Frontiers in Clinical Drug Research

(Diabetes and Obesity)

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CONTENTS

PREFACE

The sixth volume of ***Frontiers in Clinical Drug Research – Diabetes and Obesity*** comprises six comprehensive chapters that present novel approaches to combat diabetes and obesity.

Roy and Khalse summarize the current state of knowledge on the epidemiology, interrelationships of heart failure and type 2 diabetes. The review covers the pathophysiology, clinical correlates, and the current status of emerging novel therapies in the field.

Flavonoids are naturally occurring compounds which make them attractive candidates to study anti-diabetic medicines. Rammohan and Bhaskar in chapter 2 of the book emphasize the importance and therapeutic potential of flavonoids as templates for future diabetic therapeutic drugs. . In the next chapter, techniques for combining biological sensing and fluorescent nanomaterials components are explored, and the applicability of chemosensors for glucose testing is discussed .

Chapter 4 of the book summarizes the current status and prospects of synergistic drugs and polyherbal formulations in the development of safe and functional drugs for the management of obesity. In next chapter of the book, a detailed and in-depth analysis of herbal antidiabetic drugs and various commonly used anti-diabetic plants are discussed.

In last chapter of the book, Sarfraz *et al.,* discuss turmeric's (*Curcuma longa)* potential for treatment of diabetes mellitus and the hypoglycemic, antioxidant, and anti-inflammatory qualities of its chemical constituents.

I owe special thanks to all the contributors for their valuable contributions in bringing together the sixth volume of this book series. I am also thankful to the efficient team of Bentham Science Publishers for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (in-charge Books Department) and Ms. Asma Ahmed (Manager Publications).

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CHAPTER 1

The Failing Heart in Diabetes with Special Emphasis on Prevention

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Abstract: Diabetes and heart failure are emerging as twin epidemics with huge socioeconomic implications in patients across the globe. The situation is even abysmal considering the unique challenges faced by the health care sector in the lower-income countries with the growing size of the diabetes population (12.34% as reported by IDF 2019). Heart failure (HF) represents one of the most common yet less-recognized comorbidities of type 2 diabetes mellitus (T2DM). Besides, limited understanding of this multifactorial disease, together with a lack of effective therapeutics, has led to an underestimation of the risk in this population. However, until recently, the emerging classes have started to rekindle our efforts to understand this cardiometabolic conundrum once again due to the latest reports of their distinct therapeutic effects in the prevention of hospitalization of concomitant heart failure. Prevention of HF in patients with diabetes needs to be a priority for all caregivers as it is not only possible now to treat effectively but often rewarding from the patient's quality of life perspective in the long run. The present review is an attempt to summarize the current base of knowledge on the epidemiology, interrelationships of HF and T2DM and their shared pathophysiology, clinical correlates, and the current status of emerging novel therapies.

Keywords: Asian population, Heart failure, SGLT2 inhibitor, Type 2 diabetes.

INTRODUCTION

Diabetes and heart failure are interrelated clinical entities presenting as a part of the disrupted metabolic profile in the cardiovascular risk continuum. Their manifestations are generally bidirectional, worsening each other's prognosis may lead to deteriorating clinical outcomes in patients. The aging of the patient population, the increasing prevalence of obesity, and moderate survival prolongation are suggested to be contributing factors to the rising prevalence of these pandemics [1]. Conventionally the atherosclerotic macrovascular events were considered to be the significant triggering factors in cardiovascular disease

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in type 2 diabetes. However, in a nation-wide research study of CALIBER (Cardiovascular disease research using linked bespoke studies and electronic health records), which was followed up for 5.5 years on more than 1.9 million patients, developing heart failure was observed to be the second common manifestation ranking before stable angina, non-fatal myocardial infarction in diabetes [2]. Type 2 diabetes has also been an independent predictor for worse outcomes like mortality across all heart failure entities, including reduced, mid-range, and preserved ejection fraction. Though information on the burden of concomitant heart failure and diabetes mellitus in India is limited, the proportion of type 2 diabetes reported in an observational study was approximately 25% in patients with heart failure. Many contributing risk factors have been proposed to be associated with the failing heart in diabetes, such as coronary artery disease, obesity, uncontrolled glycemia, hypertension, chronic kidney disease, certain medication, and so on. Targeting these critical modifiable risk factors was a focus earlier to prevent heart failure in type 2 diabetes, but it was found to be of insignificant value in improving its outcomes. The risk of developing the incident heart failure double up in diabetes patients compared to nondiabetics [1]. The ARIC study (Atherosclerosis Risk in Communities) provided evidence of possible deleterious effects of hyperglycemia on the myocardium, showing the linear correlation between the glycemic spectrum and subclinical myocardial damage as assessed by highly sensitive cardiac troponin T level in subjects with prediabetes and T2DM [3].

However, glycemic lowering strategies with antihyperglycemic therapies have shown to have minimal effect in reducing the development of heart failure in type 2 diabetes patients. There is a possibility that factors other than glycemia might play a role in increasing the HF risk in diabetes mellitus.

HF therapies also need to be addressed, including conventional therapies like beta-blockade, RAAS inhibition, *etc* [1]. It is intriguing to notice that two classes of drugs (metformin and gliflozins), that reduce the risk of heart failure and its adverse consequences, have also been associated with improving hyperinsulinemia. The recent improvement in the prognosis of patients with heart failure is attributable to the evolving treatment paradigm, which has led to heart failure, especially the entity of reduced ejection fraction to be a treatable disease. Inhibitors of the renin-angiotensin-aldosterone system are a keystone not only for preventing the risk of heart failure and nephropathy progression in patients with diabetes but also reducing the risk of mortality due to cardiovascular causes and hospitalization in patients with established heart failure. In patients with heart failure, spironolactone/eplerenone, and sacubitril/valsartan, each reduce mortality by an additional 20–30% when prescribed with an inhibitor of the renin-angiotensin system. Moreover, in a trial of eplerenone in NYHA II heart failure,

patients categorized based on waist circumference were likely to show a reduction in morbidity and mortality with treatment [4]. A large randomized trial like COPERNICUS with carvedilol has also elucidated the effectiveness of beta-blockers in decreasing the early risk of serious cardiovascular events.

EPIDEMIOLOGY AND GLOBAL BURDEN OF HF IN DIABETES; SPECIAL FOCUS ON BURDEN IN ASIANS

There is limited knowledge on the burden and impact of concomitant heart failure in the Asian population with type 2 diabetes. In developed countries, HF represents nearly 1–2% of the adult population, with more than 10% prevalence in patients among advanced age (>70) groups [5, 6]. Diabetes mellitus is commonly present amongst patients with HF with a higher risk of worse outcomes like death than patients without diabetes or heart failure [7, 8]. The multi-ethnic comparison studied in a prospective longitudinal study of the ASIANHF registry, taking into account 6214 patients, reported a 42.5% prevalence of DM among HF patients [9, 10]. It was concluded that type 2 diabetes mellitus is associated with smaller left ventricular volumes, higher mitral E/e′ ratio, more inferior quality of life, and worse outcomes, in different HF phenotypes (HR 1.37, 95% CI 1.19-1.57; $p < 0.001$). In another multi-ethnic study, patient-level data indicated a strong correlation among Indians with coronary artery disease and hypertension and women in Malay patients [11].

In a prospective study, people with HF of Southeast Asian ethnicities had a 3-fold greater prevalence of DM despite younger age (median age 62 [54 to 70] years) and lesser obesity (19.5% obesity) when compared to Caucasian patients of HF. Similarly, a strong association is shown to exist between the presence of DM and hospitalization due to HF and all-cause mortality in Asian patients [12].

Patients with HFpEF are 65 years of age or older, more often females, and with a more common previous history of hypertension and atrial fibrillation (AF) compared with HFrEF, while a history of myocardial infarction is less common [13, 14]. A prospective survey of acute medical admissions with heart failure in the UK [15] indicated the risk of heart failure in patients aged 60–79 years in comparison to Europeans and it was noted 5.2 (95% CI 3.7 - 7.4) in South Asians and 3.1 (95% CI 1.9 4.-9) in African Caribbeans. It is difficult to derive conclusions regarding the possible reasons behind such large ethnic differences in heart failure risk in diabetes patients. The impact of the more significant burden of Ischemic heart disease in South Asians on heart failure is challenging to estimate because Ischemic heart disease at older ages has not been sufficiently studied according to ethnicity [16]. The mortality from IHD in immigrant South Asians was highest compared to the general population, as represented in Fig. (**1**)

CHAPTER 2

Flavonoids as Prominent Anti-diabetic Agents

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Abstract: Diabetic mellitus (DM) is one of the major progressive metabolic syndromes and it is estimated that currently 390 million people are suffering from diabetes and more than 592 million people would be affected by the end of 2025 worldwide. In general, DM can be broadly classified into two types: DM type-I can be caused by the lack of insulin levels due to the destruction of pancreatic β-cells in the body, and the other DM type-II can be triggered by insulin resistance. However, this impairment of glucose homeostasis leads to several complications, such as cardiovascular risks, renal disorders, risk of blindness, poor blood drift, and dermatological complications. So far, various types of therapeutic drug agents are available for the treatment of DM, for instance, α-Glucosidase inhibitors, Biguanides, Dipeptidyl peptidase-4 inhibitors, Insulin analogs, GLP-1 agonists, SGLT2 inhibitors, Sulfonyl urease inhibitors and Thiazolidinedione's, respectively. However, the long-term usage of these drugs was reported to show adverse effects. Therefore, significant attention is required to treat diabetic problems. Moreover, potential drug agents are desirable to treat DM with myriad therapeutic complications. At present, natural products are the prominent alternative and safer medications for the development of modern drug discovery. Although Western medicine is substituted for 80% of traditional medicine, in some countries, people rely on natural herbs as a remedy for the treatment of certain chronic diseases. In this concern, flavonoids are the prevalent group of natural bioactive molecules that have shown interesting biological activities, including antidiabetic properties. Hence, in the stated book chapter, we are intended to emphasize the importance and therapeutic potential of flavonoids as templates for future diabetic therapeutic drugs. Further, *in silico* studies of few reported flavonoids (rich in the edible source) have been accomplished to establish their molecular interactions with diverse diabetic targets. Therefore, the current chapter serves as a bird's eye view of anti-diabetic flavonoids for further experimental studies and to develop potent markers of therapeutic agents.

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Keywords: Antidiabetic, Blood glucose, Diabetic mellitus, Diabetic molecular targets, Flavonoids, Glucose homeostasis, Natural compounds, Oxidative principles, Polyphenolics, Structural studies.

INTRODUCTION TO DIABETES MELLITUS (DM)

Diabetic Mellitus (DM) is a cluster of chronic metabolic disorders due to uneven blood glucose levels. This might be happening due to the inability of the pancreas to produce sufficient insulin (or) dysfunction of β-pancreatic cells or together [1, 2]. Thus, the persistent DM primes to the enlargement of several macro and microvascular complications, which further leads to enlarged morbidity and mortality [3]. According to the statistics from the International Diabetes Forum (IDF) at present 390 million people are suffering from DM and more than 592 million people may be affected by 2025 [4]. Environmental factors, genetic mutations, obesity and lack of physical activities are the conceivable factors for the pathogenesis of DM [5]. Early detection and prevention of DM is even more difficult task due to the highly competitive lifestyle which comprises work-stress, smoking, alcoholic and tiny physical activity, socioeconomic status to accommodate quality food and the unawareness of people in some countries. While the symbols of prediabetes include increased hunger (polyphagia), frequent urination (polyuria), thirst (polydipsia), weight loss and oblivion, but this doesn't appear in all circumstances [6].

Therefore, this impairment of glucose homeostasis can lead to several complications such as cardiovascular risks, renal disorders, risk of blindness, poor blood drift and dermatological complications [7]. Furthermore, hyperglycemia also induces an appealing force for the development of oxidative stress [8] which stimulates Advanced Glycation End Products (AGE), Initiation of Protein Kinase C (PKC) and Expansion of more Reactive Oxygen Species (ROS) [9, 10]. Thus, the quality of life decreasing due to diabetes and often leads to "deceased or death". However, impaired blood glucose levels can be tolerated through the usage of suitable therapeutic agents or by changing lifestyle and food habits. In general, the DM can be classified (Fig. **1**) in the following ways.

DM-I/Type-1 DM

It is an autoimmune disorder and in recent years, it has become more often in children and adolescents [11]. It is triggered by a lack of insulin levels due to the destruction of β-pancreatic cells in the body. This is also known as "Juvenile Diabetes" and the person with DM-I needs to have insulin injected from a peripheral source for the rest of their life.

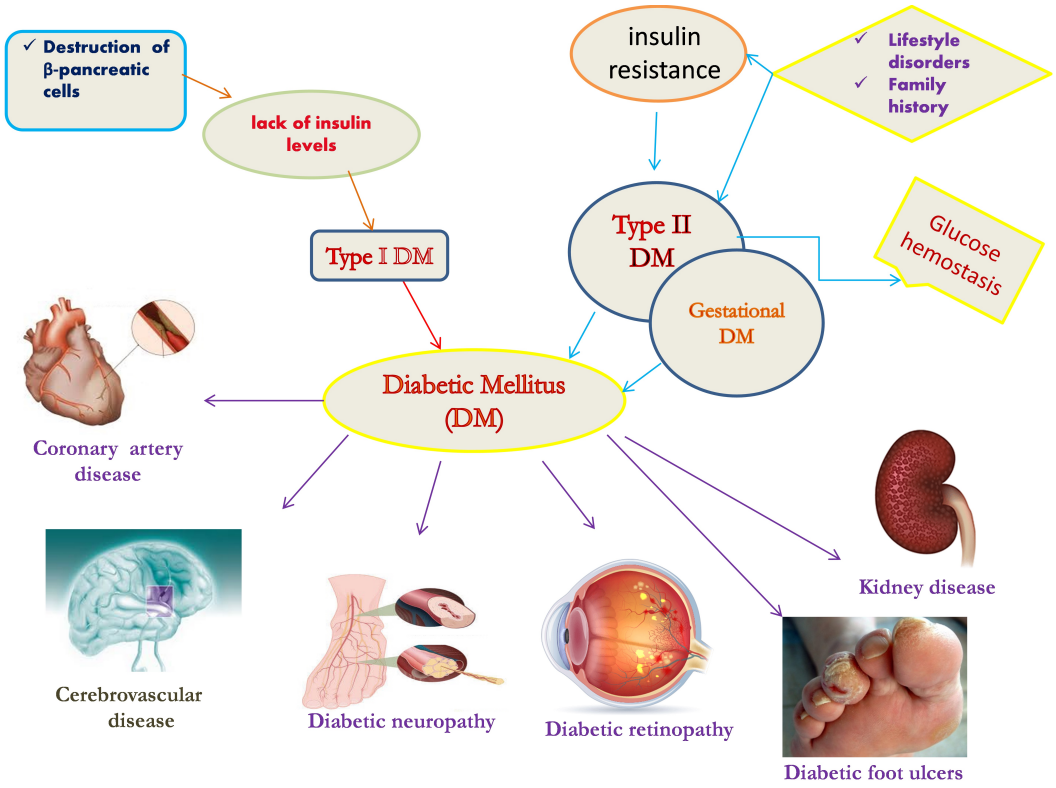

Fig. (1). Common classification of Diabetic Mellitus and their leading complication evaluated through its diagnosis.

DM-II/Type-2 DM

It is incited by insulin resistance, in which cells fail to utilize body glucose and thus leads to glucose hemostasis. It is also termed as a “lifestyle disorder” because the utmost pathogenesis occurs due to food habits (leads to obesity & hyperglycemia) and environmental factors. Currently, DM-II is steadily rising worldwide and the proportion of diabetic patients with type-2 DM is high [12, 13]. DM-II can also induce other health complications like cardiovascular disorders/heart attacks, kidney complications, neurological problems, retinopathy and dermatological diseases, *etc.* However, primary type-II diabetic complications can be preventable/supportable by a healthy diet, physical activities and regular medications.

The Third is Gestational Diabetes Mellitus (GDM)

"GDM is"due to insulin resistance and also considered as type-2 DM [14]. In the past, gestational diabetes was very rare during pregnancy, but now its ratio is

CHAPTER 3

Chemosensor in Glucose Monitoring, Advances and Challenges

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Abstract: Owing to the incidence of diabetes, glucose sensing in diabetes diagnosis and therapy is of great significance. In addition, in the drug and food sectors, glucose sensing is also important. Via different techniques, such as electrochemical or optical approaches, glucose sensing has been achieved. Sensors play an important role in the identification of chemical and biological samples and have attracted a great deal of interest in recent decades. Signals are produced by the binding of the analytical sensor. Varieties of chemical sensor, including cationic and anionic sensors, are used. In chemical sensing, molecular recognition and molecular transduction exist. There are three pieces of a chemo sensor, the binding site receptor, the device whose properties change with the binding and the spacer. The advanced glucose sensors development with high sensitivity and suitability has been facilitated by novel transducers made with nanomaterials that combine fluorescent methods. Glucose detection by a chemo sensor is discussed in this chapter. In addition, techniques for combining biological sensing and fluorescent nanomaterials components are explored, and the applicability of the chemosensor is also illustrated, making it suitable for glucose sensing. It is concluded that the extensive use of chemosensors in the health care sector makes them convenient instruments for real-time identification and long-term tracking of the environmental, biological and physical state of the human body.

Keyword: Diabetes Mellitus, Glucose Monitoring, Sensor.

INTRODUCTION

Diabetes mellitus is a condition in which glucose levels of blood surpass or drop to 65 mg/dL by more than 230 mg/dL [1]. Diabetes patients are unable to manufacture the hormone insulin to use it correctly. For the glucose

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regulation, insulin hormone is produced that interact with insulin receptor that permits glucose absorption in the cells for energy production.

The number of diabetics in the world is significant and rising. By 2045, the World Health Organization (WHO) estimates that there will be 693 million diabetics globally, compared to 451 million in 2017 [2]. Frequent testing, blood glucose, or real-time measurement and precision are important in strengthening diabetes regulation and treatment. The most accurate technique of glucose measurement to date is self-monitoring blood glucose by finger prick methodology. Though it is painful and risk of infection increases especially for those people who have to check many times in a single day. Commercially available devices are mainly electrochemical sensor enzymatic based, which include reactions catalyzed by enzymes. By the use of nano components, many non-enzymatic-based electrochemical sensors have been developed, which are more sensitive and show fast response [3 - 7]. Despite major advances in the electrochemical sensors, there is still a strong demand for totally non-invasive glucose tracking techniques, as they can be accurate, responsive, user-friendly and contribute to personalized care choices. New technologies are seeking to harness the glucose molecule's properties at various frequencies in the spectrum, from DC and ultrasound to near-infrared (NIR) and near-infrared (NIR) regions where they are visible. It is in these last two, though, that most of the promising innovations have appeared and have also been used in the production of some commercial products. Owing to the low precision, selectivity and sensitivity of the measure-ment [8], many are no longer usable, while those still available have not yet achieved accuracies equivalent to conventional methods. This scenario leaves several options still available for the dilemma of NI glucose monitoring, including the combination of many methods, which may potentially lead to the creation of a safe and cost-effective glucose monitoring system. Tura *et al*., give detailed summaries of invasive, minimally invasive and non-invasive methods for testing glucose [9 - 13]. Different glucose measuring methods based on bodily fluids like sweat, saliva and urine, were examined by different researchers [14 - 16]. The critical clinical and technological issues of minimally invasive and non-invasive glucose sensors were identified. Lin *et al*. stressed the adequate role of eight past and present non-invasive surveillance systems for in-home use [17, 18].

EMERGING GLUCOSE SENSORS

Recent electrochemical biosensors, a promising instrument for smart healthcare since biomarkers like saliva [19, 20], interstitial fluid [21, 22], and sweat [23, 24] are available in body fluids. Blood is the most important fluid to check glucose levels and warn diabetic patients about diabetes. Its normal range is around 4.9–6.9 mM [25], and may fluctuate even 40 mM or 2 mM [14, 26 - 28]. The

level of glucose in different biofluids is stimulating, in comparison to blood glucose identification. The goal of the researchers is to establish more technical resources to examine glucose concentration in other biofluids and explore the association between blood glucose and other biofluid glucose level [29, 30]. In alternate fluids, the concentration levels of glucose are between 0.006-2 mM in sweat, 2.78-5.56 mM in urine, 3.9-6.6 in interstitial fluid, and 0.03-1.39 mM in saliva [31 - 38]. It is important to use nanomaterials to allow the sensor to work under the changing situations of real biological systems. Engineered nanomaterial must be designed to customize desired electrocatalytic behavior while improving the sensor's stability. For the construction of non-enzymatic glucose sensors, materials based on tin oxide, copper oxide or titanium dioxide, patents have been published [39, 40]. Non-enzymatic sensors can be realized, due to increased surface area and beneficial electrocatalytic behavior of functional nanomaterials.

In addition, low detection cap, long shelf-life stability, and high sensitivity may be given by non-enzymatic biosensors. Another essential class has been non-enzymatic sensors; designing these non-enzymatic materials would be an alternative solution for the manufacturing of highly sensitive, stable and non-enzymatic biosensors [41 - 44]. Long-term storage and stretchability are linked to further difficulties in achieving an on-body biosensing system. Once fabricating wearable sensing systems with nanomaterials, these considerations need to be taken into consideration. The creation of nanoporous gold on a 3D micro-patterned elastomeric substrate was an example of developing a wearable and stretchable non-enzymatic glucose sensor to avoid a brittle fracturing of nano-porous gold [45]. Sensing patch comprised of biosensor electrodes on patterned polydimethylsiloxane (PDMS) substrate, the PDMS encapsulation sheet, the capillary cotton layer and the polyurethane nanofiber cover layer for connection to the scalp, as shown in Fig. (**1a**) . This concept made it possible to design a very lightweight, durable and stretchable microfluidics-integrated wearable sensor appropriate for constant sweat glucose observing. A primary conductive element, the Au-Ag alloy, was deposited by thermal evaporation on the electrode surface. For the formation of nonporous gold under high acidic condition Ag was dissolved, present as a porogen in the placed metal alloy.

While preserving robustness, an electrospinning-produced layer of polyurethane nanofibers improved the system to confirm conformability. During analytical trials, the unit demonstrated strong linearity for concentration spectrum estimation that covers glucose requirement at hyper and hypoglycemic patients with extreme sensitivity and appropriate uric acid or ascorbic acid selectivity. As there was no noticeable difference in sensitivity and analytical performance after unit stretching at 0-30 percent pressure, the sensor demonstrated high stretchability and reliability. The efficiency was constant 1000 times after stretching (at 30 percent

CHAPTER 4

Synergistic Drugs and Polyherbal Formulations for Obesity: Current Status and Future Prospectives

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Abstract: Obesity is a multifactorial disease that is characterised by excess body fat and enlarged adipose tissue. Obesity is closely associated with several non-communicable diseases, including type 2 diabetes, pulmonary arterial hypertension, dyslipidemia, non-alcoholic fatty liver diseases, hypoventilation syndrome, different types of cancers, inflammation, and cardiovascular diseases. The best preventive strategies for obesity are physical exercise, diet, and weight loss. Since this is not possible for all people, pharmacotherapy is required. The current therapy for obesity includes synthetic drugs and surgical procedures, which has high cost and many adverse effects. Hence the development of novel and natural drugs is necessary for the management of obesity. Numerous *in vivo* and *in vitro* investigations have proved that herbal medicine can ameliorate obesity, and those research findings include not only the individual plants but also different phytochemicals, extracts and polyhedral formulations. The inhibitory effects of different phytochemicals on the lipase enzyme activity, adipocyte differentiation, and promoting effects on energy expenditures and lipid metabolism are the different mechanisms that account for the management of obesity. So based on the previous research findings, researchers conclude that a synergistic drug which is formulated by combining potential medicinal herbs with a typical anti-obesity drug along with lifestyle modifications could ameliorate obesity and associated complications. This chapter summarises the current status and prospects of synergistic drugs and polyherbal formulations in the development of a safe and functional drug for the management of obesity.

Keywords: Lifestyle Modifications, Multifactorial Disease, Management of Obesity, Phytochemicals, Polyherbal Formulations, Synergistic Drug.

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INTRODUCTION

Obesity is a multifactorial disease that has emerged as a major global health issue [1 - 3]. The modern lifestyle, such as increased consumption of high-calorie food and lack of physical exercise, are the major causes of the high prevalence of obesity [1, 4, 5]. Obesity is caused by the increased agglomeration of fat in the adipose tissue, which causes expansion of adipose tissue and imbalances in energy homeostasis [2, 6]. Overweight and obesity contribute to the disruption of lipid profile of individuals, which causes serious diseases such as dyslipidemia and different types of non-alcoholic fatty liver diseases [5]. Hyperlipidemia is characterised by high levels of different lipids in the blood such as triglycerides, low-density lipoprotein-cholesterol and/or low level of high-density lipoprotein-cholesterol [7]. This excessive lipid accumulation in the liver causes lipotoxicity and organ failure [4, 8]. Hence, the management of lipid profiles is considered as a therapeutic strategy for obesity-related diseases [5, 6].

Obesity also causes kidney diseases and impaired glucose tolerance and insulin resistance, which leads to the complicated disease, type 2 diabetes mellitus [2, 6, 9]. All these diseases are major threats to the occurrence of cardiovascular diseases [2, 3, 10]. Obesity also causes different types of cancers [3, 9]. The combination of diet with physical exercise accelerates weight loss and is an easier way of weight management rather than the consumption of low calorie diet [6, 11]. Even though obesity is a multifactorial disease, the basic cause for the development of obesity is a chronic disparity between energy uptake and energy spending [10, 12 - 14]. Even if proper diet and physical exercise are the best strategies to prevent obesity, these have failed to prevent or cure obesity in most cases, hence effective pharmacotherapeutics are required/mandated [1].

Although synthetic medicines have been considered as the standard pharmacotherapy for obesity, patients also suffer from its toxic side effects and part of patients are intolerant to this [1, 9, 12]. Most anti-obesity medications that were commercialised have now been withdrawn due to consequential toxic effects [6, 9, 15, 16]. As yet, there has not been an adequate weight reduction medicine, and supplementary weight reduction remedies to have the consequences of adverse side effects. Thus, safe and efficient therapeutics are necessary to counteract the global burden of obesity and associated complications [15, 17]. Devoid of pharmacotherapeutics, the major alternative is bariatric surgery [17, 18]. Surgery is confined to patients with intense obesity or obesity with complications; it has adverse side effects and is not an alternative for most of the patients as its health risks and costs may outweigh its benefits [18].

Many bioactive compounds were documented to possess anti-obesity effects [19]. Bioactive compounds frequently come about in mixtures [10]. Mixtures of the bio-actives may synergistically enhance their biological activities than higher doses of a single compound [10, 19, 20]. A synergistic drug, alternatively, as a basis to change the ingredients and proportion by adding or substituting other herbs is a rational option for the management of obesity and associated complications [7]. The synergistic interaction of bioactive compounds with typical anti-obesity drugs may induce additive/synergistic weight loss effects, higher than the monotherapy induced effects, and/or improve harmful side effects of the anti-obesity drugs [21]. Therefore, the intake of a combination of bio-actives may be a more efficient and safe remedy to eradicate two or more diseases simultaneously [6, 9, 19].

Since metabolic syndrome is a multifactorial disease, a lot of complete studies recommended that it is perfect for treating obesity by mixing different bio-actives that tackle different anti-obesity processes [19]. The population of obese patients is heterogeneous, ranging from relatively healthy to serious diseased conditions and the heterogeneity of this population increases safety concerns, over new drugs since obesity is a chronic disease and an obesity drug could signify persistent therapy [3]. Thus, the recognition of the physiological basis of obesity, including the development of obesity-induced complicated diseases and the risks for weight recovery following weight release is a significant factor for consideration for advancing successful pharmacological therapies [15]. Thus, this chapter is focused on the different synergistic drugs and polyherbal formulations for obesity that have been investigated in *in vitro* models, animal models and humans, in order to aid researchers to comprehend their fundamental processes.

ANTI-OBESITY ACTIVITY OF SYNERGISTIC DRUGS AND POLYHERBAL FORMULATIONS

In Vitro Anti-Obesity Activity

The administration of bavachinin with PPAR-γ and PPAR-α agonists synergistically reduces glucose and fat concentrations without causing liver damage and reduces body weight in 3T3-L1 adipocytes and hence can be considered a safe and efficient therapy for metabolic syndrome [26]. The combined metformin and insulin treatment synergistically induces anti-obesity effects by hindering adipogenesis in preadipocytes, reducing lipogenic gene expression and enhancing AMPK activity and glucose intake [25]. The combination of cAMP-dependent PKA and AMPK increases kinsenoside triggered lipolysis through the AMPK-dependent pathway in $C_3H_{10}T_{1/2}$ adipocytes

CHAPTER 5

Urge for Herbal Anti-Diabetic Medicines Towards Clinical and Therapeutic Implications

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Abstract: Diabetes is a deep-seated and persistent ailment that has a comprehensive and long term effect on carbohydrate, fat, and protein metabolism. This malady is usually associated with hyperglycemia over an extended time which may be due to either flaw in the production of pancreatic insulin or implausible insulin target tissue.

Current pharmacological treatment strategies aim to promote pancreatic insulin release, reduce glucose output from the liver, or increase insulin sensitivity of adipocytes. But none of these current strategies have an appreciable curative effect on diabetes. Continuous exercise and workouts accompanied by lifestyle modifications have been found to improve glycemic control in diabetic patients which have not been well adapted with all patients. This emphasizes the role and urges herbal anti-diabetic drugs as they have a remarkably wide array of primary and secondary metabolites that have noted anti-diabetic actions accompanied by anti-oxidant action. But an herbal anti-diabetic drug has got some limitations like a difference in constituents due to different geographical locations, scientific misidentification, product contamination, inappropriate time and method of harvesting, adulteration, *etc*. So, drug standardization is an indispensable tool to ensure the safety and efficacy of herbal anti-diabetic drugs. Regulatory agencies worldwide have set up stringent regulatory frameworks that have led to the development of herbal anti-diabetic drugs positively. When two or more drugs (either herbal or synthetic) are administered together, there may be either chemical or pharmacological interaction that may alter the effect of either both or sometimes one agent which cannot be easily predicted and understandable. These interactions may affect clinical safety and efficacy *via* additive/synergistic or antagonistic interactions. While antagonistic interactions tend to receive more attention due to safety concerns, additive/synergistic interactions increase the desired pharmacological response which is a boon to us in treatment, for which special attention has to be paid. In this chapter, a detailed and in-depth analysis of herbal anti-diabetic drugs and various commonly used anti-diabetic plants are discussed. Also,

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problems associated with herbal anti-diabetic drugs and methods to overcome along with special emphasis on their clinical and therapeutic implications including reported herb-drug interactions, are examined.

Keywords: *Abelmoschus esculentus*, *Anemarrhena asphodeloides*, Anti-diabetic, *Bauhinia megalandra*, *Cryptolepis sanguinolenta*, *Capparis decidua*, Herbs, Herb-drug interactions, *Hintonia latiflora*, Natural, *Pandanus odorus*, Quercetin-3-O-β- glucopyranosyl-(1″′→6″)-glucoside, *Xanthium strumarium*.

INTRODUCTION

Herbal Anti-diabetic Medicines

Herbal medicine or phytotherapy is a fundamental and dominant form of therapy followed and supported by all civilizations throughout the world for centuries; this includes Aryans, Egyptians, Greeks, Chinese, and Arabs for whom ethnopharmacology has and will play a pivotal role [1]. According to the World health organization, about 80-82% of the world population still relies on herbal remedies for health care in one form or another [2]. Unlike synthetic anti-diabetic drugs which usually are composed of a single pure compound, herbal anti-diabetic medications contain diversified phytochemicals of one or more plants, which may help in controlling diabetes in multiple pathways [3]. Our ancestors were using herbal medicines for diabetes from time immemorial and had attained remarkable effects on treatment. But they were not able to understand the underlying mechanism or pharmacology of these plant-based drugs. With the advent of modern technologies, following the footprint of our ancestors, scientists were able to isolate the compound, elucidate its structure and explore the pharmacological relevance of these moieties in detail, which again strengthens the vast base of the plant based anti-diabetic drugs [4]. An in-depth understanding of the complex chemical nature of phytoconstituents led to herbal drug development with an accurate and precise treatment schedule for diabetes using plants. About 800-850 medicinal plants are believed to aid in the treatment of diabetes either directly or indirectly. Several factors, including environment and adulteration, affect the chemical nature and concentration of secondary metabolites, hence the dose of anti-diabetic plants may vary based on geographical locations [5]. Nowadays, more research work and money are directed towards the isolation of pure chemical compounds responsible for anti-diabetic activity from plants. The regeneration of herbal anti-hyperglycemic drugs has increased in the last 10-20 years which may be aroused by the belief that they flourished for centuries, because of their decisive strengths and since they focus not only on controlling diabetes but also other associated complications. Acceptance of the value of

science is universal. The choice of treatment of a patient is subjective and personal; at the same time, they are influenced by cultural and economic factors. Shreds of evidence suggest that diabetic patients of the modern era tend to accept both allopathic and translational medicine for diabetes [6]. A few advocates of modern medicine might claim that herbal medicines are more superior in the treatment of diabetes. But it is the result of scientific research that ascertains that medicinal plants have an important role in the management and treatment of diabetes. The use of certain plants for diabetes has been well documented in ancient works of literature, which can be considered sufficiently reliable [7]. But their practical application in diabetes must be established, for which a more practical approach should be followed. This can be done to a large extend by clinical trials of plant-based drugs on diabetic patients.

NEED FOR HERBAL ANTI-DIABETIC DRUGS

Diabetes is a multifaceted disease that cannot be controlled by a single pathway. So a multi-oriented and multitalented approach is needed for which herbal drugs can play an inevitable role. Moreover, synthetic agents have reported serious side effects due to which the importance of translational medicine containing anti-diabetic herbs had grown well in these years [8]. Synthetic drugs have shown problems associated with bioavailability, toxicity, and narrow therapeutic index besides reported cases of hypoglycemia and hypoinsulinemia. The plant-based drugs for diabetes have been used and sustained through centuries. In Ayurveda and Unani, most of the anti-diabetic preparations are concoctions of several plants and their various parts, which help in multiple targeting of diabetes through various molecular pathways. This usually shows a synergistic or additive action which ultimately leads to effective diabetes control which is far better than synthetic drugs [9]. These ayurvedic concoctions include a diverse range of phytocompounds that show anti-diabetic activity *via* diverse pathways. The currently used synthetic drugs are not fully proven safe to be used in children, which again potentiates the demand for herbal medicines [10]. Diabetes also causes various other interconnected and associated clusters of diseases like hyperlipidemia, nephrotoxicity, hepatic toxicity, and oxidative stress [11]. A single or group of synthetic drugs cannot effectively control or cure it which upsurges the need and emphasis on herbal anti-diabetic drugs [12]. Also, they are economical, easily available, and have fewer side effects. Moreover, a fact that cannot be neglected is that phytochemicals are seldom realized as xenobiotics by the body when compared to synthetic drugs which makes them acceptable without many adverse effects [13]. Some of the common problems associated with herbal anti-diabetic drug usage are:

CHAPTER 6

Curcuma Longa as Dietary Supplement and Diabetes Mellitus: Evidence from Experimental Studies

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Abstract: *Curcuma longa,* due to its broad scope of remedial possibilities, is still utilized as a diet-based remedy against diabetes mellitus and diabetic intricacies by legitimately connecting with various cellular pathways that incite diabetes mellitus pathogenesis. This chapter investigates the general valuable impacts of *Curcuma longa* on diabetes mellitus and its related complications based on experimental studies. Alongside clarifying the useful facts of *Curcuma longa*, it might be helpful to consider those cellular pathways which directly relate to diabetes. The possible mechanism of action of *Curcuma longa* as anti-hyperglycemic considered inhibition of lipid peroxidation, starch using compounds, transcriptional compounds, and activation of antioxidant enzyme capacity. Subsequently, *Curcuma longa* shows its antidiabetic restorative impacts by expanding insulin affectability, securing β-cells of pancreatic islets, diminishing fat accumulation, reducing oxidative stress, or enhancing glucose take-up by the tissues. Other than this, *Curcuma longa,* likewise, shows defensive impacts against a few diabetic-linked complications, prominently diabetic cataracts, and kidney function, along with the antioxidant agents. Taking everything into account, this work recommends that Curcuma longa help in treating diabetes and complications that occur due to diabetes; however, tolerant advising is also necessary as directing power to achieve diet-based treatment if there should be an occurrence of diabetes. In

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this chapter, we discuss basic and clinical proof of *Curcuma longa's* potential for diabetes mellitus treatment mainly due to its hypoglycemic, antioxidant, and anti-inflammatory qualities.

Keywords: Antioxidative, *Curcuma Longa*, Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus is a life-threatening disease and is turning into a worldwide issue. For the treatment of diabetes, the use of ordinary antidiabetic remedies has been reduced due to undesirable reactions [1]. Despite having numerous new therapeutic modalities [2], diabetes mellitus is yet considered among challengeable illnesses. The utilization of dietary supplements for the treatment of diabetes mellitus has consistently been empowered by ancient clinical experts [3], a training which has now attracted great attention of specialists who are in search of the biopharmaceutical properties of this food supplement. Normally, these food supplements are free from hazards due to the presence of phytoconstituents that have restorative impacts on the disease [4]. For nearly 66% of the total population, diabetes mellitus is generally treated by utilizing different medicinal plants [5 - 7]. Enormous data on plants are required to check their antidiabetic impacts. The greater part of this potential flora is also accessible as polyherbal formulations worldwide. At present, in many developing countries, various clinical experts have recommended this formulation for diabetes mellitus cure [8 - 10]. As of late, we have summed up the antidiabetic potential of *Piper nigrum*, ajwa date, and ajwa seed [11, 12].

The motivation behind writing the current article was, to sum up, the beneficial impacts of turmeric, *Curcuma longa,* on diabetes mellitus and diabetic inconveniences. Albeit a few surveys have been conducted that focus on the specific therapeutic aspects of *Curcuma longa* (including anti-inflammatory, against malignant growth, post-usable antiemetic impacts, and phytochemical and pharmacological properties) but none have widely summed up the positive impacts of *Curcuma longa* on diabetes mellitus and diabetic inconveniences [13 - 20]. Hence, we have portrayed the antidiabetic properties of *Curcuma longa* by reviewing different research studies to assess the valuable impacts of *Curcuma longa* on diabetes mellitus and its entanglements. Additionally, in this study, we have likewise represented a potential mechanistic act of *Curcuma longa* as a diabetes treatment. The important discoveries described here explain that *Curcuma longa* can treat diabetes and its difficulties by being straightforwardly involved in various cellular pathways to incite diabetes mellitus pathogenesis.

GENERAL PROPERTIES OF *CURCUMA LONGA*

As indicated by the botanical classification, *Curcuma longa,* generally known as turmeric, belongs to the family *Zingiberaceae* and is native to South-East Asia [21]. Curcumin is a bioactive chemical known as turmeric and is found in the rhizome of the Curcuma longa plant. The *in-vitro* and *in-vivo* research mentioned that Curcumin has natural characteristics, including antioxidant, anti-cardiac, anti-inflammatory, anti-microbial, nephroprotective, antineoplastic, immunomodulatory, hypoglycemic, and anti-rheumatic effects [22]. *Curcuma longa* is utilized as a flavor-enhancing agent worldwide. Its rhizome part is most commonly used for therapeutic and cooking purposes [23, 24]. *Curcuma longa* has been generally utilized in Ayurvedic prescriptions for different sicknesses as a natural treatment. These prescriptions are utilized as pain-relieving and mitigating against a tumor and headache and are emetic and thrombotic, hypolipidemic, and antioxidant for infectious illnesses and dementia [25 - 27]. *Curcuma longa* contains various phytochemical constituents that may change the contingent and state of the rhizome [28]. The nutritional value of turmeric is shown in Table **1**.

Table 1. The potential nutritional contents of turmeric.

Nutritional value of Curcuma longa (turmeric) (%)	
Nutrient	**Quantity**
Moisture Content	8.92±0.02
Dry Matter	91.00±0.01
Ash Content	2.85±0.02
Crude Fiber	4.60±0.01
Crude Protein	9.40±0.02
Fat	6.85±0.00
Carbohydrate	67.38±0.01
Alkaloid	0.76±0.01
Saponin	0.45±0.00
tannin	1.08±0.02
Sterol	0.03±0.01
Hydrogen cyanide	0.82±0.00
Flavonoids	0.40±0.01
Phenol	0.08±0.03
Riboflavin	0.59±0.02
Thiamine	0.16±0.00
Niacin	2.30±0.00
Calcium	0.21±0.01
Phosphorus	0.63±0.02
Potassium	0.46±0.03
Iron	0.045±0.02

Source: USDA Nutritional database

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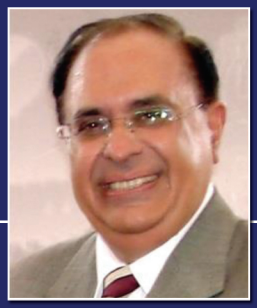

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Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.