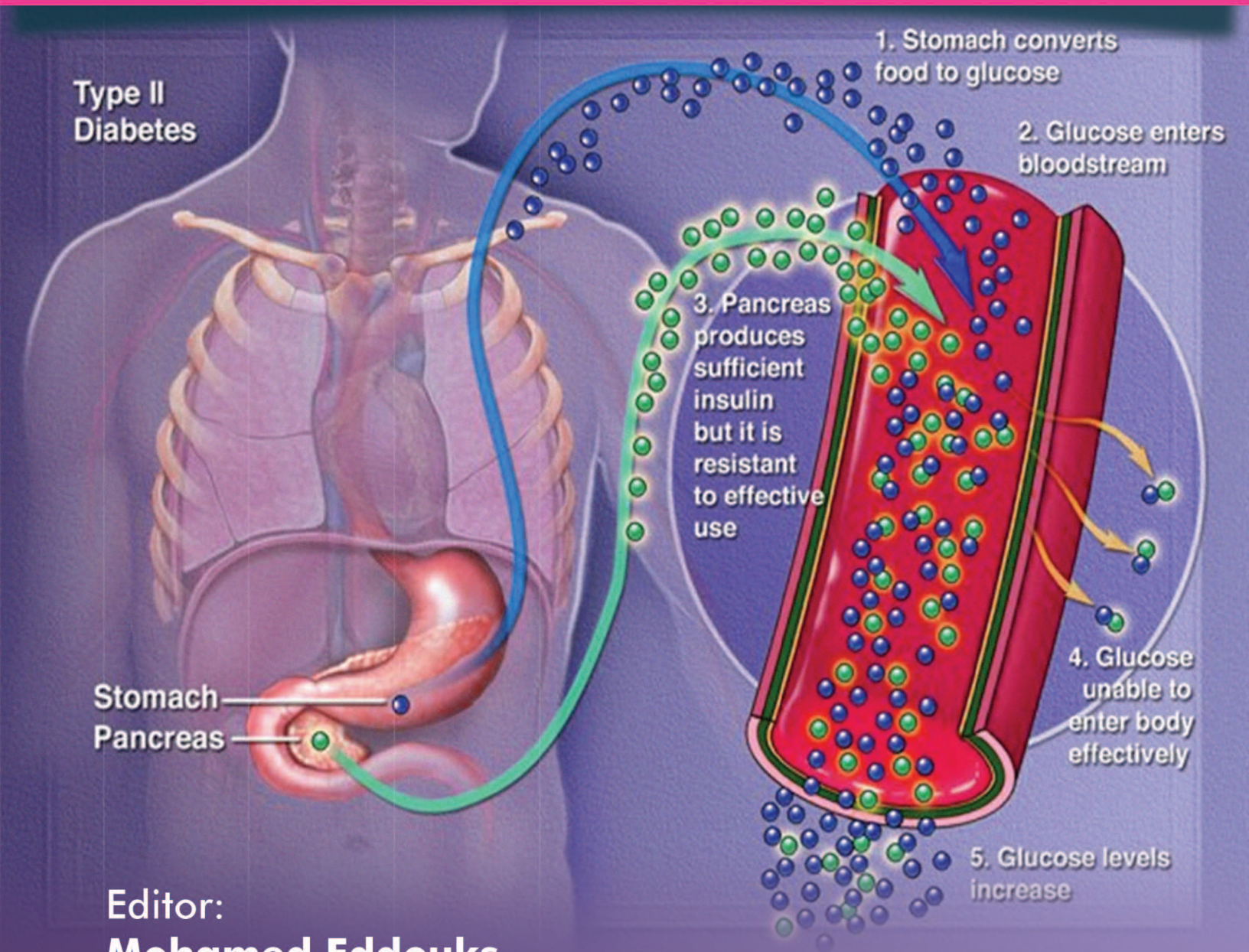
Phytotherapy in the Management of Diabetes and Hypertension



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Phytotherapy in The Management of Diabetes and Hypertension

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PREFACE

In order to provide an up-to-date overview of the phytotherapy of diabetes and hypertension, this fourth volume has been prepared as part of the ebook series "Phytotherapy in the Management of Diabetes and Hypertension". The present volume includes different aspects of the pathophysiology of diabetes and hypertension. This book adds important information related to the evaluation of the efficacy and safety of medicinal plants and their derivatives on diabetes and hypertension. The present volume includes 6 complementary chapters presenting an updates on clinical study reports of phytotherapy in the management of type 2 diabetes mellitus; curcumin: a drug of choice for the treatment of diabetes and hypertension; olive leaf, a traditional phytomedicine for diabetes and hypertension; medicinal plants from genus *Costus* in management of diabetes; antidiabetic and antihypertensive potential of *passiflora* SPP (passion fruit) - an updated review and monograph on *Anvillea radiata* Cross. & Durieu. This volume will be useful to the students, teachers, researchers, scientists, clinicians and even the common people.

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CHAPTER 1

Updates on Clinical Study Reports of Phytotherapy in the Management of Type 2 Diabetes Mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by the insufficient production of insulin and/or the development of resistance to insulin. The long-term management of T2DM with conventional oral hypoglycaemic drugs is a challenge as these drugs may worsen certain underlying comorbidities and complications, such as chronic kidney and cardiovascular diseases. Besides, because of the development of resistance to those drugs, it is difficult to control hyperglycemia for long term treatment of type 2 diabetes mellitus patients. This drawback of conventional medicines necessitates phytotherapy, herbal medicines, functional foods, nutraceuticals, and other forms of alternative medicines or the invention of new medicines for the effective and long term treatment of type 2 diabetes mellitus avoiding the major adverse-effects or minimising them. Plant-derived bioactive compounds are a great resource for the discovery of new medicines. Besides, phytomedicines in the forms of extracts, isolated compounds, combined herbal preparations or other forms can be used for the prevention and treatment of type 2 diabetes mellitus. This chapter contains updated panorama based on the evidences from clinical study reports on different forms of phytotherapy, including plant extracts, its fractions, isolated bioactive compounds, functional foods, nutraceuticals, herbal medicines formulations and other forms of plant-derived phytotherapy reported for the treatment of type 2 diabetes mellitus. The findings from clinical study reports were discussed with proper citations as well as presented in summarized form in a table. A total of 52 different types and forms of prospective phytomedicines, bioactive compounds, or formulation or extracts or fractions or decoctions or functional foods formulations having clinical study reports associated with type 2 diabetes mellitus were presented in this chapter. The molecular mechanisms involved along with the primary and secondary outcomes with phytotherapy on type 2 diabetes patients were also presented. Multiple clinical studies demonstrated very prospective and potential antidiabetic activities of Berberine, Bitter gourd, Cinnamon, Curcumin, Dia-Best™, Fenugreek, Gegen Qinlian decoction, GlucoSupreme herbal, *Gymnema sylvestre*, Magnesium, *Nigella sativa*, Resveratrol,

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Tibetan medicine herb combination, TCM multiple herbal combination, Xiaoke pill, and vitamin C. Hence, at least, these phytoremedies are recommended for the management of type 2 diabetes mellitus which may have additional benefits in diabetes management compared to conventional Allopathic medicines considering the long-term safety and effectivity of the products. The updated clinical study reports on phytotherapy presented in this chapter will be helpful for the medical, biological and pharmaceutical researchers and complementary and alternative medicine users to use these plants extracts, its fractions, isolated biomolecules, herbal preparations, functional foods, nutraceuticals and other forms of phytomedicines for the prevention and treatment of diseases as well as for the discovery of modern medicines.

Keywords: Bioactive Compounds, Clinical studies, Complementay and alternative medicine, Herbal medicine, Phytomedicine, Phytotherapy, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by high blood glucose levels. Diabetes mellitus is caused by insufficient or absence of insulin production or impairment of insulin action or both, which results with the disturbances of the metabolism of carbohydrate, protein, and fat [1]. Diabetes is classified into the following categories:

1. Type 1 diabetes mellitus (also called insulin-dependent diabetes): This occurs due to the destruction of pancreatic β-cells by autoimmunity, which leads to the complete deficiency of insulin production.
2. Type 2 diabetes mellitus (also known as non-insulin dependent diabetes): This occurs because of the progressive loss of insulin production or secretion from pancreatic β-cells or the development of resistance to insulin or because of both reasons.
3. Gestational diabetes mellitus (GDM): GDM occurs because of the hormonal and metabolic changes of pregnant women, and is diagnosed in the second or third trimester of pregnancy.
4. Specific types of diabetes: Diabetes may also be developed due to other specific reasons, such as i) monogenic diabetes syndromes: neonatal diabetes and maturity-onset diabetes of the young, ii) diseases of the exocrine pancreas: cystic fibrosis and pancreatitis, iii) drug- or chemical-induced diabetes: glucocorticoid use in the treatment of HIV/AIDS or after organ transplantation [1, 2].

Diabetes can be diagnosed by measuring fasting plasma glucose (FPG) or post-prandial plasma glucose two hours after meal (2-h PG) level or glycated hemoglobin A_1C (HbA1c) criteria [2]. People with FPG $\geq$ 7.0 mmol/L, 2-h PG $\geq$

11.1 mmol/L, HbA1c ≥ 6.5%, or random blood glucose ≥ 11.1 mmol/L in the presence of signs and symptoms are diagnosed to have diabetes [1, 3].

The prevalence and incidence of diabetes is increasing all over the world irrespective of lower-income, middle-income and developed countries. According to WHO 2018 report, the number of diabetic patients has increased from 108 million in 1980 to 422 million in 2014 [4].The global prevalence of diabetes in adults over 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014 [4]. According to the report of the International Diabetic Association in 2017, approximately 425 million adults (20-79 years) were reported to live with diabetes, which is estimated to be raised to 629 million by 2045 [5]. It was found that the highest number of diabetes patients was between the age of 40-59 years, and 50% (212 million) of the people with diabetes were undiagnosed [5]. In the year 2017, more than 1.1065 million children were found to live with type 1 diabetes mellitus, and 352 million people were at risk of developing type 2 diabetes mellitus around the globe [5]. It is also noteworthy to mention here that IDF reported 79% of adults with diabetes were living in low- and middle-income countries [5].

According to WHO report 2018, an estimated 1.6 million deaths were directly caused by diabetes in 2016 and diabetes was found to be the seventh leading cause of death [4]. Diabetes is a major cause of cardiovascular diseases such as, heart attacks and stroke, kidney failure, blindness [4]. Chronic diabetes state causes severe consequences with heart attacks, stroke, blindness (due to damage to the small blood vessels in the retina), damage nerves, causes the risk of obesity, erectile dysfunction, foot ulcers, infections, kidney failure, cancer and ultimately death of the patients [1, 4, 6, 7].

The current treatment options for diabetes mellitus are oral hypoglycemic drugs and injectables, mainly insulin. Oral antihyperglycemic drugs are classified as follows:

1. Biguanides (Example: metformin): American Diabetic Association recommends metformin as the first line oral drug for the treatment of type 2 diabetes mellitus. Metformin reduces hepatic gluconeogenesis and lipogenesis, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [8 - 10].
2. Sulfonylureas (Examples: Glimepiride, glipizide, gliclazide): Sulfonylureas are known as insulin secretagogues because of this class of antidiabetic drugs induces the secretion of insulin from pancreatic beta-cells. American Sulfonylureas are recommended as a classic second-line therapy for the treatment of type 2 diabetes mellitus. Sulfonylureas increases insulin secretion

CHAPTER 2

Curcumin: A Drug of Choice for the Treatment of Diabetes and Hypertension

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Abstract: This chapter covers the beneficial effect of curcumin, a biphenolic active compound of turmeric in diabetes and hypertension. Curcumin as a dietary component plays an important role in diabetes and hypertension inhibition as well as to mediate its anti-inflammatory effect by regulating redox status, transcription factors, fatty acids composition and various enzymatic activities. The active involvement of curcumin in the activation of activating peroxisome proliferator-activated receptor γ while the reduction in thiobarbituric acid reactive substances and succinate dehydrogenase is well known and correspondingly the disregulated adiokine which are involved in insulin resistance and development of Type 2 diabetes may be recovered by curcumin. The reduction in insulin resistance is induced by curcumin *via* activation of various transcription factors such as lipoprotein lipase, NF-E2-related factor 2, and liver enzymes involved in metabolic processes. Consequently, the molecular interaction of curcumin with adiponectin and signal transduction in various metabolic processes hinder insulin resistance, diabetes acceleration factors and other inflammatory symptoms linked with diabetes and hypertension.

Keywords: Adipokines, Curcumin, Diabetes, Hypertension, Inflammation.

INTRODUCTION

Curcumin treatment reduces blood glucose levels in diabetes patients by regulating antioxidant levels in pancreatic β-cells and by initiating peroxisome

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proliferator-actuated receptor γ (PPARγ) [1]. It additionally improved obesity related diabetes by diminishing macrophage penetration into white adipose tissue, hindering the depletion of κB (NFκB)-related markers of hepatic inflammation and increase adiponectin expression in high fat diet-induced obese and leptin-deficient ob/ob male C57BL/6J mice [2]. Moreover, curcumin is also reported to prevent diabetes-incited diminishes cancer prevention, increases in interleukin-1β (IL-1β), vascular endothelial advancement factor (VEGF), and NFκB, and covering of blood glucose levels through improved PPAR-γ ligand-confining activity in type II diabetic KK-Ay mice [3]. Curcumin hindered hyperlipidemia by stifling the serum and liver cholesterol [4]. In addition, curcumin pre-treatment guarantees against lindane-affected oxidative damage in rat's livers through the amplification of the enzymatic antioxidants [5]. This chapter aimed to provide the detailed underlying mechanisms of the multifactorial role of curcumin in the prevention and treatment of diabetes and hypertension (Table **1**).

Curcumin as a Drug of Choice for Diabetes

Scientific evidence has increased the impressive consideration of natural dietary products for the anticipation and diabetes and its associated diseases [3]. The active involvement of curcumin in diabetes treatment has been reported in traditional medicine (Fig. **1**). It is isolated as an active compound from the roots of *Curcuma longa*, which consists of curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin [6]. Curcumin can manage the immune system positively, bringing about a significant impact on diabetes [7].

Curcumins' Antioxidant and Anti-Inflammatory Effect

Curcumin regulate a number of key proteins to facilitate its antioxidant effects. Initially, curcumin regulate redox status by modulating Ca^{2+} levels and protein kinase C (PKC) activity [8]. Furthermore, it inhibits ROS production by a blockage in apoptotic changes [9, 10]. Additionally, curcumin activates enzymatic antioxidants in Wistar-NIN rats [11]. Inflammation is a major cause of diabetes. It has been shown that curcumin restores membrane stiffening and reduces the release of pro-inflammatory factors, such as monocyte chemotactic protein-1 (MCP-1) from immune and endothelial cells [12, 13]. Curcumin also inhibits ILs, MCP-1, and tumor necrosis factor-α (TNF-α) in U937 monocytes. Similar effects were observed in diabetic mice by modulating TNF-α, IL-6, glucose, and glycated hemoglobin [13]. Curcumin inhibited the expression of acetylated CBP/p300 and p300, as well as NFκB, in human monocyte (THP-1) cells [14]. Furthermore, cytokine production was increased by high glucose levels *via* epigenetic changes, which regulate HAT and HDAC activity. Dietary curcumin inhibited both HATs and HDACs, thus contributing to epigenetic modifications for diabetes control [15].

Curcumin inhibited the degradation of IκBα and activation of NFκB, reduced macrophage infiltration, and down-regulated MCP-1, intracellular adhesion molecule-1 (ICAM-1) [16]. In insulin-resistant ob/ob mice with steatosis, curcumin improved peripheral insulin resistance by inhibiting NFκB/RelA DNA-binding activity, decreasing mRNA levels of IL-6 and TNF-α, and enhancing the production of IL-4 in adipose tissue macrophages and hepatic iNOS-producing dendritic cells [17]. Dietary curcumin decreased macrophage infiltration in white adipose tissue and hepatic NFκB activity, and ameliorated abnormal metabolic effects by increasing the production of adipose tissue adiponectin in high-fat diet-induced obesity and leptin-deficient ob/ob mice [18]. The potential role of curcumin in diabetes and hypertension-related diseases are discussed below.

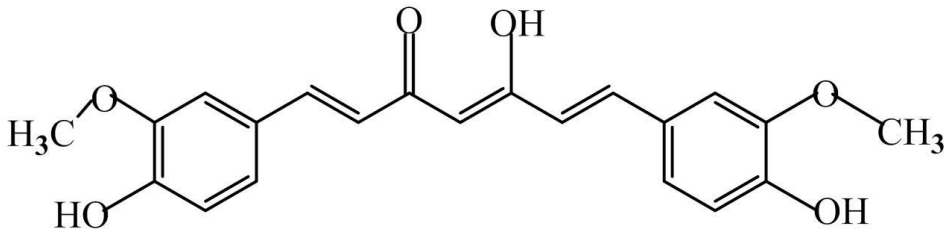

Fig. (1). Structure of Curcumin.

Curcumin Improves Adipose Tissue Dysfunction

Adipose tissue controls whole-body glucose homeostasis. Dysregulation of adiponectin secretion may lead to the development of T2DM [19, 20]. It has been reported that curcumin enhanced the differentiation of human adipocytes and blocked the accumulation and activation of macrophages in adipose tissue by regulating the secretion of adiponectin [21, 22]. Curcumin also suppressed NFκB activation and MCP-1 release in 3T3-L1 adipocytes [23]. Moreover, it suppressed adipogenesis *via* activation of β-catenin signaling D1 [24]. Both c-myc and cyclin D1 are well known downstream target genes of β-catenin and have the potential to prevent adipogenesis [25, 26].

Curcumin Inhibits Diabetes-Associated Liver Diseases

Most of the time diabetes patients develop liver diseases [27]. It has been reported that 8 weeks of curcumin administration improved STZ-induced diabetes in rats by modulating creatine, albumin, and inorganic phosphorus. Curcumin is also beneficial in reducing MDA level in urine and plasma [28]. Furthermore, the hypolipidemic action of curcumin is mediated by activation of hepatic cholesterol-7β-hydroxylase in STZ-induced diabetic rats [29]. Oral curcumin

CHAPTER 3

Olive Leaf: A Traditional Phytomedicine for Diabetes and Hypertension

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Abstract: Olive leaves are used in Mediterranean folk medicine for the treatment of diabetes, hypertension, and hypercholesterolemia since ancient times. In the last decade, different authors have studied their chemical composition and ratified their pharmacological properties both *in vitro* and *in vivo*, and, more recently, clinical trials focusing on their effects on diabetes and hypertension have been developed. Oleuropein and hydroxytyrosol seem to emerge as promising bioactive phenolics responsible for these beneficial effects. In this chapter, information about recent studies on the olive leaf is compiled, including its effects on the specific subject of this chapter, but also its other potential pharmacological effects.

Keywords: Antidiabetic, Antihypertensive, Hydroxytyrosol, Hypoglycemic, *Olea europaea*, Oleuropeoside.

INTRODUCTION

According to the last revision of The Plant List [1], the Oleaceae family includes 25 accepted and 7 unassessed genera. The genus *Olea* comprises 35 accepted species and, among them, *Olea europaea* L. has the highest relevance. Classically, about 10 varieties and 4 subspecies were described, but, at present, all of them are considered synonyms of *Olea europaea* L., the only taxon accepted [1]. This species is widely known and used for its fruits and the oil obtained from

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them in the Mediterranean diet [2]. *Olea europaea* is included in the taxonomical group of flowering plants (Spermatophyta) and the class of dicotyledons (Magnoliopsida). The whole taxonomy is compiled in Table **1** according to the United States Department of Agriculture classification [3].

Table 1. Taxonomy of *Olea europaea* [3].

Biological Group	Taxonomy	Common Name
Kingdom	Plantae	Plants
Subkingdom	Tracheobionta	Vascular plants
Superdivision	Spermatophyta	Seed plants
Division	Magnoliophyta	Flowering plants
Class	Magnoliopsida	Dicotyledons
Subclass	Asteridae	
Order	Scrophulariales	
Family	Oleaceae	Olive family
Genus	*Olea* L.	Olive
Species	*Olea europaea* L.	Olive

The olive tree is an evergreen tree (Fig. **1**) or shrub of variable height (8-15 m) and diameter, depending on the kind of olive, variety, age of the tree, and if it grows wild or cultivated. The leaves have about 4-10 cm length, 1-3 cm width, and are pale green with few scales on the top, and silvery-whitish at the below. The fruit is an ovoid drupe, blackish-violet when ripe, normally of 1.0-2.5 cm long, smaller in wild plants than in orchard cultivates. It has a central pit that encloses the seed surrounded by the edible fleshy mesocarp. Genetically, an olive tree is a diploid species [4, 5].

Olive trees are distributed along the Mediterranean coast, including southeastern Europe, northern Iran (south end of the Caspian Sea), western Asia, and North Africa. The fruit and leaves of the olive tree are also important in the context of religion because they are cited in both New and Old Testaments [4]. The principal producer of olives and olive oil is Spain, followed by Italy and Greece, whereas, out of Europe, the United States of America and Argentina are the major producers [4 - 6]. The cultivation of olive dates goes back to more than 7000 years for commercial purposes in Crete, Greece, and the Middle East, and from where it was spread to the West to the Italian and Iberian peninsulas, as well as France. It reached the American continent with Spaniards when they arrived in Peru, Mexico, and California [4]. The olive tree is a typical component of the thermo-Mediterranean climate; it is a thermophile species adapted to tolerate

drought and salinity stress and grows on a wide range of soils [5].

Fig. (1). *Olea europaea*. The olive tree, leaves, and fruits.

OLIVE, A MEDITERRANEAN TREE WITH A HIGH VALUE FOR ECONOMY AND HEALTH

The olive tree is probably the most economically important crop tree of the Mediterranean region [5]. It is appreciated for its wood [7], fruits [8], and oil [9]. The olive tree wood is heavy and very tough, and it is usually employed for manufacturing high-end furniture, inlays, turned objects, and handcrafts [5, 7]. It is also appreciated as firewood because it burns even when wet and to obtain charcoal [5, 7, 10]. The fruit is edible after processing because the natural fruits are extremely bitter and need a process for reducing the bitterness. This process usually includes soaking the fruits in salt-water to make them more palatable, processing them with NaOH, or drying them in the sun [8]. Pickled, canned, or otherwise prepared table olives are eaten as a relish or used in bread, salads, or other preparations [5]. In the case of olive oil, its principal use is as food (in crude) or for cooking, but other relevant uses make this oil of high interest [11]. Its uses include medical and pharmaceutical use as well as for ointments, lighting (burning without smoke), and medical uses [5, 9]. Virgin olive oil is the principal component of the Mediterranean diet, and it is of a high value for its beneficial properties for human health due to the high amounts of unsaturated fatty acids [5]. Mediterranean countries produce more than 77% of the olive oil in the world, with Spain (36%), Italy (24%) and Greece (17%) being the major producers, whereas 17.4% oil is from the Mediterranean countries of Africa, and the rest of the world produces 5.6% of the total production [9].

CHAPTER 4

Medicinal Plants from Genus *Costus* in the Management of Diabetes

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Abstract: Diabetes is a chronic metabolic disorder characterized by a persistent increased level of glucose in the blood. The uncontrolled glucose level in the blood is associated with a defect in insulin secretion, insulin action, or both, which leads to the progression of oxidative stress. It also affects metabolic, genetic, and haemodynamic systems by activating the polyol pathway, protein kinase C pathway, and hexosamine pathway. According to the World Health Organization (WHO) report, globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980.

Various medicinal plants, as well as phytochemicals like alkaloids, glycosides, terpenes, and polyphenols, have been thoroughly studied for their activity in the management of diabetes. Recent data showed that around 1200 traditional plants have been used for real or perceived benefit in the treatment of diabetes. *Costus* (Linn.) is an important genus belonging to the family '*Costaceae*' containing approximately 200 species. The plants have spirally arranged leaves and rhizomes being free from aromatic essential oils and tropically distributed in nature. In Ayurveda, the rhizomes of plants are described to be astringent, acrid, cooling, aphrodisiac, purgative, anthelmintic, depurative, and expectorant. Aerial parts of the plants and rhizomes are an edible and good source of carbohydrate, starch, amylase, proteins, and lipids. Recent literature shows that many species of *Costus* like *Costus pictus*, *Costus afer, Costus spirali, Costus speciosus*, and *Costus igneus* possess a significant glucose-lowering capacity. They are commonly known as 'insulin plants'. The chapter provides scientific information on plants from *genus Costus* focusing on phytochemistry, pharmacological effects specifically in diabetic conditions.

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Keywords: Diabetes, Genus-*Costus*, Hyperglycemia, Insulin plants, Medicinal plant, Traditional medicine.

INTRODUCTION

In many countries, traditional plant-based medicines are considered as an important part of health care. Many regions of Asia, Africa, and Central and South America have literature on traditional medicines, which is freely available and assessable by the people. In many countries like China, India, Europe, and Germany, traditional medicines are being integrated through regulation into the human healthcare system [1]. According to a report by the World Health Organization (WHO), the estimated annual global market of herbal medicine in the year 2003 was around $60 billion and by 2012, the global industry in traditional and complementary medicine (TCM) alone was reported to be worth of $83 billion. Based on the current information of the year 2019, 170 countries have confirmed their use of traditional and complementary medicine. These are the countries which have developed law, policies, rules, regulations, and offices for TCM [2].

Nowadays, healthcare systems around the world are facing major issues related to chronic illness, population aging, and healthcare cost. Traditional medicines are often seen as more accessible, more affordable, and more acceptable to local populations and can, therefore, be a tool for achieving universal health coverage [3]. 80% of people worldwide believe in herbal medicine for their primary healthcare. According to the WHO data, around 21,000 plant species are reported to have medicinal properties and around three-quarters of the world population utilizes medicinal plants and their extracts for treating various diseases [4].

Diabetes mellitus is a chronic metabolic disorder associated with the prolonged increased level of glucose in the blood [5]. Long term increased level of glucose in blood results in vascular changes and dysfunctions which are the main reasons behind mortality and morbidity among diabetic patients. Diabetes mellitus has a high prevalence rate throughout the world [6]. According to a recent statistic by the International Diabetic Federation 2017, four out of five people live with diabetes in low and middle-income countries. 425 million people have been reported to have diabetes till the year in 2017 in the world and it has been predicted that it will reach to 629 million by the year 2045 [7].

An uncontrolled level of glucose in the blood is because of abnormality in insulin secretion or insulin action. Abnormality in insulin secretion because of damaged β-cells of the pancreas is linked to the development of type-I diabetes, whereas, resistance to secreted insulin is associated with the development of type -II diabetes. Prolong uncontrolled hyperglycemia in both cases leads to the formation

of reactive oxygen species by activation of the polyol pathway, protein kinase C pathway, and hexosamine pathway. It also increases advanced glycation end products (AGEs) formation. Various vital organs like kidney, eye, nerve, and heart are affected by prolonged increased blood glucose level [8 - 11].

There is an unmet need for the treatment of diabetes due to high prevalence, rapid growth rate, variable pathogenesis, and development of complications. Various treatment options like insulin therapy, blood sugar monitoring, diet therapy, and pharmacotherapy are available for diabetes [12]. Blood glucose-lowering agents like sulfonylurea or meglitinides work by stimulating insulin secretion from β cells of pancreas and drugs like biguanides and thiazolidinediones increase peripheral absorption of glucose [13]. Delay in intestinal carbohydrate absorption by α-glucosidase and reduction in hepatic gluconeogenesis by biguanides (Metformin) are another therapeutic approach for the treatment of diabetes [14]. Besides all the therapeutic benefits, these treatments are associated with some disadvantages like drug resistance, hypoglycemia, side effects, and toxicity. Drugs like sulfonylurea develop resistance in 44% of people after 6 years of treatment and many anti-diabetic drugs are withdrawn from the market because of drug-drug interactions [15]. To minimize the adverse effect of anti-diabetic drugs, many people nowadays use plant-based medicinal therapy for the management of diabetes. Plants contain various constituents like alkaloids, glycosides, polyphenols, tannins, flavonoids, and terpenoids which are reported for their anti-diabetic property [16 - 18]. Plant-based medicines act as insulinomimetic or secretagogues by restoring the function of β-pancreatic cells or inhibiting intestinal absorption of glucose. More than 400 plant species are available in the literature that possess anti-hyperglycemic activity [19].

Costaceae family of order Zingiberales is reported for its medicinal value worldwide and is commonly known as Spiral ginger. *Monocostus, Dimerocostus, Chamaecostus, Costus, Paracostus, Cheilocostus,* and *Tapeinochilos* are various genera of the Costaceae family out of which *Costus* is the largest genus which contains more than 175 species [20]. Plants from this genus are mostly found in the tropical and sub-tropical regions of Asia, Africa, and America. China, Malaysia, New Guinea, Taiwan, and India are some countries where genus *Costus*are is found in hilly regions. Detailed scientific studies have also been carried out on various species of *Costus* for its use in the treatment of cough, inflammation, rheumatism, arthritis, and diabetes. Besides this, they have also been used as anti-bacterial, anti-viral, hypolipidemic, diuretic, laxative, and purgative (Fig. **1**) [21]. Some important phytoconstituents present in genus *Costus* plants responsible for pharmacological activities are mentioned in Table **1**. In addition, genus *Costus* has potent anti-diabetic properties. Eight species of genus *Costus* have been studied in detail for the antidiabetic potential. This chapter

CHAPTER 5

Antidiabetic and Antihypertensive Potential of *Passiflora* spp. (Passion Fruit) - An Updated Review

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Abstract: Herbal medicines have been in use since stone days as an alternative therapy for the treatment of number of diseases. In this chapter, medicinal application of *Passiflora* genus in the treatment of diabetes mellitus, hypertension and related anxiety disorders are discussed. *Passiflora* belongs to the genera of Passifloraceae family. Species of the *Passiflora* fruits are edible and other parts of the plant including leaves, seeds, flowers and fruit peel are used in traditional system of medicine. Phyto constituents namely, Flavonoids, glycosides, phenolic compounds, alkaloids and volatile constituents are reported. Various studies carried out in the recent years reported various biological activities in the genus, including antioxidant, diuretic, anxiolytic, anti-inflammatory, analgesic, and antiviral properties. They also exhibited hypoglycemic, antihypertensive and antianxiety properties. The focus of this review is to preset the current state of knowledge and research findings associated with the use of the *Passiflora* species in the treatment of hyperglycemia and hypertension. Co-presence of diabetes mellitus and hypertension increases the risk of many health problems. In this chapter, we reviewed the findings of various species *viz*. *Passiflora edulis*, *Passiflora alata*, *Passiflora ligularis*, *Passiflora quadrangularis, Passiflora glandulosa, Passiflora incarnata*, Passiflora nitida, Passiflora nepalensis with the above mentioned activities. This chapter also aims to provide latest information on the medicinal benefits of *Passiflora* species which can be helpful to prevent hyperglycemia and related manifestation of Type 2 diabetes and hypertension.

Keywords: Antidiabetic potential, α amylse, α Glucosidase, Hypertension, *Passiflora*, Type 2 Diabetes.

INTRODUCTION

Diabetes and hypertension are both considered as major public health challenges

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globally. Diabetes mellitus (DM) is a metabolic disorder in which abnormal level of blood sugar levels occur as a result of partial or complete lack of insulin secretion [1 - 3]. This may also result in other complications such as retinopathy, neuropathy, and nephropathy. DM is generally classified as type I and type II diabetes. Type I diabetes is (autoimmune disease or due to mutation), results from absolute deficiency in the production of insulin due to destroying beta (β) cells of pancreases. Type I represents only 10% of all diabetic cases, it affects all age groups, but the majority is more than 5 years. Type II diabetes is also known as non-insulin dependent diabetes mellitus. Type II is a common form of DM, which accounts for more than 80%, results from insulin deficiency or insulin resistance. Other minor types of DM are gestational diabetes mellitus (GDM), occur during pregnancy due to high blood glucose concentration. Currently, although type I cannot be prevented, type II is preventable with good health, exercising and healthy diet. Type II affected high population and led to complications in several body parts, heart, nerves, eyes, kidney and so on. Diabetes or hyperglycemia increases vulnerability to mortality and morbidity in patients. Diabetes may induce several other health related microvascular and macrovascular complications or could exist with other diseases. The macrovascular leads to more severe diseases like coronary disease, stroke and peripheral neuropathy. The microvascular are more erratic and in long-term may lead on macrovascular complications are diabetic retinopathy, diabetic nephropathy and diabetic foot. The clinical management of diabetic patients, health professionals combat with diabetic complications which are very common and come in broad spectrum of manifestations. The prevalence of diabetes has increased in adults and it raises the global public health burden and in another decade it can be predicted that India, China and USA will have the largest number of people affected with type II diabetes [4 - 7].

According to the World Health Organization, the clinical presentation of hypertension, which scientifically indicates the increase of blood pressure, has been defined as systolic (SBP)/diastolic (DBP) blood pressures of $\geq$ 140/90 mmHg [8]. There are basically two types of hypertension. Primary hypertension, which accounts for about 95% of cases, usually has no traceable cause. Secondary hypertension associated with endocrine diseases, kidney disease, glucose intolerance and obesity. As it is commonly known that hypertension is related with several cardiovascular diseases such as arteriosclerosis, coronary artery disease, and myocardium infarction, renal insufficiency, stroke and dissecting aneurysm of aorta and if, hypertension, not promptly managed, results in decreasing ventricular function and, consequently, in heart failure. It is related to changed lifestyle and dietary habits that led to advanced cardiovascular events and arteriosclerosis both of which are linked with high blood pressure. Gender, age, socio-demographic characteristics and geographical location could also promote

hypertension prevalence. Among the comprehensive lifestyle modifications, better dietary habits are one of the most effective measures for keeping hypertension under control [8 - 11].

The correlation among insulin resistance, diabetes and hypertension are complex and interrelated. It is estimated that about 25–47% of persons with hypertension have insulin resistance or impaired glucose tolerance. Correlation may be due to a common genetic and environmental factor promoting both diabetes and hypertension which along with obesity have been documented in several populations. Resistance to Insulin, renin-angiotensin-aldosterone system, endothelial dysfunction, and autonomic nervous system dysfunction play an important part in the pathogenesis of hypertension and diabetes [3].

Biguanides, Sulphonylureas, Glinides, Thiazolidinediones serves as oral hypoglycemic agents which are available along with insulin for the treatment of diabetes [4], while for hypertension, ACE inhibitors, Ang II receptor blockers, beta blockers, calcium channel blockers, renin inhibitors and diuretics are the common drugs. But side effects associated with their uses are reported. ACE inhibitors and diuretics are usually the first line of drugs in hypertension, which reduces the risk of kidney failure and cardiovascular events. However at the same time, these anti-hypertensive drugs are used in combination with anti-diabetic drugs, which may cause drug interactions and increase the risk of drugs-associated side effects in patients with diabetic and hypertension [12 - 14].

Similarly patients with anxiety disorders had a higher prevalence and a higher incidence of hypertension than that in the general population. Age, male sex, diabetes, and hyperlipidemia were risk factors for hypertension in patients with anxiety disorders. The impact of stress on the individuals's health covers changes in blood pressure, heart rate and an increased risk of cardiovascular diseases such as coronary heart disease. The link between major depression, insomnia and anxiety disorders impairs the function of immune and cardiovascular systems. Selective serotonin (5-HT) reuptake inhibitors (SSRIs), including citalopram, sertraline, fluoxetine are currently first-line drug treatment options for most anxiety disorders as they are proposed to have a better benefit/risk ratio than any other form of current pharmacotherapy. Long-term use of these drugs causes multiple inevitable side effects or tolerance. Also there has been considerable popular interest in using natural extracts and plant preparations to treat anxiety. Moreover, herbal medicines are considered as alternative of synthetic drugs. Relevant literature were collected by searching the major scientific databases including PubMed, Sciencedirect, Medline and Google scholar for plant species of *Passiflora* that have been investigated for anti-diabetic and antihypertensive activity [15, 16].

CHAPTER 6

Monograph on *Anvillea radiata* Coss. & Durieu

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Abstract: *Anvillea radiata* Coss. & Durieu (*A. radiata*) which belongs to the Asteraceae family is an aromatic and medicinal plant, endemic of Morocco and Algeria and usually used in the traditional medicines to treat obesity, hypertension and diabetes. The phytochemical analysis of *A. radiata* reveals the presence of a number of bioactive compounds such as germacranolids. The present chapter summarizes the most recent ethnobotanical, pharmacological and phytochemical studies conducted on this herb.

Keywords: *Anvillea Radiate*, Diabetes, Hypertension, Medicinal plant, Phytochemistry, Pharmacology.

INTRODUCTION

Anvillea radiata Coss. & Durieu is a wild plant which belongs to the Asteraceae family (Fig. **1**). This plant is endemic of North Africa (Morocco and Algeria). Based on ethnopharmacological surveys, folkloric practices and phytotherapeutic *A. radiata* as a medicinal plant is used for the treatment of gastroenteritis, spasms, colic, hepatitis, arthritis and rheumatoid, indigestion, lung diseases, obesity and diabetes [1 - 4]. It has been reported to possess many biological effects. This plant showed an antihypertensive effect on L-Name-induced hypertensive rats [5], antihyperglycemic activity in streptozotocin(STZ)-induced diabetic rats [6], and antifungal [8], antitumor [9], and hypolipidemic activities [10] on high-fat diet fed mice [7]. The evaluation of three compounds (two epimergermacranolides, and a phenolic acid) purified from this plant has revealed their potential anticholinesterase and anti-tyrosinase activities, α-glucosidase inhibitory activity, and cytotoxic activity against MCF-7 cancer cell lines [11]. This chapter summarizes traditional uses, phytochemistry and discusses the potential biological activities of *A. radiata*.

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Taxonomy and Geographical Location

A. radiata is inherent to North Africa, especially in Morocco and Algeria. It is locally called *Negd*, *Negdsehraoui*, *tehetit*, *nougdl'hoor*, *Ajri*, and *Gijou* [12 - 15].

The taxonomy of *A. radiata* is as follows:

Kingdom: Plantae

Subkingdom:Tracheobionta

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Subclass: Asteridae

Order: Asterales

Family: Asteraceae

Genus: Anvillea

Species: radiata

Fig. (1). *Anvillea radiata*.

Use in Traditional Medicine

A. radiata is an endemic plant in Morocco and Algeria. The most common ailments treated with this plant are digestives disorders, affections of glands, infections, pulmonary disorders, and diabetes. Table **1** summarizes the ethnopharmacological uses of *A. radiata* in Morocco and Algeria.

Table 1. Traditional use of *Anvillea radiata*.

Region	Ailments	Parts of Plant	Mode of Preparation	Reference
Morocco	Urinary infections: pyelonephritis pyelonephritis and cystitis	Leaves Leaves	Recipe based on *Anvillea radiata*, *Origanum compactum, Ricinus communis*, in powder associated with butter, honey and seedless dates is used in the form of suppositories, covered with henna powder and dried in the shade. A recipe based on *Anvillea radiata, Artemisia herba alba, Lavandula dentata, Hyoscyamus albus and Hyoscyamus muticus*, in powder added to *Allium sativum* cooked at steam and dates with no seeds, is used underform suppositories	[14]
	Gastric complaints the cold of the back	Leaves Leaves	The powder The powder of the leaves of *Anvillea radiata* associated with goats' butter is used as suppositories	[13]
	Uro-genital and metabolic disorders; Affections of the glands	Leaves, Whole plant	Infusion, decoction	[15]
	Pathologies of the digestive system, diabetes, Dermocosmotology	Roots, Whole plant	Decoction Oral administration or inhalation	[16 - 18]
	As cholagogue	Flower	Decoction	[19]
Algeria	Diabetes, Indigestion, cold, the stomach aches and the pulmonary diseases	leaves and stems	Maceration, decoction, infusion or inhalation	[20]
	Pulmonary infection, Indigestion	leaves and stems	Infusion, maceration	[21]
	Stomach and liver diseases; Diabetes	aerial parts	Internal use by infusion	[12]

SUBJECT INDEX

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“The phytotherapeutic approach is fundamental both for the validation of traditional therapies, employed by a large number of people in the world, and for the abundance of bioactive molecules among natural substances. This series is edited by Dr. Eddouks - one of the leading international researchers in this sector - and covers important and emerging aspects in the treatment of diabetes, hypertension and more generally, the metabolic syndrome.

Professor Vincenzo De Feo
State University of Salerno
Italy”

Mohamed Eddouks
Moulay Ismail University
Morocco

Mohamed Eddouks is Professor at Faculty of Sciences & Techniques Errachidia, Moulay Ismail University of Meknes, Morocco. His contribution to the field of medicinal plants includes 6 international books, 6 special issues in indexed international journals and more than 120 indexed peer-reviewed articles and 21 book chapters of international repute. He is classified by the reputed American database Expertscape among the top 3 experts in the world in the field of diabetes mellitus induced by streptozotocin (October, 2020). He has been awarded the first Prize of the Federation of Arab Scientific Councils in 2016 and the first Prize of Scientific Research of the Moroccan Association of Research and Development in 2008. He has been the founding Dean of Polydisciplinary Faculty of Errachidia, Morocco.