



CHAPTER 2

Literature review

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DM, which primarily affects the working-age population and emerging nations, is quickly progressing to the worst stage and poses a serious threat to global public health. Morbidity and death are most commonly caused by chronic, non-communicable diseases. Elevated blood glucose episodes are linked to a large number of deaths before the age of 70. The predicted age-standardized frequency of diabetes jumped dramatically from 9.8% in 1999–2000 to 14.3% in 2017–2018, according to the National Health and Nutrition Examination Survey (NHANES) [147]. According to WHO data, countries with low or middle incomes are home to the majority of the world's approximately 422 million diabetes patients, and the disease is the only cause of 1.5 million deaths per year. 366 million individuals worldwide had diabetes in 2011, according to the International Diabetes Federation. By 2030, 439 million individuals are expected to develop diabetes [148]. Males and females are equally affected by the rising incidence of DM in regions that are both urban and rural [149]. Between 45 and 64 years of age, T2DM is rising [150]. Numerous factors, such as geographical location, stress levels in the environment, and lifestyle choices, might contribute to diabetes.

One metabolic syndrome is T2DM. This metabolic condition is among the most alarming aspects of the 21st-century lifestyle. DM that is not insulin-dependent is the term for it. Hyperglycemia, insulin resistance, and relative insulin insufficiency are the three most prevalent types of diabetes mellitus. T2DM is also impacted by the interaction of behavioral, environmental, and genetic risk factors [151]. Important tissues and cells are harmed by oxidative stress, which results in metabolic diseases. Reactive oxygen species (ROS) induce membrane lipid peroxidation and subsequent membrane damage when a person is hyperglycemic [152]. Plant-derived antioxidant chemicals and their association with T2DM

Literature Review

have been extensively studied. An *in silico* examination of the literature indicates that plant compounds are quite beneficial in lowering diabetes symptoms [153-154]. Because antioxidants slowed down the production of T2DM, people preferred consuming them in their diets [155]. Patients with T2DM may experience a range of consequences, including blood vessel problems, neuropathy, nephropathy, retinal dysfunction, and cardiac cardiomyopathy [156]. Many drugs are available to lessen these issues in diabetes mellitus, but they come with certain drawbacks. Plants with medicinal properties have been shown to alter the Krebs cycle, glycolysis, gluconeogenesis, synthesis of glycogen, and metabolism of carbohydrates [157]. DM may occur if this mechanism is dysregulated.

Because of this, scientists are now concentrating on low-cost, readily available medications made from plants that have fewer adverse effects. The information below represents an attempt to compile every substance with antidiabetic qualities. Researchers focusing on chemicals and plants for their studies might find it useful. The current study uses online data to compile a list of beneficial plants, fruits, and vegetables, as well as the phytochemicals that they contain that have anti-diabetic effects.

2.1 Medicinal plants and their antidiabetic activity

Plants are the primary source of medicinal substances used to treat illnesses and ailments, according to the chronology of human civilizations. Ayurveda literature by authors like BhavaprakashaNighantu, DhanvantariNighantu, Raja Nighantu, and KaiyadevNighantu also mentions reports of the use of plants as medicine. A comprehensive collection of data on numerous herbal formulations from various types of plants can be found in classic texts such as the CharakaSamhita, SushrutaSamhita, Ashtangahridaya, MadhavaNidana, BhaishajyaRatnavali, HaritaSamhita, KashyapaSamhita, SharngadharaSamhita, and Yogaratnakara.

Plant-derived anti-diabetic chemicals are a valuable resource for medication development.

Minimal negative consequences are associated with herbal medications applied to treat diabetes. Many plant combinations, as well as components taken from plants, have been shown to have ameliorative actions against oxidative damage and to lessen the difficulties associated with diabetes [158]. Currently, herbal therapy is the primary source of beneficial therapies for 80% of diabetic patients worldwide (World Health Organization, 2008). More than 150 plants are reportedly utilized to lessen the effects of diabetes [159].

Numerous studies have been conducted to examine the mitigating effects of herbal formulations on the hyperglycemic and hypoglycemia effects in streptozotocin (STZ) and alloxan-induced diabetic rats. The mechanism of action was investigated after extensive research on in-vivo trials utilizing a suitable animal model of T2DM [160]. It has been discovered that insulin hormones are largely eliminated in these models of experimentation. Through the alteration of DNA alkylation and GLUT1-4 (glucose transport 1-4), STZ partially destroys β cells and inter- β beta cells [161]. The therapeutic benefits of medicinals are found in their phytoconstituent profiles, which show potential antidiabetic activity. Medicinally important plant-based constituents consisted of polyphenols, anthocyanins, alkaloids, tannins, flavonoids, triterpenoids, steroids, and saponin classes, among others. Based on literature surveys, a number of compounds derived from these plants have been found to have antidiabetic effects.

PHE, which originates from the ayurvedic treatment employed in this study [162], comprises ethanolic extracts of six out of eleven conventional medicinal plants: the entire herb of *Andrographispaniculata* Nees. (Acanthaceae); the stem of *Berberisaristata* DC. (Berberidaceae); the leaves of *Nyctanthesarbostratis* L. (Oleaceae); and *Premnaintegrifolia* L. (Lamiaceae), fruit from *Terminaliachebula* Retz. (Combretaceae family), fruit from *Terminaliabellerica* Roxb. (Combretaceae family), roots of *Cyperusrotundus* L. (Cyperaceae family), fruit of *Emblicaofficinalis* Gaertn. (Euphorbiaceae family), rhizome of

Literature Review

Picrorhizakurroa Royle ex Benth. (Plantaginaceae family), stem branch of *Tinosporacordifolia* (Menispermaceae family), and root of *Citrulluscolocynthis* L. (Cucurbitaceae family). Many clinical trials have been carried out, and it has been established that the medicinal herbs used to prepare this PHE are effective in treating conditions like diabetes mellitus. Therefore, the discovery of safer and more effective diabetic treatments- especially those derived from medicinal plants- has always been, and still is, the main focus of global research on the disease. Since these combinations usually constitute PHE, synergy between many drugs, numerous routes, and multiple targets is typical of PHE. However, this intricacy also implies that the effectiveness of specific medications is questionable and that the mode of action is poorly known [163].

Network pharmacology is a technique that may be used to investigate the relationship between networking elements such as genes, chemicals, proteins, and target diseases. It offers systemic, collaborative, and meta-analysis modalities. One of the most significant resources for several targets for a single medication is the network pharmacology study for natural goods. Among the significant features of this study are a model switch from one target to several targets and a concept switch from one medicine to multiple drugs. Network pharmacology has created a new path for elucidating the intricate mechanics of drug-target relationships [164]. Review is a helpful method for clarifying the links between drugs with biological activity and their synergistic effects, as these linkages are frequently ambiguous [82].

2.1.1 Andrographispaniculata

The plant is known as *Andrographispaniculata* (Burm. f.) Wallen ex Nees. The name "King of the Bitters" or "Kalmegh" is often used to refer to this annual plant, which is a member of the Acanthaceae family. There are a number of countries in Southern and Southeastern Asia that are habitats for this species, particularly China, Bangladesh, Malaysia, Hong Kong,

Indonesia, Myanmar, the Philippines, and Thailand [165]. Its natural habitats include India and Sri Lanka. Additionally, the apical parts, roots, and foliage of *Andrographispaniculata* are typically utilized in various applications. All of these plant parts are utilized usually in powder, infusion, or decoction form in two ways: alone or in a mixture using another medicinal plant for the therapy of loss of appetite, diabetes, jaundice, leprosy, liver complaints, peptic ulcer, gonorrhoea, respiratory tract infections, scabies, boils, skin eruptions, chronic and seasonal fevers, griping, irregular bowel habits, alopecia, general debility, dyspepsia, hemopathy, cough, oedema, dysentery, malaria, enteritis, helminthiasis, herpes, skin infections (topical use), and snake-bites (topical use) [165]. It possesses several terpenoids like furanoidditerpene, ecdysterone, makisterone, tinosporide (Furanolactone diterpene), furanolactone clerodane diterpene, tinosporaside, and several glucosides isolated as poly acetate, phenylpropene disaccharides cordifolioside A, B, and C, cordifolioside D and E, tinocordioside, cordioside, palmatosides C and F, and sesquiterpene glucoside tinocordifolioside, sesquiterpene tinocordifolin) [166–176], alkaloids (Tinosporine, Magnoflorine, Choline, Jatrorrhizine, Berberine, 1,2-Substituted Pyrolidine), steroids (Giloinsterol, β -Sitosterol, 20 α -Hydroxyecdysone) [177], and others.

2.1.2 *Premnaintegrifolia*

This plant, a member of the Lamiaceae family, is a tropical and subtropical plant found in Australia, Asia, and Africa that is used medicinally [178]. It is regularly employed as an antibacterial, antioxidant, antipyretic, hypoglycemic, cardiogenic, and diuretic medication in traditional medical practice [179]. Its roots as well as leaves have been combined to be used as a fever remedy in Indonesia. Women often use the leaves of a plant to care for their babies [180]. Its leaves possess a variety of plant-derived compounds, including tannins, saponins, flavonoids, and phenolics [181–182], which may be the cause of its antioxidant action. *Premnaintegrifolia* ethanolic extract exhibits strong analgesic, antidiabetic, antiulcer,

Literature Review

antibacterial, and antioxidant properties [183]. Extracts from *Premnaintegrifolia* leaves have hepatoprotective properties against carbon tetrachloride [184].

2.1.3 *Berberis*

Berberis has approximately 550 species, and it belongs to the family Berberidaceae. It is found all over the world. One of the popular traditional recipes for treating diabetes is a decoction made from the roots of *Berberis* plants [107, 185]. Numerous studies have documented the conventional uses of *Berberis* plants for the prevention and management of metabolic illnesses (e.g., diabetes and hyperlipidemia) in multiple nations, especially China, India, Pakistan, and Iran. *Berberis* species have been discovered to contain a variety of bioactive chemicals, including flavonoids, polyphenols, alkaloids, and anthocyanins, in addition to different vitamins and mineral components [186–187].

2.1.4 *Nyctanthes arbor-tristis*

The Oleaceae family plant *Nyctanthes arbor-tristis* L. (Parijat) is widely known in India and around the world for its significant effects on general well-being and health. It is one of the most adaptable and legendary medicinal plants, having a wide range of biological activity and excellent therapeutic efficacy in Ayurveda. For a very long time, the primary source of discovery for novel drugs has been plant-based natural compounds. Every component of *Nyctanthesarbortristis* is used to make folk remedies and has a variety of ethnopharmacological uses [188]. The plant's flower and leaf parts have been shown to have antioxidant [189] as well as anti-plasmodial [190] capabilities in scientific literature. Freshly ground seed powder paste mixed with aromatic compounds is applied topically to treat a variety of skin conditions, including dermatitis, alopecia, scurfy scalp affections, and skin eruptions. It is also used as an emollient. It has been stated that the seeds contain glycerides of myristic, stearic, lignoceric, oleic, palmitic, and stearic acids [191]. Notable anti-helminthic qualities can be found in the ethanolic extract of *Nyctanthesarbortristis* seeds [192]. Anti-

leishmanial qualities are present in the n-butanol fraction of the *Nyctanthesarbortristis* seed extract [193]. From the ethanolic extract of the seeds, the iridoid glycoside (arbortristoside-A) was identified and shown to have anti-inflammatory and anti-nociceptive properties [192].

2.1.5 *Terminaliabellerica*

Widely prevalent in tropical places, *Terminaliabellerica* (TB) Roxb (Combretaceae) is a huge deciduous tree usually known as belericmycobalane [194–195]. Ayurvedic and conventional medical systems have long valued it for treating a variety of ailments with a multitude of pharmacological characteristics, including anemia, asthma, constipation, chronic ulcers, fever, and jaundice. Beta-sitosterol, belleric acid, ellagic acid, galloyl glucose, mannitol, glucose, gallic acid, ethyl gallate, chebulagic acid, galactose, fructose, rhamnose, arjungenin, bellericoside, cannogenol, three lignans, and one flavan have all been reported to be present in the phytochemical analyses of *Terminaliabellirica* fruits [196]. There have been reported hepatoprotective and anti-hypercholesterolemia effects from *Terminaliabellirica* fruit extract [195]. The fruit of *Terminaliabellirica* has significant antioxidant and α -amylase inhibitory action when extracted in ethanol and water. Extracts have been found in diabetic rats to lower blood glucose while also improving body weight, lipid profile, and kidney function [104].

2.1.6 *Terminaliachebula*

The kernels of *Terminaliachebula* fruits are edible, and they have also been used medicinally in many Asian countries since ancient times. The pericarp of the mature fruits, called *Chebulaefructus*, is used as a crude drug in many traditional medicine systems [101]. Fruits are used in Ayurveda and Siddha traditional medicines to treat chronic diarrhea, gastroenteritis, constipation, malabsorption syndrome, asthma, ulcers, dyspnea, dyspepsia, hemorrhoids, cough, candidiasis, antiparasitic, hepatomegaly, urinary discharge, antitumor, skin disease, memory loss, epilepsy, cardiovascular disease, diabetes, anorexia, homeostatic, and also as diuretic, antitussive, and wound healer [101].

2.1.7 *Cyperusrotundus*

Known by its popular name, mustaka, *Cyperusrotundus* Linn. (Family Cyperaceae) is a perennial weed that emerges from an underground tuber system and has dark green, glabrous culms. In streptozotocin (STZ)-induced diabetic Swiss mice, the ethanolic extract of *Cyperusrotundus* (EECR) rhizomes was tested for antidiabetic activity. The results showed that EECR can significantly reduce hyperglycemia in STZ-induced diabetic mice. Additionally, the extracts improved lipid profile, SGOT, SGPT, and body weight. These biochemical markers may be helpful in the treatment of diabetes [197].

2.1.8 *Emblicaofficinalis*

Emblicaofficinalis (EO) contains ellagic acid, which promotes insulin secretion and reduces glucose intolerance by acting on the pancreatic β -cells. This action has anti-diabetic properties. Rich in polyphenolic components and vitamin C, EO is consumed as a fruit in many regions of the world and could be a good option for a DA in the treatment of type 2 diabetes. Through its action on the pancreatic β -cells, EO has anti-diabetic effects via boosting antioxidant status, promoting β -cell shape and morphometry, decreasing blood glucose, and increasing serum insulin. It is a good option for diabetic drug development due to its low cost, accessibility, affordability, and safety profile, which make it a comparatively low-risk substitute for conventional glucose-lowering medications [198].

2.1.9 *Picrorhizakurroa*

The Indian Himalayan herb *Picrorhizakurroa's* roots and rhizomes have long been used to treat fever, hepatitis, allergies, respiratory tract infections, and other inflammatory ailments. A hydroalcoholic extract of the rhizome of *Picrorhizakurroa* that had undergone metabolic characterization showed great potential for β -cell regeneration, as well as improved hepatic and renal functioning, insulin expression, and antihyperglycemic actions. Moreover, PKRE has a higher potential for insulin-stimulated glucose absorption [199].

2.1.10 *Tinosporacordifolia*

Tinosporacordifolia (TC) stems are frequently used in Indian traditional folk medicine to treat diabetes. *Tinosporacordifolia* has succulent stems that have thick, long, filiform aerial roots growing from the branches. It is commonly used as a general tonic, hepatoprotective, antiperiodic, anti-spasmodic, anti-inflammatory, anti-arthritis, anti-allergic, and antidiabetic in folk and ayurvedic medicine systems. The antidiabetic benefits of AFTC may be attributed to a number of processes, including gluconeogenesis inhibition, insulin release, and insulin sensitization. Therefore, it makes sense to assess the efficacious components of AFTC and three of its alkaloids—magnoflorine, jatrorrhizine, and palmatine—in more detail [200].

2.1.11 *Citrulluscolocynthis*

This study uses histopathological analysis in streptozotocin-induced diabetic rats along with invitro α -amylase enzyme inhibition to examine the hypoglycemic and insulinomimetic effects of aqueous and ethanolic extracts of *Citrulluscolocynthis*. When the extract was taken orally, it significantly reduced blood glucose and inhibited the α -amylase enzyme in vitro. Because of the extract's insulinomimetic effect, it was also discovered that the groups that received treatment had higher amounts of insulin and glycogen. *Citrulluscolocynthis* has a very powerful anti-hyperglycemic potential, according to the data, which supports using the medication to treat diabetes mellitus [201].

In Indian ayurvedic medicine, triphala is used as an antioxidant, immunomodulator, rejuvenator, antiaging, analgesic, antimutagenic, anticancer, antibacterial, and blood purifier. According to Naik et al. (2004), it is made up of the fruits of three trees: *Terminaliabellerica*, *Emblicoefficialis*, and *Terminaliachebula*. Rasayana-based medications have long been used to treat a wide range of ailments for which modern medicine has found no pathophysiological explanation [202]. The medicinal qualities of triphalarasayana include antibacterial, diabetic, cancer prevention, immune-modulating, and anticataracting effects. In

Literature Review

the diagnosis and management of gastrointestinal illnesses, especially functional gastrointestinal disorders (FGIDs), it serves as a cornerstone as well. Rasayan's affordability, accessibility, and ease of administration have contributed to its rising popularity worldwide [203].

Particularly, naturally occurring phenols are known to possess outstanding qualities as food preservers [204]. They have also been shown to be important in the prevention of numerous pathological disorders, including cancer, brain dysfunction, and atherosclerosis [205]. It is helpful in medicine because of qualities like laxative, antibacterial, cardiogenic, diuretic, hyperlipidemic, and anticancer [206–207]. The fruits may be used as a natural contraceptive because of their anti-fertility qualities [208]. In the manufacturing industry, phenols are also used for a wide range of purposes, such as natural food preservatives and colorants. It is now essential to provide food security by consuming high-quality foods that provide essential nutritional and bioactive components [209–210].

Numerous plants have been shown to be helpful in the treatment of different systemic illnesses in traditional medical systems. One of the major issues facing the traditional medical system is its lack of comprehensive uniformity, which makes many of the traditional or indigenous medical systems less effective than the modern medical system. The literature from antiquity provides ample documentation of the idea of polyherbal formulation. The polyherbal formulation has a greater and longer therapeutic potential than a single herb. Therefore, the goal of the current investigation was to create and standardize a polyherbal formulation utilizing a plant that is known to have antidiabetic properties and then assess the formulation's therapeutic benefits in rodents [211].

A total of over 800 plants were said to have antidiabetic qualities in ancient texts [212]. More than 1200 plants are utilized in traditional medicine for their hypoglycemic properties, according to ethanopharmacological surveys [213]. Many dravyas (items with biological

activities and properties) that have been claimed to be useful in treating madhumeha (diabetes) have been listed in ancient Indian medicine [214]. Major pharmaceutical corporations are already conducting substantial research on plant materials for their potential therapeutic benefits as the demand for herbal remedies grows tremendously worldwide. A growing number of research manuscripts based on herbal medications can be found in numerous national and international journals.

There have been numerous analysis-based studies done in the past on pharmaceutical research in India [215–217]. To obtain the benefits of synergism and appropriate antidiabetic action, plant formulations and combination extracts of plants are typically used as the drug of choice in the conventional system of plant medicine, as opposed to individual ones [218]. Polyherbalism is a unique idea in Ayurveda medicine. The SarandgharSamhita emphasizes the idea of polyherbal compositions' synergism. It is clear that there are numerous herbal preparations with differing levels of potency. Because these preparations function through various pathways, it is conceivable that combining these extracts will result in a more effective therapeutic outcome [219].

By using an in-vitro model, the polyherbal extract formulation's total phenolic and total flavonoid contents demonstrated inhibitory actions against α -amylase and α -glucosidase, as well as glucose adsorption, diffusion, and absorption at the cellular level. Therefore, in order to validate claims for an antidiabeticpolyherbal formulation, our investigation primarily highlights different pathways for the hypoglycemic activity by which this formulation can control blood glucose levels [220].In the liver, SCFAs have been shown to decrease glycolysis and gluconeogenesis and increase glycogen synthesis and fatty acid oxidation. Additionally, SCFAs have been shown to improve glucose uptake in skeletal muscle and adipose tissue by elevating the expression of GLUT4 through AMP kinase (AMPK) activity. Moreover, in the skeletal muscle, SCFAs reduce glycolysis with a consequent accumulation

Literature Review

of glucose-6-phosphate and an increase in glycogen synthesis [221]. It makes sense to think that these results will help us understand how these bioactive compounds work together to prevent DM. They will likely provide strong evidence for at least some of the metabolic diseases that this PHE could potentially prevent. In this study, we used high-throughput 16S rRNA gene sequencing to look at how PHE affected the gut microbiota of DM rats and find key genera that were closely linked to PHE treatment. This helped us figure out if the gut microbiota was an appropriate target for PHE during the improvement of DM symptoms. Additionally, we correlated diabetic parameters with gut microbiota enrichment linked to increased SCFA content in order to ameliorate DM.

Many compositions and bioactive plant-based constituents have been demonstrated to be beneficial in improving insulin secretion, sensitivity to insulin, glucose absorption, enzymatic function regulation, molecule-level overexpression, and oxidative stress management. Some of these plants have been the subject of scientific study, while others are used in traditional ways. This extensive study includes details on experimental models to look into the potential antidiabetic effects of the plants and their phytochemicals. Additionally, anti-diabetic bioactive plant-based constituents and their structures were emphasized in the analysis. In order to successfully cure diabetes, this study offers comprehensive details regarding a variety of significant plants and their plant-based constituents. These can be further investigated using scientific methods.
