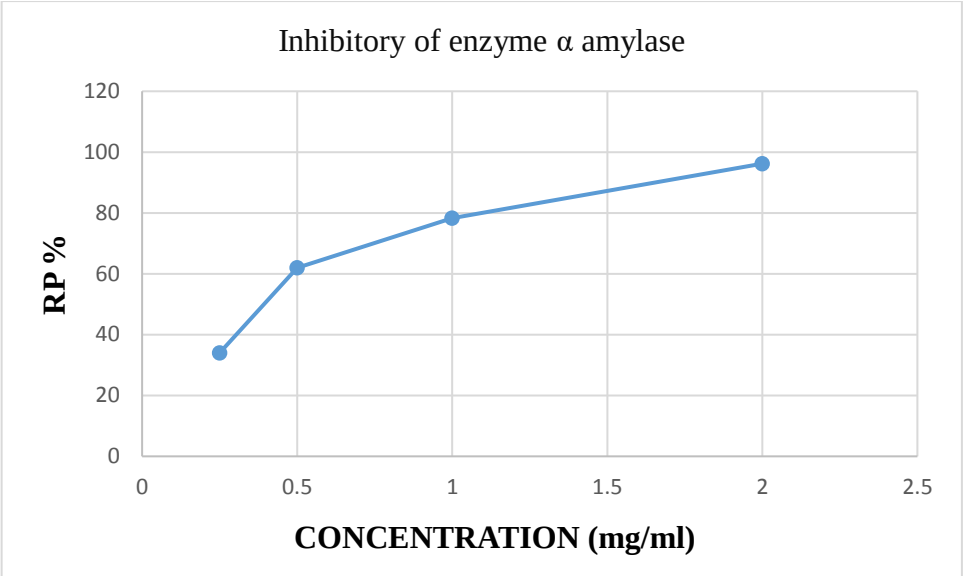


Figure 30: inhibitory activity of date nuts extract on the enzyme α amylase.

Through our study of the effect of date seeds of the Ghars type in inhibiting the activity of the α amylase enzyme at different concentrations (0.25, 0.5, 1, 2) mg/ml, the reducing power was (43, 62,78.3, 96.2) %, respectively, and the IC50 was estimated at 0.229 mg/ml.

Found in **(SIRISENA. 2016)** study at the concentration of 1 mg/g, the reducing power was estimated at 23.98% at Deglet Nour, considering it a smaller percentage than our study, which is represented 78.3% and at the Medjool date type, it was estimated at 57.84%.

By studying **(SHAKOOR. 2020)** for the effect of date seeds in inhibiting alpha-amylase activity, it was found that the reducing power of a concentration of 0.4 mg/ml was estimated at 84.68%, which was compared to tea polyphenol extract, which in turn is known as an inhibitor of alpha-amylase, and whose study concluded that it has the most effective activity of the extract Tea polyphenols.

Alpha amylase enzyme participates in the hydrolysis of starch into simple substances such as disaccharides and monosaccharides. Inhibiting the enzyme hinders the catabolism of starches and thus reduces the concentration of glucose in the blood **(SHAKOOR. 2020).**

Studies have confirmed that flavonoids are effective in inhibiting the α amylase enzyme, as they are characterized by their direct binding to amino acid residues in the active site of the enzyme, thus excluding the binding of the substrate **(ZHU. 2020).**

10.HPLC

The results of separation of the crude hydromethanolic extract of date seeds, ethyl acetate extract, and butanol extract by HPLC are shown in the chromatogram (Figure 31. 32. 33).

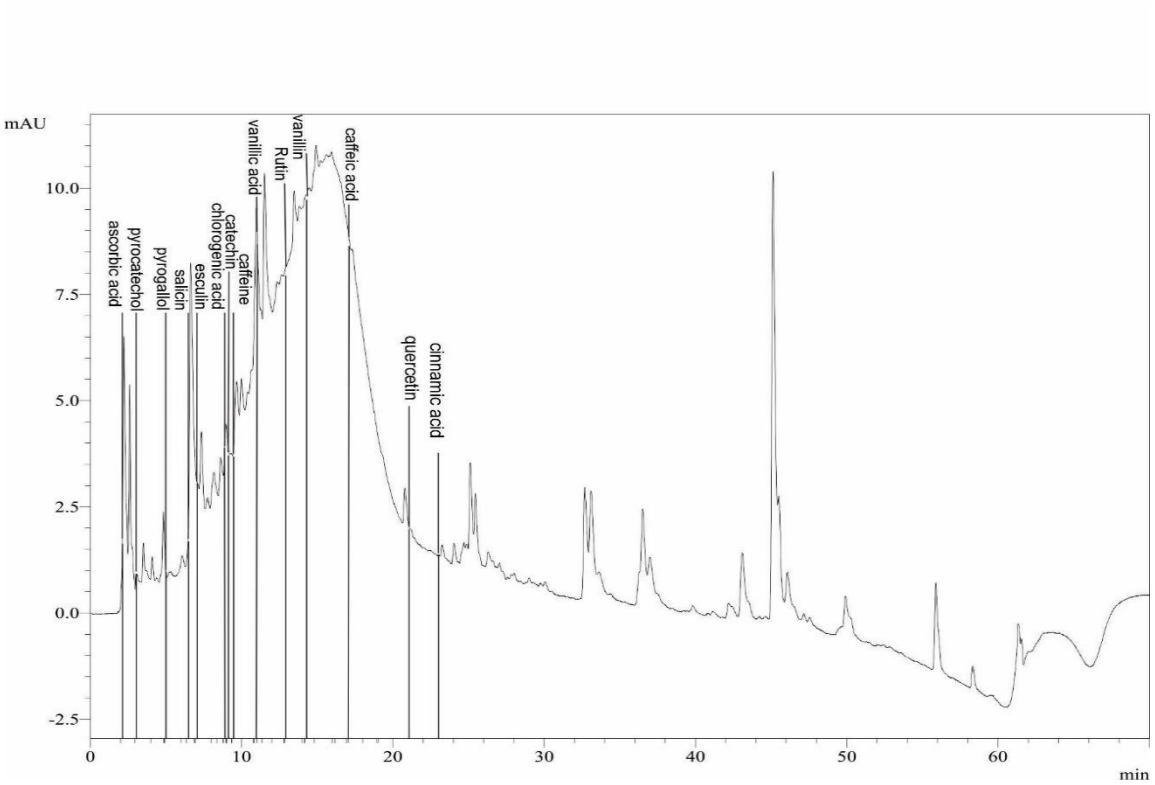


Figure 31: Profile of HPLC chromatogram of hydromethanolic extract of date seeds.

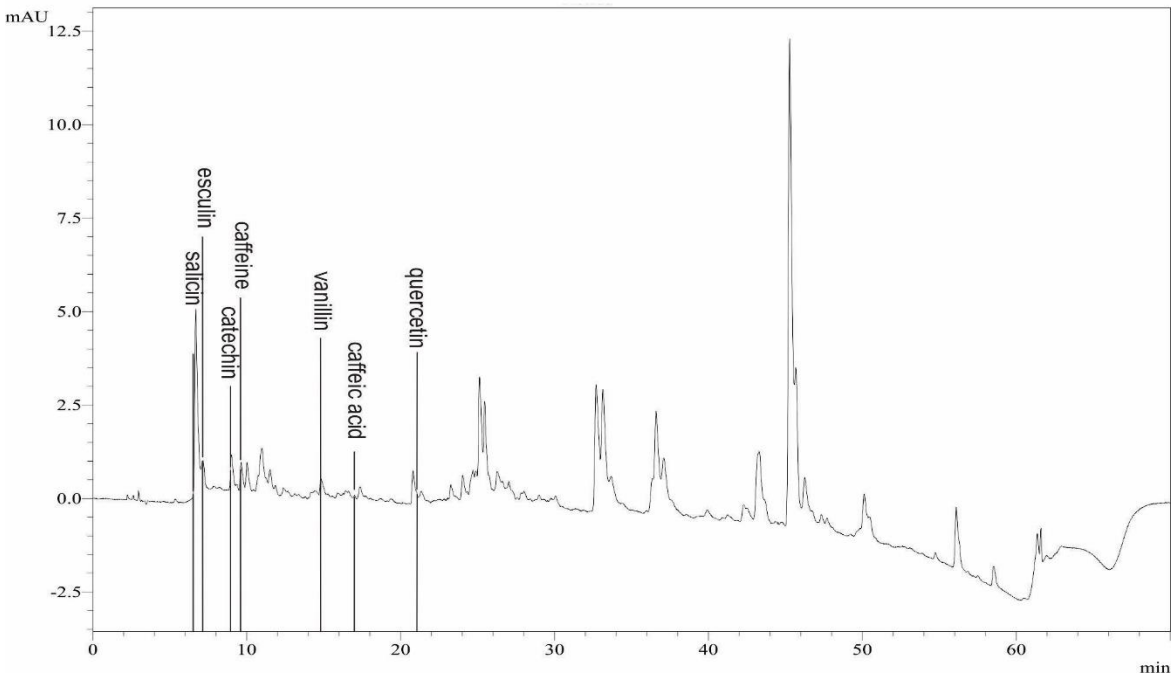


Figure 32: Profile of HPLC chromatogram of ethyl acetate extract.

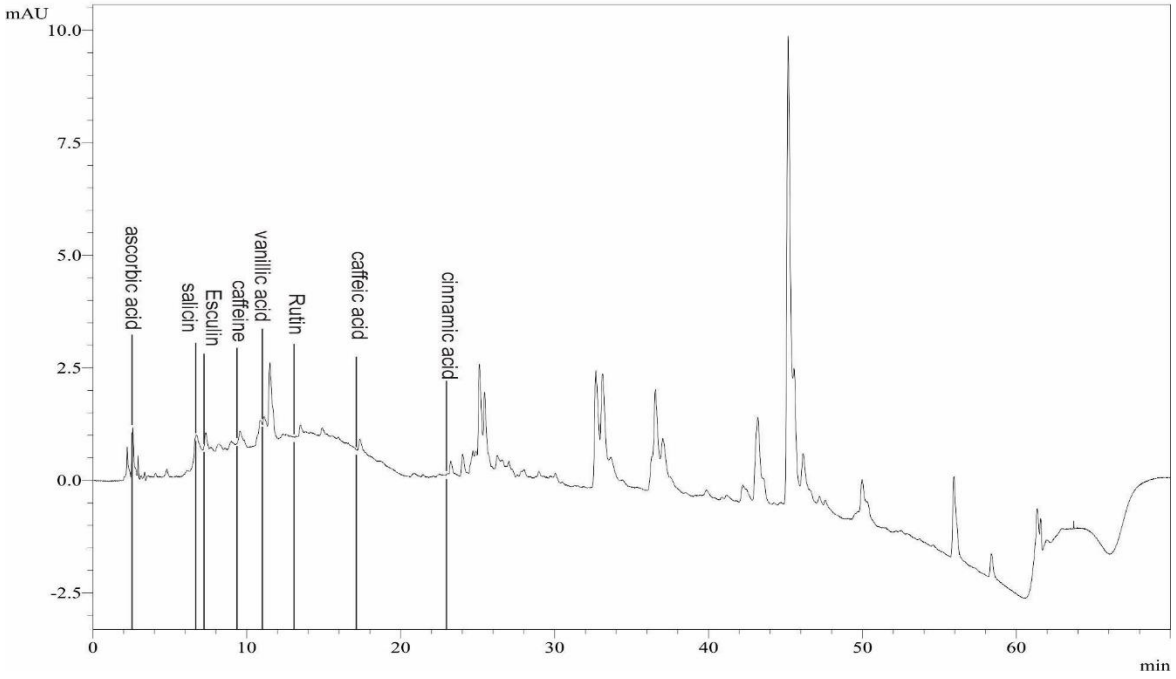


Figure 33: Profile of HPLC chromatogram of butanol extract.

In the hydromethanolic extract of date seeds: HPLC identified 14 phenolic compounds, which are: Ascorbic acid, Pyrocatechol, Pyrogallol, Salicin, Esculin, Chlorogenic acid, Catechin, Caffeine, Vanillic acid, Rutin, Vanillin, Caffeic acid, Quercetin, Cinnamic acid. The concentrations of the compounds and their retention time were recorded in the table 05.

Table 05: Retention time and the concentration of some phenolic compounds identified in hydromethanolic extract of date seeds "Ghars".

Compounds	Retention time (min)	Concentration (µg/mg)
Ascorbic acid	2.220	0.085568
Pyrocatechol	3.755	0.040095
Pyrogallol	5.310	0.054255
Salicin	6.634	16.447814
Esculin	7.338	0.456625
Chlorogenic acid	8.961	0.4429
Catechin	9.333	1.038671
Caffeine	9.674	0.330887

Vanillic acid	11.296	0.040994
Rutin	13.469	1.579202
Vanillin	14.450	0.626251
Caffeic acid	17.301	34.92047
Quercetin	21.216	0.00752
Cinnamic acid	23.252	0.0035

Ethyl acetate extract: The following 7 compounds were identified: Salicin, Esculin, Catechin, Caffeine, Vanillin, Caffeic acid, Quercetin. The concentrations of the compounds and their retention time were recorded in the table06 .

Table 06: Retention time and the concentration of some phenolic compounds identified in ethyl acetate extract of date seeds "Ghars".

Compounds	Retention time (min)	Concentration (µg/mg)
Salicin	6.688	6.7193
Esculin	7.148	0.1008
Catechin	9.003	0.4731
Caffeine	9.633	0.0236
Vanillin	14.826	0.0236
Caffeic acid	17.361	0.1998
Quercetin	21.341	0.0206

As for the butanol extract: 8 compounds were recorded as follows: Ascorbic acid, Salicin, Esculin, Caffeine, Vanillic acid, Rutin, Caffeic acid, Cinnamic acid. The concentrations of the compounds and their retention time were recorded in the table 07.

Table 07: Retention time and the concentration of some phenolic compounds identified in butanol extract of date seeds "Ghars".

Compounds	Retention time (min)	Concentration (µg/mg)
Ascorbic acid	2.600	0.011145
Salicin	6.714	1.4633
Esculin	7.335	0.050332
Caffeine	9.549	0.016369
Vanillic acid	11.126	0.00801
Rutin	13.496	0.01007

Caffeic acid	17.354	0.18954
Cinnamic acid	23.253	0.00332

According to the results, 4 phenolic compounds were found in common between the three extracts, which are: Salicin, Esculin, Caffeine, Caffeic acid. More compounds were recorded in the raw extract, which gives it greater effectiveness and efficiency in terms of the extract's properties, compared to fewer compounds in the ethyl acetate and butanol extracts.

We can explain the benefit of these compounds in the following table.

Table 08: Benefits of phenolic compounds.

Compounds	Benefit
Ascorbic acid	A catalyst for oxidation and reduction and a catalyst for biochemical reactions (JOHNSTON. 2007).
Pyrocatechol	Shows anti-inflammatory activity (FUNAKOSHI. 2020).
Pyrogallol	Molecular glues that bind to biological molecules (SHIN. 2019).
Salicin	Treatment for fever and neuralgia (TOBEY. 1874).
Esculin	Neuroprotection, anti-coagulation, anti-virus (LI. 2022).
Chlorogenic acid	Antibiotic effect (COLONNA. 1970).
Catechin / Quercetin / Rutin	Antioxidants (MEDVIDOVIC-KOSANOVIC. 2010).
Caffeine / Caffeic acid	Pharmaceutical stimulant (KIHLMAN. 1974)
Vanillic acid / Vanillin	Flavor agent, preservative, food additive (SHARMA. 2020).
Cinnamic acid	A role in treating bacterial infections and neurological disorders (RUWIZHI. 2020).

General Conclusion

Many people consider date pits to be waste that is discarded or incorporated into animal feed. However, date pulp provides a variety of health and nutritional benefits that make it indispensable in life and in the fields of medicine and the food industry. It has unique physical properties that make it suitable for use in a variety of applications, including the food, cosmetics and pharmaceutical industries. It is rich in dietary fiber and vitamins and minerals such as potassium, magnesium and calcium. From a chemical standpoint, date pits contain a variety of active compounds that contribute to promoting health and fighting diseases. Many studies show that date pits contain antioxidant compounds such as flavonoids and phenols that protect cells from damage resulting from oxidation and reduce from the risks of chronic diseases such as heart disease and cancer. Through research analyses, it appears that the date kernel has an antimicrobial effect that contributes to preventing the growth of harmful bacteria. These properties make the date kernel the ideal choice in maintaining the health of the system. It is important to emphasize that these benefits depend on consuming date seeds as part of a balanced and varied diet.

Keeping up with the developments of modern science and its recent developments, and in order to find a natural treatment for chronic diabetes, as well as in order to value the products of desert plants, our primary goal was to contribute to estimating part of the chemical content of the pulp of the Ghars date variety and to study the effect of the date seeds on the activity of carbohydrate-digesting enzymes, so that it was Determination of some phytochemical characteristics (date seeds yield, detection of the presence of tannins, alkaloids, saponins, flavonoids, polyphenols), quantitative estimation of primary metabolites (carbohydrates, lipids, protein), and hydromethanolic extracts were exploited in the quantitative estimation of secondary metabolites (polyphenols, flavonoids and tannins) and tested their efficiency in antioxidant activity by testing the iron recovery capacity (FRAP), and also tested their effectiveness in antimicrobial activity and anti-diabetic activity. Through our results we reached:

- The yield of hydromethanolic extract of Ghars seeds was estimated at 12.25%.
- Through chemical testing, it was found that the date seeds are rich in secondary metabolic products (flavonoids, tannins, polyphenols, alkaloids, saponins). They are of great importance in defending against pests and diseases and have health benefits for humans.
- The date seed has a high protein content and a low carbohydrate and lipid content.
- The quantitative content of polyphenols, flavinoids, and tannins recorded the highest value for them, as the highest percentage of polyphenols at the concentration of 100 mg/ml was estimated at 0.0916 ± 0.012 mg/g, and the highest percentage of the flavonoid content at

the concentration of 150 mg/ml was estimated at 1.12 ± 0.056 mg/g. As for the content of tannins at the concentration of 100 mg/ml was estimated at 1.183 ± 0.02 mg/g.

- In order to study the biological activity of date pulp, we examined the antioxidant activity by relying on the FRAP iron recovery ability test. We found that the date seed extract has a strong antioxidant activity, with the IC50 of the extract being 323.21 ± 0.025 mg/ml, ascorbic acid 4.57 ± 0.025mg/ml.
- We conducted a study on the antimicrobial activity of gentamicin bacteria (positive control). We found that *Escherichia coli* bacteria are more sensitive to the extract, followed by *Staphylococcus aureus* bacteria in a very close percentage, and they are less sensitive to *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacteria.
- In order to study its antidiabetic activity, we used two methods:
  - The first method is to use *saccharomyces cerevisiae* yeast cells to determine the effect of date seed extract on increasing glucose absorption. Through our results, we have proven that date seed extract increases the ability of yeast to absorb glucose at concentration 20 mg/ml. This confirms that the date seed also improves glucose absorption by human cells, thereby helping Blood sugar levels in diabetics.
  - The second method: using the α amylase: Through our results, we found that the higher the concentration of date seed extract, the greater the rate of inhibition of the amylase enzyme, which prevents the conversion of starch into glucose, and the IC50 was estimated at 0.229 mg/ml.
- We also identified some phenolic compounds in date seed extract, through qualitative analysis using an HPLC device, which revealed the presence of 14 compounds, which are: Ascorbic acid, Pyrocatechol, Pyrogallol, Salicin, Esculin, Chlorogenic acid, Catechin, Caffeine, Vanillic acid, Rutin, Vanillin, Caffeic acid, Quercetin, Cinnamic acid.
- In order to improve this study and support the results, we suggest:
  - Complete the analysis of the date seed by examining the content of minerals, fiber and acidity.
  - Evaluating the health effects of consuming date seeds, such as its effect on blood sugar levels and weight.

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