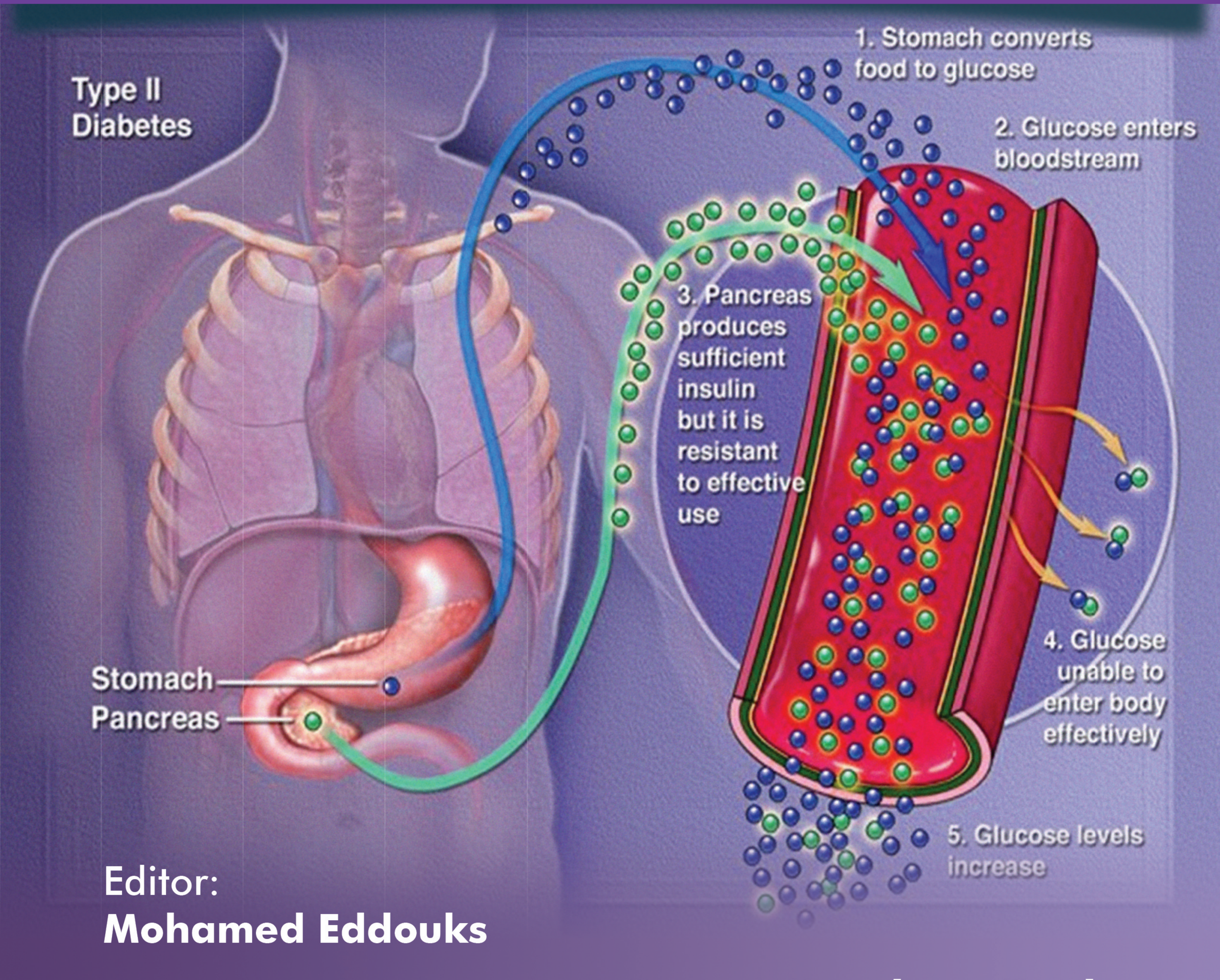
Phytotherapy in the Management of Diabetes and Hypertension



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Phytotherapy in the Management of Diabetes and Hypertension

(Volume 3)

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PREFACE

The volume 1 of the present ebook series "Phytotherapy in the Management of Diabetes and Hypertension" has emphasized the basic Biochemistry of diabetes mellitus and hypertension, and described many aspects of these lifestyle diseases and its control or remediation through a cost effective, safe, easy-going, easy-adaptable method through the age-old practice validated by scientific research. In response to requests from WHO in providing safe and effective herbal medicines for use in national health-care systems and to prepare monographs of used medicinal plants around the world, the volume 2 of this e-book series has been published in 2016 and contained monographs related to antihypertensive and antidiabetic plants. The present volume 3 is dedicated to different aspects including the evaluation of the efficacy and safety of medicinal plants and their derivatives on diabetes and hypertension. The study of the mechanisms of action of medicinal plants is deeply discussed. This volume includes 7 complementary chapters that describe different aspects including the biochemistry of type 2 diabetes, the pathophysiology of diabetes and hypertension, the role of essential oils extracted from medicinal plants in the management of diabetes and hypertension, the mechanistic perspectives of the treatment of diabetes and hypertension, some important phytochemicals with beneficial action on diabetes and hypertension, and detailed monographs concerning some potential medicinal plants used in the treatment of diabetes and hypertension. This volume will be useful to the students, teachers, researchers, scientists, clinicians, herbalists, and even the common people interested to know about the subject.

ACKNOWLEDGMENTS AND GRANTS

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CHAPTER 1

Biochemistry of Type 2 Diabetes Mellitus

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Abstract: Diabetes mellitus, a metabolic disorder, characterized by chronic hyperglycemia results from defects in insulin secretion, insulin action, or both. Insulin is an anabolic peptide hormone that possesses pleiotropic activity. It can hinder with multiple physiological processes by either upregulating or downregulating various metabolic intracellular pathways. The complex insulin signaling system makes it vital in a variety of biological responses. This chapter describes the biochemistry of type 2 diabetes mellitus, as well as the features underlying its pathophysiology.

Keywords: Diabetes, Glucose Uptake, Insulin, Insulin Receptor, Insulin Resistance, Metabolic Disorder.

INTRODUCTION

Diabetes mellitus (DM), a metabolic disorder, characterized by chronic hyperglycemia results from defects in insulin secretion, insulin action, or both. Diabetes mellitus is classically characterized into two types *viz*.Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM, which is also known as insulin dependent diabetes mellitus (IDDM), is caused due to deficiency of insulin secretion from β cells of the pancreas. T2DM, which is also known as non-insulin dependent diabetes mellitus (NIDDM), is associated with diminished sensitivity of insulin in target tissues. This reduced sensitivity to insulin is a characteristic of insulin resistance. The reduced insulin levels or the resistance to insulin reduced the uptake of glucose by most of the tissues of the body except the brain [1]. This leads to an increase in blood glucose concentration along with a decrease in utilization of glucose by cells which results in an increase in the utilization of fats and proteins. The clinical features of patients with T1DM and T2DM are shown in Table **1**.

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Table 1. Clinical features of patients with T1DM and T2DM [1].

Features	T1DM	T2DM
Age of onset	Usually less than 20 years	Usually greater than 30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin, DPP4 inhibitors, PPAR-γ agonists, incretins, SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin)

EPIDEMIOLOGY OF T2DM

The number of people with T2DM is progressively increasing. According to the World Health Organisation (WHO), there were 422 million adults with diabetes worldwide in 2014. The prevalence in adults increased from 4.7% in 1980 to 8.5% in 2014, with a higher increase in low and middle-income countries compared to high-income ones [2]. Further, the International Diabetes Federation (IDF) estimates to have 374 million people at an increased risk of developing T2DM. Without any intervention to slow down this rise in T2DM, there will be at least 700 million people with diabetes by 2045. The demographics of T2DM and the percentage of the population by geographical location are illustrated in Fig. (**1**). The lower rate of diagnosis of diabetes and the difficult access to diabetes care in low- and middle-income countries lead to 90% of all diabetes-related premature deaths and, 87% of all diabetes-related deaths [3]. Consequently, high blood glucose causes almost 4 million deaths each year [2]. The demographic and geographic outline of diabetes worldwide is shown in Fig. (**1**).

ETIOLOGY OF T2DM

T2DM, the more prevalent form of diabetes, is a heterogeneous disorder triggered by a multitude of genetic factors related to diminished insulin secretion, insulin resistance and related factors, such as obesity, overeating, sedentary lifestyle, stress and aging [4]. This multifactorial disease involves numerous genes as well as environmental factors [5]. There is an acute need for insulin by the body in T2DM to avoid the ketoacidosis. Predominately it is not an autoimmune disorder. Also, there is no identification of the susceptible genes that may account for a predisposition to T2DM in most patients. This can be accounted to the heterogeneity of the genes accountable for the susceptibility to T2DM.

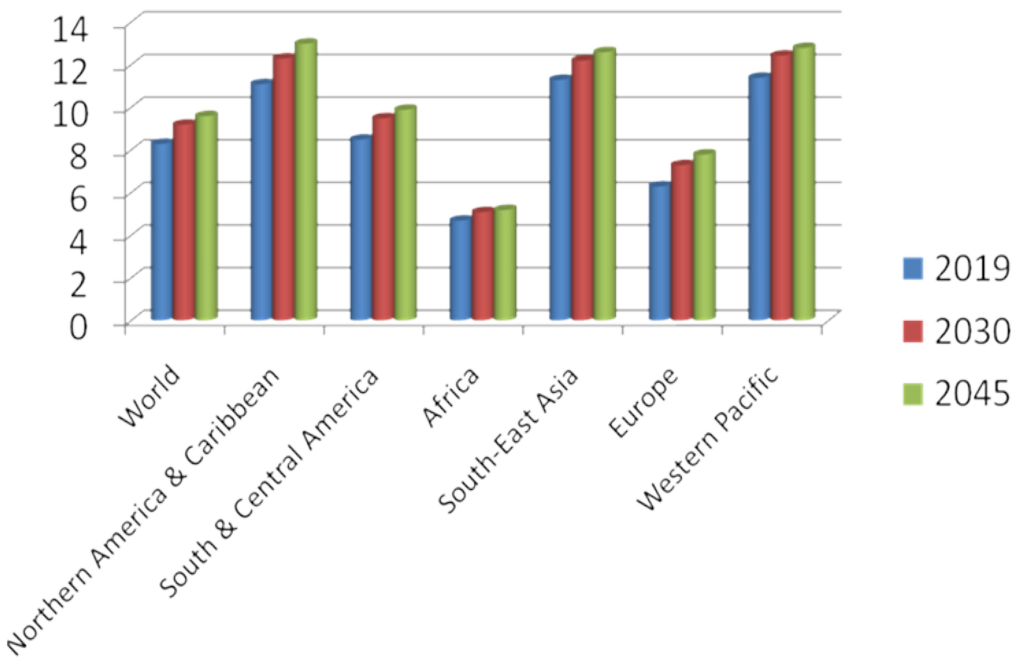

Fig. (1). Demographic and geographic outline of diabetes.

SOME MAJOR CAUSES OF DEVELOPING INSULIN RESISTANCE INCLUDE

1. Obesity, especially accumulation of adipose tissue surrounding the viscera.
2. Mutations in insulin receptor genes.
3. Mutations of the peroxisome proliferator activator receptor-γ (PPAR-γ) genes.
4. Mutations that cause genetic obesity, *e.g.*, melanocortin receptor mutations.
5. Higher glucocorticoids, *e.g.*, Cushing's syndrome or steroid therapy.
6. Higher growth hormone (acromegaly).
7. Pregnancy leading to gestational diabetes.
8. Polycystic ovary disease (PCOD).
9. Hypertension, *i.e.* (≥140/90 mmHg)
10. HDL cholesterol level(<35 mg/dL (0.90 mmol/L) or triglyceride level >250 mg/dL (2.82 mmol/L) or both).
11. Acquired or genetic lipodystrophy associated with accumulation of lipids in liver.
12. Hemochromatosis.

CHAPTER 2

Diabetes Mellitus and Protective Approaches of Medicinal Plants: Present Status and Future Prospects

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Abstract: Diabetes mellitus is one of the major health problem worldwide, its incidence and mortality are increasing day by day. Conventional antidiabetic drugs are available with unavoidable side effects. On the other hand, medicinal plants act as an alternative source of antidiabetic agents. From ancient times, herbs and spices have been widely used in the food and for medicinal purposes. In culinary practices, these are used as colorant, preservatives, and flavor substitution. In medicine, oxidative stress and inflammation associated with noncommunicable diseases can be treated or managed through herbs and spices. Phytochemicals like carotenoids, phenolic compounds, sterols, terpenes, alkaloids, glucosinolates, and other sulfur-containing compounds may be responsible for their protective and therapeutic effects. In this modern era, it is necessary to inform consumers about the benefits of botanical compounds. Many herbal plants have potential health claims that are not significantly demonstrated. Since herbs and spices can be used to get better food value and human health, as functional food ingredients they are helpful to decrease the risk of chronic diseases. Much trial evidence for the use of herbal plants to treat diabetes mellitus has uniformly demonstrated safety. However, further studies are needed to explore the health beneficial effects of these herbal plants used for diabetes mellitus.

DIABETES MELLITUS

Diabetes includes a varied set of ailments categorized as the production of sufficient insulin or decreased sensitivity due to many reasons; chronically increased glucose concentration is one of the common characteristics. Due to this, several metabolic complications raised; in blood, increased ketone bodies due to stern insulin deficiency [1]. In the pathogenesis of diabetic complications, hyperglycemia plays a significant role and those people are at higher risk, who have poor glycemic control. Although in various studies it has been mentioned that the destruction of beta cells and insulin resistance are the major factors of

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diabetes, several signaling pathways are also involved in diabetes as summarized in Fig. (**1**) [2].

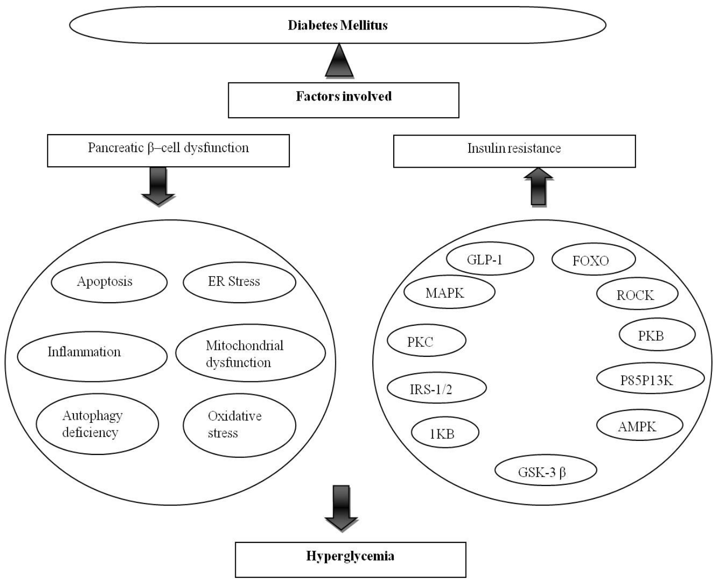

Fig. (1). Representative mechanism involved in the development of diabetes mellitus. Glucagon-like peptide 1 (GLP-1); insulin receptor substrate 1 and 2 (IRS-1/2); mitogen-activated protein kinases (MAPK); AMP-activated protein kinase (AMPK); IkB kinase (IkB); protein kinase C (PKC); Rho-associated coiled-coil containing protein kinase (ROCK); protein kinase B (PKB); forkhead box protein O (Foxo); PI3K subunit (p85); phosphatidylinositol 3-kinase (PI3K); Glycogen synthase kinase-3b (GSK-3b).

Pathophysiology and Complications

The specific acute metabolic complications of diabetes mellitus are diabetic ketoacidosis, lactic acidosis, hyperosmolar non-ketotic coma and hypoglycemia. In addition to acute complications, the long–lasting consequences of diabetes mellitus are the progressive development of some severe complications like retinopathy with prospective blindness, nephropathy that can cause kidney failure, neuropathy and diabetic foot, *etc.* Persistent hyperglycemia in diabetes may result in macroangiopathy and microangiopathy that are considered to be poly etiological disorders. Diabetic patients are generally more prone to coronary artery disease, diabetic cardiomyopathy, peripheral vascular and cerebrovascular disease [3].

Effects of Diabetes Mellitus on Biological Parameters

In diabetic animals, a strong relationship exists between hyperglycemia and reduced body weight. Weight decreased may be due to body's inability to utilize and storage of glucose which leads to malnourishment and weight loss [4]. Pancreatic beta cells produce insulin which helps glucose transportation across cell membrane. Insulin insufficiency disturb the transportation of glucose in blood as a result level increased in blood and urine [5]. Carbohydrate and fat metabolism is impaired during diabetes. In mammals, various sites of lipid metabolism are affected by insulin. In hyperglycemic state, lipid peroxidation alterations are very common which is related to free radicals. These radicals cause lipid disruption . They are also involved in diabetes complications. Antioxidants neutralize these radicals which prevent complications induced by diabetes in experimental animal models [6]. In hyperglycemic condition, increased lipid peroxidation and accumulation of its products is caused by oxidative stress. Adefegha and Ganiyu, reported that in alloxan-induced diabetic rats malondialdehyde levels increased as compared to normal rats. Imbalance between oxygen free radicals production and cell defense mechanism also cause destruction of liver and pancreatic tissues that leads to complications [7]. Ragavan and Krishnakumari, studied that in diabetic conditions liver sections revealed structural alterations (hepatocyte necrosis) due to insulin absence [8]. Moreover, Hashemnia described the degenerative changes in hepatocytes such as hepatic cord disorganization, congestion of central veins and infiltrated sinusoids in diabetic rats [9].

Diabetes Mellitus Management

Managing of a disease is very important. Several aspects, such as less physical activity, obesity, smoking and use of alcohol, effects the incidence of diabetes. Lifestyle modifications can reduce the risk of disease incidence. High fiberous and low total fats diet will prevent diabetes. WHO also recommended that improving factors of lifestyle like stay away from fatness lastly from hyperglycemia [10].

Conventional and Traditional Treatments for Diabetes

Diabetes is considered a global problem world widely. The purpose of its treatment to get better life and prevention from its complications. Most commonly for type 1 diabetes short and long acting insulin and for type 2 biguanides and sulfonylureas are used in allopathy. The sulfonylureas include tolbutamide, glibenclamide, chlorpropamide, glipizide, acetohexamide, gliclazide and tolazamide. Several factors have been involved in therapeutic effects of sulfonylureas for type II diabetic patients, including pancreatic and extrapancreatic. Sulfonylureas directly encourage release of insulin from the β-cells in the islets of Langerhans, and this effect does not require the existence of

CHAPTER 3

Anti-Diabetic and Anti-Hypertensive Potentials of Essential Oil Bearing Medicinal Plants

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Abstract: Medicinal plants have long been the area of great interest and a hot topic of current scientific investigations for the biochemists, chemists and pharmaceutics. These researches play an important role in discovering the new natural resources and developing the potential drugs for the treatment of various unknown diseases. These drugs are supposed to have more effectiveness and no side effects unlike most other synthetically produced modern drugs. In accordance with the World Health Organization (WHO), approximately four billion people constituting eight percent population of the world, use herbal based natural drugs for the majority of primary health care problems. Diabetes mellitus and hypertension are the two most common diseases that sometimes also coexist and enhance the chances of neuropathic disorders, brain strokes, retinopathic symptoms, peripheral vascular diseases and cardiac arrest. This chapter describes various medicinal plants having anti-diabetic and anti-hypertensive potentials along with their detailed mechanisms and mode of actions. Some potential anti-diabetic plants are alkanet, asthma weed, bamboo, basil, caraway, chirayita, coleus, cubeb, cumin, cypress, damask rose, fennel, fenugreek, fig, frangipani, ginseng, guava, henna, Indian globe thistle, Indian pennywort, ma-huang, moringa, olive, puncture vine, saffron, sweet lemon, tree turmeric, walnut, corn and tawa tawa. Anti-hypertensive plants discussed in this chapter include basil, black piper, coleus, curry leaf, puncture vine, sesame seed, yarrow, passion fruit, onion, garlic, celery, oat, barberry, black cumin, ylang ylang, garden cress, ginger and sweet lemon.

Keywords: Anti-diabetic, Anti-hypertensive, Brain Stroke, Cardiac Arrest, Essential oils, Medicinal Plants.

INTRODUCTION

Mother-nature has provided us a complete store-house of remedies in order to

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cure all sorts of ailments, proving to be catastrophic for human races. According to an estimate, a major portion of the world's population utilizes medicinal plants either in parts or as a whole plant [1]. Some additional medicinal uses of curative plants are recognized to learn more about the potential future perspective of medicinal plants. Medicinal remedies derived from plants, either by getting information through traditional knowledge or by exploring literature, are now being handed down generation after generation. Various pharmaceutical industries are now looking for some other natural alternative resources proven to be environmentally benign and potentially viable in nature. Nowadays, scientists are working to explore the potential anti-biotic, anti-oxidant, anti-microbial, anti-diabetic and crop protecting agents for the sustenance of all life forms on earth. Medicinal plants generally provide a great source of a wide variety of natural bioactive compounds including phenolics, nitrogenous compounds, terpenoids, vitamins and various other secondary plant metabolites showing potential bioactivities *e.g.*, anti-oxidants, anti-tumor, anti-inflammatory, anti-mutagenic, anti-bacterial, anti-carcinogenic and anti-viral activities [1].

Essential oils are the natural, complex, volatile aromatic compounds containing a number of structurally different organic constituents isolated from different scented plants having high commercial importance and extreme therapeutic potentials. Essential oils have extensively been used as a potential ingredient in order to enhance the functionality of a number of commercial products like green pesticides, cosmetic products, pharmaceuticals, perfumes, soft drinks and food stuff. Currently, global research is mainly focused on the development of eco-friendly techniques and innovative ideas for the extraction of essential oils and to stabilize them through proper encapsulation for bringing the natural products under the label of generally-recognized-as-safe. Essential oil is a biochemical product and a mixture of a large number of structurally related compounds, produced inside the cytoplasmic fluid and are then transported into intracellular space in the form of smaller droplets. These chemical compounds are highly volatile in nature and have a characteristic aroma. They are generally composed of a combination of aromatic and non-aromatic compounds having specific chemical composition and characteristic aroma [2].

Aromatic oils or scents contain approximately more than two hundred known complex chemical compounds having hydrogen, oxygen and carbon as the backbone of all complicated molecules. Essential oils can be broadly classified as (i) volatile and (ii) non-volatile components. Approximately 90 to 95 percent chemical constituents of essential oils such as alcohols, aliphatic compounds, esters, aldehydes, monoterpenes, sesquiterpenes and hydrocarbons along with their oxygenated derivative, are highly volatile in nature. Only 1 to 10 percent of molecules out of total weight are non-volatile in nature including hydrocarbons, sterols, waxes, fatty acids, carotenoids and flavonoids. Chemical composition of the essential oils significantly changes with the duration of the growth period, environmental conditions, harvesting time and extraction technique. Composition of an essential oil significantly varies by changing the plant source and chemical constituents can range from a few dozens to hundreds of complex molecules. Oxygenated derivatives of hydrocarbons are accountable for the flavors and fragrances while higher phenolic contents help to improve the antibacterial activities [3].

The aromatic oils contain natural anti-oxidants that restrict the free radical reactions of deoxyribonucleic acid (DNA), unsaturated lipids, amino acids and proteins. Human body is known to have a strong defense mechanism against free radicals abundantly found in most of the body cells. The balance between the amount of antioxidants and free radicals can only be achieved by an external supply of natural or synthetic anti-oxidants. Scented aromatic oils are richly supplied with phenolic compounds that significantly contribute to determining free radical scavenging activities and anti-oxidant potentials. Essential oils of thyme, oregano, nutmeg, clove, cinnamon and basil are known to have strong anti-oxidant and free radical scavenging potentials in DPPH radical assay [4]. Some essential oils have strong anti-bacterial potentials against a wide spectrum of disease-causing bacterial strains such as *Salmonella typhimurium*, *Staphylococcus aureus*, *Bacillus cereus*, *Shigella dysenteria*, *Escherichia coli*, *Salmonella typhimurium*, *Listeria innocua* and *Listeria monocytogenes*. The volatile essential oil of *Commiphora africana* is known to inhibit the various pathological bacterial strains such as *Helicobacter pylori*, *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* [4].

Essential oils are generally added as food flavors and also act as anti-fungal and anti-bacterial additives. Macro-dilution technique is helpful in accessing the anti-microbial potentials of essential oils. Similarly, significant inhibition in mycelial growth of fungi can be observed on applying different concentrations of varied essential oils on an experimental basis. Essential oil extracted from thyme, tea tree, cinnamon and catnip exhibits maximum anti-microbial potentials. Some recent evidences have indicated that *in-vitro* applications of essential oil of *Thymus schimperi* Ronniger can act as a strong anti-bacterial agent against wide spectrum pathogenic fungal isolates such as *Microsporum gypseum*, *Beauveria bassiana*, *Aspergillus minutus*, *Aspergillus tubingensis*, *Verticillium* sp. and *Penicillium chrysogenum* [4].

Diabetes mellitus is a severe endocrinological metabolic disorder, rapidly spreading across the globe. Major symptoms of diabetes mellitus are high blood glucose levels as a consequence of inadequate secretion of pancreatic insulin or

CHAPTER 4

Management of Diabetes Mellitus by Natural Products: Glucagon-like Peptide 1 Perspective

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Abstract: Diabetes Mellitus (DM) has become a major and serious health problem worldwide. To overcome this lifestyle disease, natural products can be explored systematically. These natural products act on various targets and show their effect in diabetic conditions. Out of this, GLP-1 Receptor is one of the promising targets. Cells in the small intestine secrete Incretin hormones upon nutrient ingestion. Glucagon-like peptide-1 (GLP-1) is a primary incretin hormone in metabolism that has a potent antihyperglycemic effect. Insulin will release, in the presence of hyperglycemia, GLP-1 stimulates the pancreas to release insulin, stops glucagon release, gastric emptying slows down and increases satiety by acting on the hypothalamus. Storage of GLP-1 is mainly in secretory granules of L cells, in small intestinal distal portion and colon. When the cells are activated, this peptide is released into the main bloodstream.GLP-1 secreted mainly upon the ingestion of oral glucose or the ingestion of a mixed meal. Other factors like neurotransmitters and intestinal hormones also affect GLP-1 secretion from the intestine. Considering the above-mentioned parameters, regulation and control of GLP-1 are necessary as GLP-1 secretion is hampered in T2DM.

The present chapter focuses on scientific information about natural products specifically acting as GLP- 1 Receptor Agonist (GLP-1 RA).

Keywords: Diabetes Mellitus, GLP-1 Receptor Agonist, Herbal Medicine, Insulinotropic, Natural Products.

INTRODUCTION

The number of individuals suffering from diabetes has reached 425 million. International Diabetes Federation data shows that in 2045 there will be 629 million people affected with diabetes. At the global level, India is going to be one

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of the major countries having a large number of diabetic patients. Regular exercise and a healthy lifestyle can reduce the risk of this disease. The invention of a new drug molecule which is safer and better than the existing one, newer methodology and approach is need of an hour. All these invented drugs will help in reducing diabetes and its complications and as a result decrease in mortality and morbidity [1, 2].

Synthetic antidiabetic drugs have drawbacks like poor bioavailability, the too short or too long half-life, low therapeutic index, non – linear kinetics because of saturable clearance mechanism, on repeat, dosing increased clearance because of auto induction, multiple metabolites not covered by toxicity studies [1].

Considering the above points, there is utmost need to find out more efficacious, better and safer alternatives in the management of diabetes [2]. In recent years various natural products have been evaluated and proved for their beneficial effects in the management of diabetes.

In the ancient era, medicinal plants which are collected from the forest were only the basic source of drugs for all types of ailments. Hence more Weightage is given to these traditional and herbal drugs which can be used to treat all types of diseases. Thus medicinal natural products are playing a crucial role in the management of health care. Over twelve hundred medicinal plants have been identified and have been claimed as a remedy for diabetes and out of those, several hundred have been evaluated for the said treatment [3]. Several synthetic compounds have been discovered from medicinal plants like metformin, which was based on biguanide compound from plant *Galanga officinalis* [3]. Throughout the world, more than 400 plants, over 700 recipes and compounds have been broadly evaluated for T2D treatment [4]. In the human body, these natural products act on various targets and show their effects.

Glucagon-Like Peptide - 1

Upon oral glucose intake, gastrointestinal tract secretes incretin hormones [5]. These are gut peptides generally secreted after food intake and augment insulin secretion. Incretin hormones like Glucose-dependent insulinotropic polypeptide and Glucagon-Like Peptide -1 are secreted by upper K cells and lower enteroendocrine L cells of gut respectively.

Also, GLP-1 has different and multiple effects on different organs. GLP-1 is responsible for decreasing apatite which is linked with food intake and weight loss. GLP-1 is synthesized from the posttranslational modification of proglucagon, by Prohormone Convertase 1 (PC1). It stimulates Glucose Stimulated Insulin Secretion (GSIS) when glucose and free fatty acids are taken orally [6]. It has been reported that GLP-1 has insulinotropic action. High sugar intake results in increased GLP-1 secretion and ultimately in the stimulation of β-cells which secrets insulin. This proves that GLP-1 mimetics or its receptor agonists can be used for the management of diabetes [7].

Chemically, GLP-1 is available in two forms: GLP-1 (7–36) amide (80% of circulating GLP-1) and GLP-1 (7–37) amide. GLP-1 (1–36 amide) is predominantly secreted in the pancreas, whereas GLP-1 (1–37) is secreted in the ileum and hypothalamus [8 - 13].

Secretion of Incretin Hormones in Healthy Human Subjects

Carbohydrates like glucose and sucrose, starch; amino acids, triglycerides and proteins stimulate the secretion of GLP-1.

Proteins serve as a relatively weak stimulus for GLP-1 secretion. For this purpose, a minimum fixed rate of gastric emptying is required to have measurable secretion. Despite the distal location of secretory L cells in the gut, GLP-1 will be secreted immediately after ingestion of nutrients and meals [14].

Deacon and Holst identified that for degradation of GLP-1, dipeptidyl peptidase 4 (DPP-4) enzyme in plasma is responsible [15] and also showed that this degradation could be prevented by inhibiting enzyme DPP-4 [16]. GLP-1 has a very short half-life (<2 min) because of its speedy cleavage by Dipeptidyl peptidase-4 (DPP-4) [7]. Studies on pigs showed that practically it was possible to prevent degradation of GLP-1 by DPP-4 and this action showed a marked increase in insulin in response to glucose and GLP-1 [17].

GLP-1 affects levels of insulin and glucagon to decrease elevated blood sugar levels in two ways. First GLP-1 increases the body's natural insulin secretion in response to a meal and second GLP-1 lowers levels of the hormone glucagon after eating. Glucagon works opposite to insulin and raises blood sugar levels', so decreasing glucagon level helps to lower blood sugar. For insulin production, β-cell protection and β-cell proliferation, attenuating gastric emptying, reducing glucose secretion, decreasing appetite/weight, GLP 1 has a pivotal role [18, 19].

Various medicinal plants extracts have also reported increasing secretion of GLP-1. Natural products stimulate GLP-1 receptor on the enteroendocrine cells of GIT. As a result, depolarization of the enteroendocrine cell membrane by an increase in the level of intracellular calcium concentration and secretion of GLP-1 (Fig. **1**).

CHAPTER 5

Terpenes and Terpenoids in Management of Diabetes & Cardiovascular Diseases

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Abstract: Diabetes mellitus is a chronic metabolic disorder and is one of the major leading causes of death worldwide. According to the World Health Organisation, the burden of diabetes has increased almost two-fold in 2014 compared to 1980 in low- and middle-income countries. Uncontrolled levels of glucose in the blood are because of improper insulin secretion or insulin action which is associated with abnormalities in metabolic, genetic and hemodynamic systems. The term cardiovascular disease is used for all types of disorders associated with heart and blood vessels. Many researchers are trying to develop new therapeutic approaches for the treatment of diabetes and cardiovascular disease. Herbal medicines are one of the oldest and alternative therapeutic treatment options for diabetes and hypertension. Around 1200 traditional medicinal plants have been used for their beneficial effects on diabetes. These plants are rich in alkaloids, glycosides, flavonoids, polyphenols and terpenoids. Terpenoids are a diverse category of cyclic compounds obtained naturally from the isoprene unit. Among all reported natural products, about 60% of compounds are from terpenoids. More than 40,000 terpenoids are isolated from secondary metabolites of plants. Most of them are of plant dietary origin. Plants produce terpenoids as a secondary metabolite. More than hundreds of new terpenoid structures are reported every year for their activity in many disease conditions like cancer, malaria, inflammation, and a variety of infectious diseases. Various reports have shown that terpenoids are beneficial in the treatment of diabetes and cardiovascular diseases. The chapter is focused on terpenoids and their role in the treatment and management of diabetes and cardiovascular diseases.

Keywords: Arjunolic acid, Cardiovascular diseases, Corosolic acid, Diabetes, Glycyrrhetinic acid, Ginsenoside, Lupeol, Limonene, Pomolic acid, Terpenoids, Ursolic acid.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine disease with a severe impact on modern global health. Diabetes occurs either when the pancreas does not produce the required amount of insulin or when the body cannot use the insulin produced by the pancreas. Blood glucose levels are mainly monitored by insulin. Hyperglycemia is an effect of uncontrolled diabetes. Continuous hyperglycemia leads to damage to nerves and blood vessels. World health organization (WHO) has classified diabetes into six types as type 1, type 2, hybrid forms of diabetes, other specific types, unclassified diabetes and hyperglycemia first detected during pregnancy. Type 1 diabetes mainly occurs due to β-cell destruction. Type 1 diabetes is immune-mediated and there is an absolute deficiency of insulin. The onset of type 1 is common in children and adults. Type 2 diabetes is the most common. Type 2 diabetes mainly occurs due to insulin resistance and various degrees of β-cell destruction. Type 2 diabetes is associated with overweight and obesity. Hybrid forms of diabetes are subdivided into two categories as slowly evolving, immune-mediated diabetes of adults and ketosis-prone type 2 diabetes. Slowly evolving, immune-mediated diabetes of adults is similar to type 1 but mainly due to metabolic syndrome of glutamic acid decarboxylase autoantibody and ketosis-prone type 2 diabetes is due to ketosis and insulin deficiency. Other specific types of diabetes have again classified into seven subdivisions including Monogenic diabetes (single gene defects of β-cell function or insulin action), Diseases of the exocrine pancreas (any defect to pancreas like inflammation, trauma and tumor), Endocrine disorders (over secretion of hormones that are insulin antagonists), Drug- or chemical-induced (impairment of insulin secretion or action due to medicines and chemicals), Infection-related diabetes (associated with viruses having direct β-cell destruction property), Uncommon specific forms of immune-mediated diabetes and other genetic syndromes sometimes associated with diabetes (due to chromosomal and any genetic disorders). Unclassified diabetes in this category of diabetes does not fit in any above classification. Hyperglycaemia first detected during pregnancy is subdivided into two types as follows diabetes mellitus in pregnancy (type 1 or type 2 diabetes diagnosed for the first time during pregnancy) and gestational diabetes mellitus (hyperglycemia below the diagnostic thresholds for diabetes in pregnancy). Diagnosis criteria for diabetes have been updated by the WHO in 2019. The person is said to be diabetic if 2-hour post-load plasma glucose equal to or more than 11.1 mmol/L, fasting plasma glucose equal to or more than 7.0 mmol/L or HbA1c equal to or more than 48 mmol/mol. Criteria for a pregnant woman are with 1-hour post-load plasma glucose equal to or more than 10.0 mmol/L, 2-hour post-load plasma glucose 8.5–11.0 mmol/L or fasting plasma glucose 5.1–6.9 mmol/L [1]. It is estimated that around 422 million people living with diabetes in 2014 this prevalence almost doubled since 1980 in low- and middle-income countries. The WHO also reported that 1.5 million deaths occurred due to diabetes and 2.2 million deaths occurred due to hyperglycemia in 2012 [2].

Cardiovascular Diseases (CVDs) are one of the leading causes of death in the world. CVDs include conditions like hypertension, angina (chest pain due to decreased blood flow to the heart), arrhythmia (irregular heartbeats), heart attack (blockage to the heart's blood vessel) and heart failure. According to the WHO, around 17.9 million people died from CVDs in 2018. Out of this, 85% of deaths are due to heart attack and heart failure. CVDs affect equally in men and women. It is estimated that 23.6 million people will die from CVDs by 2030 [3].

DM is responsible for the development of vascular diseases. The major risk factors include modern lifestyle, junk food, less physical activities, obesity, genetic factors, physical and mental stress [4].

Interconnection between Diabetes and Cardiovascular Diseases

Persistent hyperglycemia causes activation of molecular pathways like polyol, hexosamine, advanced glycation end products (AGEs) and protein kinase C (PKC), which may damage vital organs like brain, eyes, kidney and heart. Hyperglycemia alters cellular, sub-cellular and molecular mechanisms mainly by upregulating the pro-inflammatory biomarkers like interleukins, cytokines, transforming growth factor-β (TGF-β) and nuclear factor kappa B (NF-κB) [5].

About 50% of diabetics, either type 1 or 2 have chances to develop CVDs. The prevalence of CVDs in diabetes may vary with age, sex, basal mass index, presence of kidney disease and others. Hyperglycemia may lead to impairment in systolic and diastolic functions of the heart in diabetic patients independent of the presence of coronary heart disease [6]. Clinical and epidemiologic data from the last two decades have shown that the prevalence of hypertension and heart failure in diabetes is very high. It is predicted that the rate of mortality and morbidity is around 27 per 1000 diabetic patients per year compared to those without diabetes [7, 8].

Scientists are working to understand the exact mechanism of CVDs in diabetics. The literature revealed that continuous functional and metabolic alterations lead to prompt irreversible changes in heart of diabetics. The altered metabolism is associated with increased oxygen consumption in myocardial tissue and increased concentrations of free fatty acids (FFA) in the serum. The excess FFA uptake and hyperglycemia leads to dysfunction of mitochondria present in the heart. This leads to increased calcium sensitivity in cardiomyocyte and abnormality in contractile and regulatory protein expressions in diabetics. It is also reported that reduced activity of calcium pump and the rate of calcium removal of sarcoplasmic

CHAPTER 6

Antidiabetic and Antihypertensive Medicinal Plants of Asia: Active Ingredients, Safety, Pharmacology, and Traditional Uses

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Abstract: Diabetes mellitus and hypertension are the two most common diseases in modern civilized countries. It is suggested that hypertension is more likely to be associated with type II diabetes as the patient acquires both diseases at old age. Though several therapeutic approaches were developed to treat the complications, plant-based therapeutics remains one of the most promising approaches. Moreover, traditional medicine remains as a primary health care system in the resource constraint societies. The use of medicinal plants for therapeutic uses has a long tradition in Asia in the form of Ayurveda, Traditional Chinese Medicine, Unani, Jamu, *etc*. In recent years, the scientific community has focused on natural products derived from ethnomedicinal plants for their wide therapeutic potentials, including diabetes mellitus and hypertension. Phenformin, metformin, repaglinide (Prandin), nateglinide (Starlix), pioglitazone, rosiglitazone, acarbose, miglitol are some of the antidiabetic marketed drugs of plant origin. Lignans, cinnamaldehyde, and protodioscin are newly isolated anti-diabetic drugs from plant sources. This chapter attempts to highlight the medicinal plants of Asia used for antidiabetic and antihypertensive purposes with regard to their phytochemical potentials, biosafety, and scientific evaluation of their traditional uses.

Keywords: Antidiabetic, Antihypertensive, Asia, Medicinal plants, Plant-based therapeutics, Traditional medicine.

INTRODUCTION

Diabetes

Diabetes mellitus (DM) is an important chronic disease triggered by an inappropriate balance of glucose homeostasis [1]. DM is a severe chronic

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metabolic disorder that affects health, quality of life, and life expectancy of patients, as well as the health care system. According to the World Health Organization (WHO), 171 million people worldwide suffer from diabetes; this number is expected to be more than double by 2030 and around 3.2 million deaths every year are attributable due to diabetes; six deaths every single minute [2]. Reports of the WHO showed that the diabetes epidemic is more pronounced in India than in other parts of the world. 32 million people had diabetes in the year 2000 [3]. The International Diabetes Federation (IDF) estimates the total number of diabetic condition subjects to be around 40.9 million in India, and this is further set to increase to 69.9 million by the year 2025. Reports of WHO have also shown that non-insulin-dependent diabetes mellitus (NIDDM) and its complications are increasing in sub-Saharan Africa. and the incidence of the disease is growing annually [4]. Diabetes is the most heterogeneous challenging disease. It can merely be categorized into type 1 diabetes mellitus and type 2 diabetes mellitus [5]. The distinction between type 1 and type 2 diabetes mellitus solely depends on the clinical appearance, such as age at disease commencement, the incidence of ketosis, and insulin dependence. Type 1 diabetes mellitus, occurring mainly in childhood or young adulthood, is earmarked by T cell-mediated autoimmune destruction of beta cells, absolute insulin dependence, and the need for insulin treatment. Type 2 diabetes mellitus, mainly occurring in adulthood, is the outcome of insulin resistance and relative insulin deficit [6]. Diabetes or hyperglycaemic condition can be caused through the inhibition of key enzymes α-glucosidase and α-amylase for starch digestion. Drugs that are in use now, such as miglitol, acarbose, nojirimycin, voglibose, and 1-deoxynojirimycin possess unbearable toxicity, which triggers the finding of natural inhibitors of glucosidase and amylase from the plant sources [7].

Hypertension

High blood pressure or hypertension (HTN) is a common cardiovascular complication, which has become a global problem. 15–20% of all adults with ailments, such as arteriosclerosis, stroke, myocardial infarction, and end-stage renal diseases are due to hypertension [8]. It is stated that NIDDM is the result of prolonged hypertension complications. These two diseases (NIDDM and hypertension) are interconnected metabolic syndromes. Prolonged persistent hypertension serves as a risk factor for stroke and chronic renal failure [9]. Angiotensin-I converting enzyme (ACE) is a key enzyme that controls the regulation of blood pressure. It translates angiotensin I to angiotensin II, which is an effective vasoconstrictor. The inhibition of ACE activity provides an antihypertensive potential by simultaneously lowering blood pressure in non-diabetic and diabetic patients [10]. Lisinopril, captopril, and enalapril are drugs currently used as ACE inhibitors and have been reported to be harmless and effective. Search for non-toxic ACE inhibitors provides a direction towards the use of dietary phenolic phytochemicals and is shown to have promising effectiveness [11]. In recent decades, the consumption of vegetables for antihypertensive and antidiabetic phytochemicals has attracted growing interest. Many experimental and epidemiological studies have reliably verified a positive connection between the intake of these natural foodstuffs and reduced risks of several degenerative diseases, including NIDDM [7]. Phytochemical rich foods consist of several antioxidants, especially antioxidative vitamins, including ascorbic acid (vitamin C), α-tocopherol (vitamin E), and β-carotene (provitamin A), which may provide a defensive role against these complications. Studies indicated that polyphenolic compounds are the main phytochemicals, with greater antioxidant properties found in plants [7]. Phenolics in plant products are present in free or aglycone and bound or glycoside forms [12]. The free phenolics are more easily absorbed and thus provide helpful bioactivities in food assimilation. However, the number of different bound phenolics are assimilated and absorbed at several sites of the gastrointestinal tract where they do their duty for the benefit of health [7]. Type 2 diabetes mellitus and hypertension are two highly predominant diseases among the aged that make them vulnerable to vascular disease. The occurrence of type 2 diabetes in the age group of 65 years and older is approximately between 15% and 25% [13], whereas, for hypertension, the range is between 50% and 70% [14].

Diabetes and Hypertension

Diabetes and hypertension are interconnected in most diabetic people and the prevalence of getting hypertension is two folds that of the non-diabetic person [15, 16]. Prolonged diabetes damages arteries and causes a condition called atherosclerosis. This condition leads to the development of high blood pressure along with other circulatory hindrance. In type 2 diabetes due to insulin resistance, hyperinsulinemia develops, which regulates the Angiotensin-I converting enzyme to convert Angiotensin-I to Angiotensin-II. As a result, Angiotensin-II regulates the vasoconstriction and develops hypertension in diabetic condition [10]. Below mentioned Fig. (**1**) demonstrates the connection link between diabetes and hypertension.

CHAPTER 7

Chrysophyllum Cainito L.

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Abstract: *Chrysophyllum cainito* L. is part of the family Sapotaceae and native to the Greater Antilles and the West Indies. This specie is a medicinal plant used around the world by many cultures, commonly known as "star apple" or "caimito". Some studies have reported that *C. cainito* possesses many pharmacological properties as antidiabetic, anti-hypersensitivity, antihypertensive, anti-inflammatory, antimicrobial, antinociceptive, antioxidant, gastroprotective and immunosuppressive. Also, phytochemical evidence has revealed that the main secondary metabolites in *C. cainito* are alkaloids, tannins, flavonoids, phenols, sterols, coumarins and triterpenes which are responsible for their pharmacological benefits. *In vitro* and *in vivo* toxicology studies have suggested human consumption of *Chrysophyllum cainito* leaves as safe. This chapter includes scientific information of pharmacology, toxicology and phytochemistry of *C. cainito* seeds, leaves, and fruits with the purpose to contribute valuable scientific information to future research in drug development based on *C. cainito* as a source of raw material.

Keywords: Antidiabetic, Anti-inflammatory, Antimicrobial, Antinociceptive, Antioxidant, *Chrysophyllum cainito* L., Immunosuppressive, Medicinal use, Pharmacology Phytochemicals, Toxicity.

INTRODUCTION

Chrysophyllum cainito is part of the family Sapotaceae and native to the Greater Antilles and the West Indies. It is spread in the lowlands of Central America and now is very common and cultivated throughout the tropics, including Southeast Asia [1]. The fruit is named as star apple, cainito, caimito or cayumito, and its fla-

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vor is a mixture between green grapes and litchi. This specie is used in folk medicine for the treatment of inflammation such as laryngitis, pneumonia, rheumatoid arthritis, and diabetes mellitus [2]. The chemical analysis has described several secondary metabolites including alkaloids, flavonoids, phenols, sterols, and triterpenes which are well known to have pharmacology properties. The biological activity of *C. cainito* has been also investigated comprehensively [1 - 3], and in this chapter, we assemble the information of *C. cainito* describing the ethnomedical, chemical, pharmacological, and toxicological properties providing wide scientific evidence of its medicinal benefits and worthiness as a source of new chemical agents in the drug discovery process.

SYNONYMS

C. cainito L is also known by many other synonyms around the world. The most common synonyms are *Cainito pomiferum* Tusac, *Chrysophyllum bicolor* Poir, *Chrysophyllum bonplandii* Klotzsch ex Miq, *Chrysophyllum monopyrenum* Sw, *Chrysophyllum sericeum* Salisb, *Cynodendron bicolor* (Poir.) Baehni [1], and *Achras caimito* Ruiz & Pavon [2].

BOTANICAL FEATURES [3]

Kingdom: Plantae
Subkingdom: Viridiplantae
Division: Tracheophyta
Class: Magnoliopsida
Superorder: Asteranae
Order: Ericales
Family: Sapotaceae
Genus: *Chrysophyllum* L.
Species: *C. cainito* L.

VERNACULAR NAMES

Chrysophyllum cainito is most commonly known as “caimito” or “cayumito”. However, many names are reported of this specie (Table **1**).

C. cainito is an evergreen tree with alternate oblong-lanceolate leaves and flowers blooming from May to October, which are small, white to greenish in color. A green to purple fruit with approximately 5-8 cm in diameter is characterized by fleshy and edible pericarp. The epicarp or peel is hard on the external tissues and soft on the internal ones [8]. The fructification is mixed; the first fruits appear in July and are prolonged until the following year [9]. *C. cainito* is propagated by seed and it can germinate to about 60% by mechanical scarification [10 - 13].

Table 1. Reported vernacular names for *Chrysophyllum cainito* L. worldwide.

Geographical Region	Vernacular Name	Reference
AMERICA		
North America		
Mexico	Caimito or Cayumito	[1]
Oaxaca	Canela	[4]
Chiapas	Chicle de monte	[4]
San Luis Potosi	Isi, ocotlan	[4]
United States		
Florida (southern)	Star apple	[6]
Caribbean	Star apple (overall)	[5]
Haiti	Pied caimite or caimitier a feuilles d'or	[2]
French West Indies	Pomme surette, or buis	[2]
Virgin Islands	Cainit	[2]
Trinidad and Tobago	Caimite or kaimit	[2]
Barbados	Star-plum	[2]
Central America	Star apple (overall)	[5]
Belize	Damsel	[2]
El Salvador	Guayabillo	[2]
Nicaragua (eastern)	Apil	[7]
South America	Star apple (overall)	[5]
Colombia	Caimo, caimo morado (purple variety) or caimito madura verde (green variety)	[2]
Bolivia	Caimitero, or murucuja	[2]
Surinam	Sterappel, apra or goudblad boom	[2]
French Guiana	Macoucou	[2]
Argentina	Aguay or olivoa	[2]
EUROPE		
Spain	Caimito or Estrella	[2]
Portugal	Cainito orajara	[2]
France	Caimite or caimitier	[2]
ASIA		
Singapore	Chicle durian	[2]

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> Standing on the shoulders of giants, Professor Eddouks has crafted a nice book on phytotherapy. Shining light on the management of diabetes and hypertension, with many knowledge gaps being filled for phytotherapists. Every chapter has its merits.
>
> *William Cho Biomedical Scientist*
> *Hong Kong Precision Oncology Society, Hong Kong*

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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.