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Review

Antidiabetic Plants for the Treatment of Type 2 Diabetes Mellitus and Associated Bacterial Infections

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Abstract: Type 2 diabetes mellitus (T2DM) is the metabolic disease with the highest morbidity rates worldwide. The condition is characterized by hyperglycemia, insulin resistance, hyperlipidemia, and chronic inflammation, among other detrimental conditions. These decrease the efficiency of the immune system, leading to an increase in the susceptibility to bacterial infections. Maintaining an optimal blood glucose level is crucial in relation to the treatment of T2DM, because if the level of this carbohydrate is lowered, the risk of infections can be reduced. Currently, this is achieved using synthetic drug treatments that seek to moderately inhibit digestive enzymes (e.g., α-amylase and α-glucosidase), such as acarbose, voglibose, miglitol, etc. However, the use of these compounds also generates unwanted side effects such as nausea, diarrhea, stomach aches and a loss of appetite. Therefore, there is an increasing demand to find effective and safe alternatives for treating T2DM, such as herbal treatments. As a result, there has been a search for possible drugs from plants with both antidiabetic and antibacterial activity. This study presents a review of the molecular and cellular mechanisms of T2DM, secondary effects of the disease such as bacterial infections, and general comprehension of synthetic and natural product treatments to help patients.

Keywords: type 2 diabetes mellitus; bacterial infection; hyperglycemia; antidiabetic plants; antibacterial plants

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most widespread and important metabolic diseases nowadays in Mexico (Figure 1A, [1]) and worldwide [2]. Despite being non-contagious, it can be considered a pandemic, inflicting enormous physiological and psychological strain on patients and extreme costs on public and private healthcare systems, particularly for the treatment of complications and provision of preventive pharmaceuticals (Figure 1B, [3]). Estimates suggest that more than 600 million patients will be diagnosed with T2DM by the year 2035, painting a grim picture of the future [4] (Figure 1C, [5]). Therefore, there is an urgent need for substantial and sustainable improvements in all aspects of T2DM management, from diagnosis to treatment and, hopefully, to prevention. Importantly, T2DM is one of the five diseases with the highest morbidity rates worldwide [6]. In Mexico, for example, T2DM cases and mortality are rising particularly fast, which is at least partially based on the increasingly urban lifestyle of the population [7]

(Figure 1D, [4]). This change of lifestyle correlates with a pronounced increase in carbohydrate consumption, which is estimated to comprise 61% of the average diet [8]. T2DM is the most common cause of death in women and the second most common cause of death in men in Mexico [7,9]. The denominator of T2DM-related pathologies is a persistent state of hyperglycemia, which upsets and dysregulates nutrient metabolism, mostly via impaired insulin signaling processes [10]. Therefore, maintaining physiologically normal glucose levels in the blood of patients is one of the chief priorities in the treatment of T2DM. It is important to highlight that although diabetes is an irreversible condition, a lack of control of this condition leads to a decrease in the patient's lifespan and quality of life, in addition to the development of diseases such as peripheral arterial disease, stroke, ischemic heart disease, heart failure, and chronic kidney disease, increasing the risk of death [11–13].

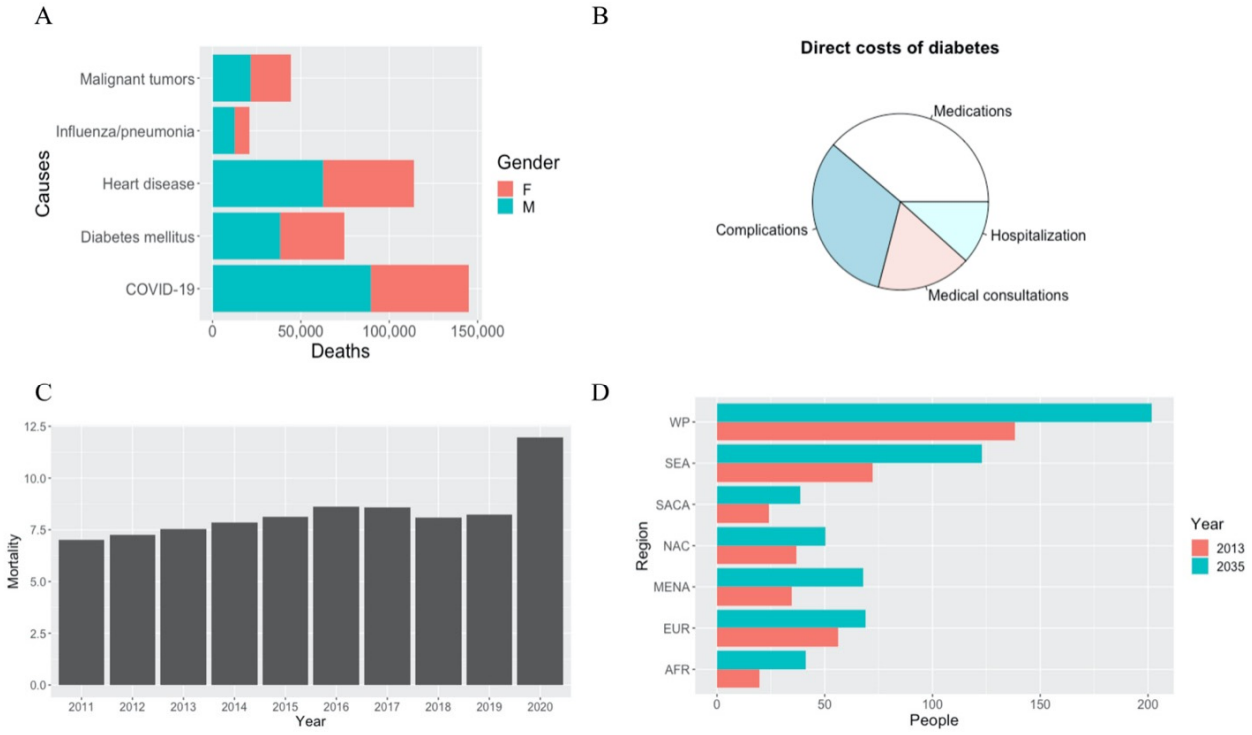

Figure 1. Overview of data related to T2DM. (**A**) Number of deaths due to the five primary causes in the January–June 2021 period in Mexico, according to INEGI (Instituto Nacional de Estadística y Geografía). Orange portions of bars indicate female deaths and green indicate male deaths. (**B**) Pie chart representing the main direct costs of diabetes, where medications are the biggest portion, according to Bello-Chavolla et al., 2017. (**C**) Evolution of the mortality rate of DM from 2011–2020 per 10,000 inhabitants, according to INEGI (**D**) Projections of diabetes cases by 2035 compared to cases in 2013, according to Guariguata et al., 2014. WP: Western Pacific; EUR: Europe; AFR: Africa; MENA: Middle East and North Africa; NAC: North America and Caribbean; SACA: South and Central America; SEA: South-East Asia.

Nowadays, many patients with T2DM have access to synthetic drugs that can control carbohydrate homeostasis. One of the strategies for achieving this goal is a moderate downregulation of digestive enzymes (e.g., α-amylase and α-glucosidase). In addition to prescribing synthetic drugs, this can be achieved using acknowledged traditional medicine approaches with the help of natural extracts. Extracts from plants have been useful for treating T2DM [14–17]. The latter strategy represents an interesting alternative, with increased accessibility in certain regions and reduced side effects for the patient who is under treatment. Treatments often include ways to combat bacterial infections that can occur as a secondary pathology in diabetic patients (see Section 3). An important example is diabetic foot infections, which can originate due to hyperglycemic damage to blood

vessels and nerves in the foot [18]. Often, standard antibiotic therapies are the method of choice for the treatment of these infections [19].

In this review, we first provide a summary of synthetic drugs and their uses, before moving on to the treatment of bacterial infections in T2DM patients and continuing with an overview on T2DM-relevant compounds isolated from medical plants. Finally, we propose some new directions for effectively utilizing medical plant extracts as an interesting alternative for the treatment of T2DM.

2. Brief Overview of Strategies to Combat T2DM

In this section, we give a short overview of established and commonly prescribed pharmaceuticals for the treatment of T2DM (Figure 2 and Table 1). For a detailed description of compounds for the treatment of T2DM and their modes of action, the reader is referred to several excellent reviews on this topic [20–22].

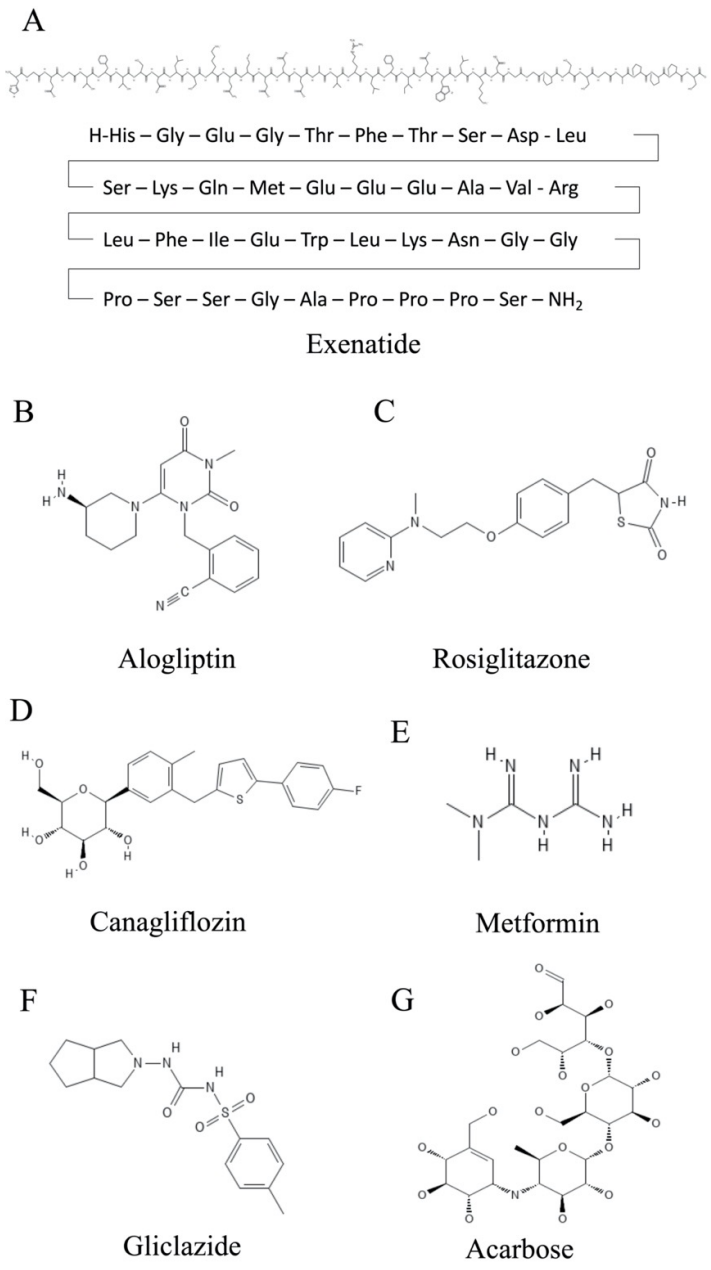

Figure 2. Chemical structures of compounds used for the treatment of T2DM. (**A**) Exenatide. (**B**) Alogliptin. (**C**) Rosiglitazone. (**D**) Canagliflozin. (**E**) Metformin. (**F**) Gliclazide. (**G**) Acarbose.

One strategy to treat T2DM is to enhance both the production and release of insulin from pancreatic β cells by modulating signaling via the GLP1 (glucagon-like-peptide 1) system [23,24]. GLP1 is a peptide hormone that is formed in the intestine. GLP1 interacts with its receptor, GLPR1 (glucagon-like-peptide receptor 1), which is located on the β cells of the pancreas and on the neurons of the brain. In addition, by increasing insulin levels, the amount of the insulin antagonist glucagon circulating in the blood is decreased. A further effect mediated by GLP1 signaling is reduced food intake [25]. Consequently, agonists of GLP1R are attractive compounds for treating T2DM-associated complications. Among these are drugs such as dulaglutide, exenatide (Figure 2A and Table 1) and liraglutide. Dulaglutide is a recombinant DNA-produced analog of GLP1 (7-37) that is covalently connected to each Fc arm of human IgG [26]. Exenatide has a natural origin, as it was first identified in the saliva of the North American Gila monster (*Heloderma suspectum*), a venomous lizard, although it is now manufactured biotechnologically [27]. A new strategy is the use of dual GIP (glucose-dependent insulinotropic polypeptide)/GLP-1 receptor agonists such as tirzepatide, which has recently been approved by the European Medicines Agency [28]. This approach seems to be promising, as the treatments demonstrate improved efficacy, i.e., better reduction of glycated hemoglobin (HbA1c) and body weight than the exclusive use of GLP-1 analogues such as dulaglutide and semaglutide [29].

GLP1 is subject to degradation by the enzyme dipeptidyl-peptidase 4 (DPP4) [30]. In addition to several other complications, T2DM patients present elevated DPP4 levels. In addition to maintaining higher levels of detrimental glucose, disease phenotypes of hepatocytes are manifested, e.g., fibrosis or even apoptosis [24]. The gliptins are competitive inhibitors of DPP4 and can, therefore, counteract the detrimental action of this proteolytic enzyme. Among these are compounds such as alogliptin (Figure 2B and Table 1) and linagliptin, in addition to a few others [31].

Another way to combat T2DM is to enhance the sensitivity of the body to respond to insulin. Here, thiazolidinedione insulin sensitizers play an important role [32]. Two established members of this family are pioglitazone and rosiglitazone (Figure 2C and Table 1), which are both capable of strongly activating the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) [33]. This receptor has various important roles in the differentiation and function of adipocytes. Ligand binding to PPARγ leads to the stimulation of adipokine production and processing and increases the sensitivity of target cells to insulin, among other functions [34,35]. This process is accompanied by a decrease in free fatty acids in the blood plasma. Both pioglitazone and rosiglitazone have additional mechanisms of action [36]. Pioglitazone has been shown to decrease gluconeogenesis in the liver and reduce the quantity of glucose and glycated hemoglobin in the bloodstream [37]. In addition to its insulin-sensitizing function, rosiglitazone shows anti-inflammatory effects [38]. This is due to an increase in the NF-κB inhibitor (IκB), which targets the molecular signal nuclear factor kappa-B (NF-κB), thereby reducing the inflammatory response.

The Na-dependent glucose transporter SGLT2 is necessary for the reabsorption of glucose in the kidney's proximal tubule epithelium [39]. As such, it is also an attractive target for pharmacological intervention for the treatment of T2DM. The inhibition of SGLT2 by gliflozins (e.g., canagliflozin (Figure 2D and Table 1) and dapagliflozin) results in the elevated excretion of excess glucose, in addition to reducing both body weight and risks of complications in the cardiovascular system [40,41].

Metformin is one of the oldest pharmacological substances for lowering glucose levels in plasma. It was already described in 1922 [42,43]. The biguanide metformin (Figure 2E and Table 1) has several modes of action that help patients suffering from T2DM and obesity. For example, it inhibits the metabolic pathway of gluconeogenesis in the liver, mostly by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase [44,45]. Furthermore, it is proposed to down-regulate the mitochondrial respiratory chain via binding to complex I and to activate the metabolic regulator kinase AMP-activated protein kinase (AMPK) [46].

Although it is the first line of treatment against T2DM and obesity, its exact molecular mechanisms remain to be elucidated.

There are also ways to increase the secretion of insulin by the β cells of the pancreas. The sulfonylureas (e.g., gliclazide (Figure 2F and Table 1)) offer relevant treatment options in this regard [47,48]. They block the potassium channels of the β cells. The subsequent cell depolarization leads to an influx of calcium ions, which elicits exocytosis of insulin-containing vesicles from the β cells. This helps to lower the glucose levels in the blood.

In 1996, the Bayer group introduced acarbose as an intestinal drug. This compound originates from soil bacteria (*Actinoplanes utahensis*) [49]. Acarbose ($C_{25}H_{43}NO_{18}$) is a tetrasaccharide-derived metabolite that is constituted by valienamine bonded via nitrogen to isomaltotriose (Figure 2G) [50]. This is a drug used in the treatment of T2DM, and it plays a fundamental role as a mixed non-competitive inhibitor of α-amylase and competitive inhibitor of α-glucosidase in delaying the complete release of glucose for absorption into the bloodstream, meaning glucose will not appear in the digestive system but will appear completely in the distal parts of the intestine [51,52]. Said enzymes participate in the decomposition of carbohydrates or the hydrolysis of oligosaccharides (sucrose and glucose), that is, the inhibitor slows down the metabolism with the aim that the foods consumed with a high sugar content are more slowly assimilated for people with diabetes [53]. In other words, acarbose blocks the ability of the previously mentioned digestive enzymes to break down starch and carbohydrates in the gastrointestinal tract.

Acarbose is one of the most widely used drugs because it is an affordable compound. However, acarbose is not currently the most widely used inhibitor by the medical community due to its gastrointestinal side effects (i.e., flatulence and abdominal discomfort). The doses of its application range from 25 mg to 200 mg, with 100 mg being the average dose of its oral administration three times a day after food ingestion [54].

Lastly, there are further options to pharmacologically target α-glycoside hydrolases in the intestine using iminosugars such as the drug miglitol [55]. Mechanistically, the conjugate acid mimics the positive charge characteristic of the transition state for the enzymatic hydrolysis of the glucoside bond [56]. One route to synthesize iminosugars is via chemical conversion of 1,2-azidoacetates [57]. This approach allows the production of potential antidiabetic drugs such as novel piperidine derivatives [58].

Table 1. Several pharmacological compounds for the treatment of T2DM.

Compound	Molecular Weight	Description of Function	References
Alogliptin	339.39 g/mol	A highly selective DPP4 inhibitor, it results in the prolonged effect of incretin GLP1 and, thus, increases insulin secretion and inhibits glucagon secretion, helping to lower blood glucose and to achieve improved glycemic control in T2DM patients.	[59]
Rosiglitazone	357.43 g/mol	Through activation of PPARγ, it has primary effects on adipose tissue and decreases insulin resistance by reducing hepatic triglycerides, decreasing visceral fat mass, and increasing subcutaneous fat mass.	[36]
Canagliflozin	444.52 g/mol	As a competitive, reversible, and highly selective SGLT2 inhibitor, it leads to a reduction in glucose reabsorption from primary urine. The induced glucosuria results in optimized glycemic control as well as an energy deficit, which translates into a body weight reduction.	[60]

Table 1. *Cont.*

Compound	Molecular Weight	Description of Function	References
Metformin	129.16 g/mol	Exact mechanisms remain elusive. It acts as an antihyperglycemic agent, possibly through a decrease in hepatic glucose production partially caused by an interaction with the mitochondrial respiratory chain complex I.	[61]
Gliclazide	323.41 g/mol	Belongs to the group of sulfonylureas that stimulate basal and meal-stimulated insulin secretion through binding to the B cell receptor SUR1, a subunit of an ATP sensitive potassium channel, which, when blocked, leads to an increase in insulin secretion.	[62,63]
Exenatide	4186.63 g/mol	A GLP1R agonist, it acts to increase glucose-dependent insulin secretion from B cells, suppress glucagon secretion, and delay gastric emptying, and it leads to a reduction in calorie intake and body weight.	[64,65]

3. The Treatment of Bacterial Infections in T2DM Patients

Individuals with T2DM are at a higher risk of developing infectious diseases. The main reasons for this are an impaired immune system, a hyperglycemic environment, and other associated factors [66]. In addition, there is a relationship between diabetes and bacterial infections, since bacterial infections such as malignant otitis externa, periodontitis, emphysematous pyelonephritis, and emphysematous cholecystitis are much more frequent in diabetic patients. These can be more serious in diabetics than in non-diabetics [67]. These infections are usually the first manifestation of unrecognized long-standing diabetes [68]. The most common bacteria are streptococci, pneumococci, and enterobacteria, and several reasons can explain this correlation [69–71]. In T2DM patients, more glucose is available that can be used by invading bacteria as a source of metabolic energy, which boosts the proliferation rate. Perhaps even more pronounced is the link between a strongly activated and compromised immune system and bacterial infections in T2DM patients [66]. The end products of choline degradation by Firmicutes, Actinobacteria, and Proteobacteria have been associated with the development of cardiovascular disease and diabetes as products that favor the development of harmful oxidative stress [72].

In addition to the medical complications seen in patients suffering from T2DM, an elevated risk of contracting bacterial infections is observed, with *Klebsiella pneumoniae* and *Escherichia coli* being regarded as the most common ones [73]. The most frequent site of infection is the urinary tract (UTIs, urinary tract infections) [74–77] (Figure 3), leading to acute pyelonephritis and asymptomatic bacteriuria, among other complications. In 2005, Brown et al. identified further risk factors for infections of the urinary tract, such as age and additional conditions (e.g., primarily diabetic cystopathy and nephropathy) [78]. The main risk factors for UTIs in T2DM are inadequate glycemic control, duration of T2DM, diabetic microangiopathy, impaired leukocyte function, recurrent vaginitis, and anatomical and functional abnormalities of the urinary tract [79,80].

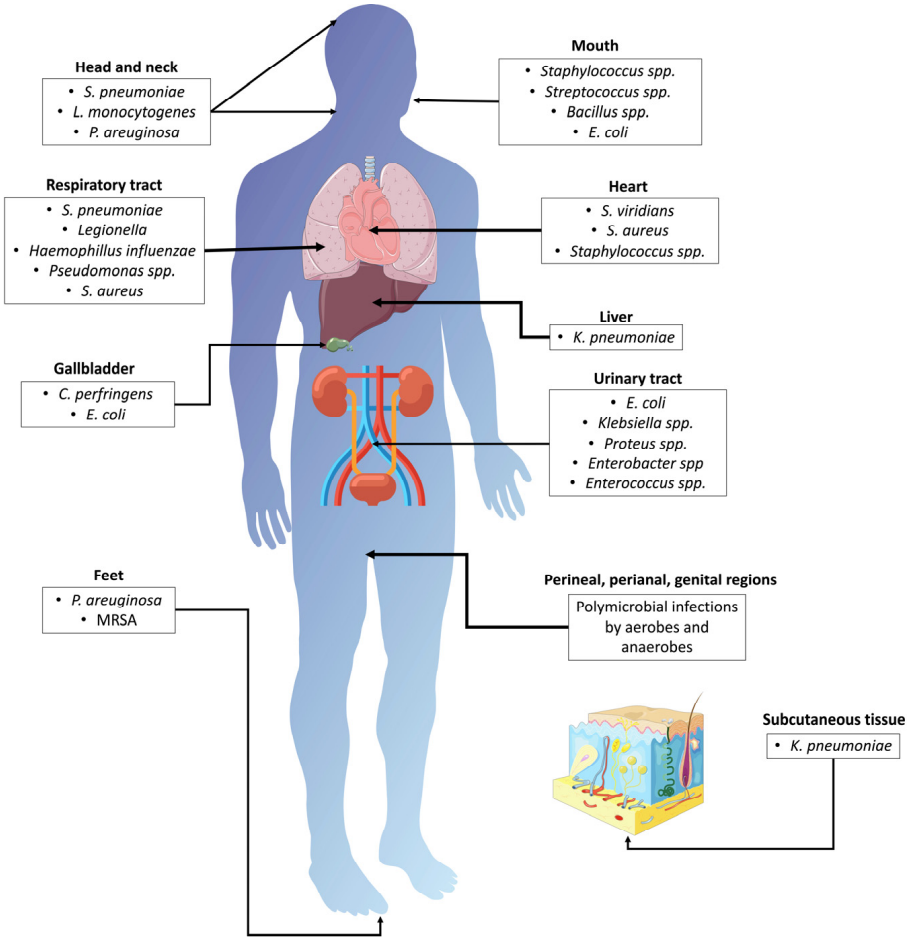

Figure 3. Bacterial infections associated with T2DM. MRSA: methicillin-resistant *Staphylococcus aureus*; *S. pneumoniae: Streptococcus pneumoniae*; *L. monocytogenes: Listeria monocytogenes*; *E. coli: Escherichia coli*; *S. aureus: Staphylococcus aureus*; *S. viridians: Streptococcus viridians*; *K. pneumoniae: Klebsiella pneumoniae*; *C. perfringens: Clostridium perfringens*; *P. aeruginosa: Pseudomonas aeruginosa*.

Several reasons can explain this correlation. In T2DM patients, there is a clearly documented link between a strongly activated and compromised immune system and bacterial infections in T2DM patients [76,81]. Here, various aspects can be distinguished [82]. First, the rheological attributes of blood cells are significantly altered in many T2DM patients [83]. For example, blood viscosity is increased, leading to a multitude of adverse effects, such as limited oxygen concentrations in the microenvironment of immune cells. Therefore, only a limited defense can be mounted against intruding bacteria, increasing the chance of severe bacterial infections. Another example is the lowered blood pH that is often seen in patients suffering from hyperglycemia [84]. This effect is mainly caused by diabetic ketoacidosis and can result in a decreased blood pH below the physiological value of approximately 7.3. Further biochemical alterations that might favor infections in T2DM patients are an impairment of the pentose phosphate pathway, which is participating in the antioxidant defense by synthesizing the reduction equivalent NADPH [85], and the limited functionality of the Na^+/K^+ ATPase [86], which regulates a plethora of cellular functions.

Diabetes-associated immunodeficiency is also a predisposing factor for pneumococcal and *Haemophilus influenzae* meningitis, which can cause bacterial meningitis, leading to an altered mental status and increased mortality [68]. Cefotaxime/ceftriaxone plus amoxicillin/ampicillin/penicillin G are the standard antibiotics used in these cases [87,88].

Foot infections are a serious and common complication of DM. High blood sugar levels can damage the nerves and blood vessels in the feet, leading to poor circulation and decreased sensation [89]. This can make it difficult to detect injuries, such as cuts or blisters,

which can then become infected and potentially lead to more serious complications [89]. In fact, foot infections are one of the most common reasons for hospitalization among people with diabetes [89]. If left untreated, they can lead to serious complications such as osteomyelitis (infection of the bone), gangrene, and even amputation. In severe cases, foot infections can also lead to sepsis (a potentially life-threatening infection that spreads throughout the body) [90]. *Staphylococcus aureus* and *Staphylococcus epidermidis* are isolated from around 60% of all infected ulcers. Enterococci, streptococci, and enterobacteria are less frequent, and 15% of infected ulcers contain strictly anaerobic bacteria [90]. Therefore, it is important for people with diabetes to take proper care of their feet, including daily washing and inspection, wearing appropriate footwear, and seeking prompt medical attention for any injuries or signs of infection [89]. This can help prevent foot infections and reduce the risk of serious complications.

The three most serious head and neck infections in diabetic persons are invasive external otitis (IEO), rhinocerebral mucormycosis, and periodontitis [66]. IEO, also known as malignant otitis externa, is a serious infection that can affect the ear canal and skull base. It is most commonly seen in elderly patients with poorly controlled diabetes, although it can also occur in individuals with weakened immune systems or those with chronic ear infections [91]. Rhinocerebral mucormycosis is another serious infection that can affect the head and neck region [92]. It is a rare but life-threatening fungal infection that can affect the sinuses, brain, and other organs. It is a rare, opportunistic and invasive infection caused by fungi of the class *Zygomycetes* [92]. Periodontitis is more common in persons with T2DM and is considered the sixth most common complication of DM [93]. This condition initiates or disseminates insulin resistance, thus affecting glycemic control. Poor glycemic control has been associated with a greater incidence and progression of gingivitis and periodontitis [94]. This pathogenesis is mainly caused by *Porphyromonas gingivalis*, which acts as a critical agent by altering host immune homeostasis [95]. Lipopolysaccharides, proteases, fimbriae, and other virulence factors are among the strategies used by *P. gingivalis* to promote bacterial colonization and facilitate the growth of the surrounding microbial community [95]. These virulence factors modulate various host immune components by evading bacterial clearance or inducing an inflammatory environment [96].

Fournier gangrene is a type of necrotizing fasciitis that affects the male genitalia and surrounding areas. The most common bacteria that cause this condition are *E. coli*, *Klebsiella* spp., *Proteus* spp., and *Peptostreptococcus* spp. [97]. However, it is not uncommon for the infection to be polymicrobial, involving several different types of bacteria such as Clostridium, aerobic or anaerobic streptococci, and Bacteroides [67]. Approximately 70% of patients with Fournier gangrene have DM, which is a risk factor for developing this condition. The infection typically starts in the scrotum but can extend to involve the penis, perineum, and abdominal wall [75]. It is important to note that despite the severity of the infection, the testicles are usually spared from the disease [67]. Early diagnosis and aggressive treatment are crucial to preventing the spread of the infection and reducing mortality rates. Treatment involves surgical debridement to remove the infected tissue, along with broad-spectrum antibiotics to target the bacterial infection [98]. Patients with Fournier gangrene often require hospitalization and intensive care management [99].

Respiratory tract infections are responsible for many medical appointments by persons with T2DM [79]. The most frequent respiratory infections associated with DM are caused by *Streptococcus pneumoniae* and the influenza virus, and persons with DM also have a high possibility of being infected with *Mycobacterium tuberculosis*. Table 2 gives an overview of bacterial pathogens that are associated with T2DM.

Some of the drugs described in the previous section have been investigated in terms of whether they have beneficial functions for treating bacterial infections in T2DM patients. Only metformin is reported to have clear effects on reducing the pathophysiology of infectious disease mediated by bacteria [100,101]. In a mouse model, metformin administration reduced infections mediated by bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* [102]. Specifically, *P. aeruginosa* growth is inhibited by metformin in an epithelial

cell line of the lungs (Calu-3) [103]. Furthermore, metformin administration also reduces the risk of infections by *Mycobacterium tuberculosis* [104]. For other commonly used drugs to combat T2DM, either no data are available at the time of writing or they have no effects [82].

Table 2. Associated pathogenesis of bacterial infections in T2DM.

Disease	Microorganism	Symptoms	Conventional Treatment	References
Head and neck infections	*Streptococcus pneumoniae* and *Listeria monocytogenes* *Pseudomonas aeruginosa*	Bacterial meningitis Malignant *otitis externa*	Cefotaxime/ceftriaxone plus amoxicillin/ampicillin/penicillin G. Long-term monotherapy with oral ciprofloxacin.	[68,105,106]
Periodontitis	*Staphylococcus* spp., *Streptococcus* spp., *Bacillus* spp., *E. coli*	Inflammation in the periodontal tissues is stimulated by the long-term presence of subgingival biofilm, suppuration from periodontal pockets, and tooth loss	Oral and periodontal health (intensive periodontal treatment) and glycemic control.	[107]
Respiratory infections	*Streptococcus pneumonia*, *Legionella* spp., *Haemophilus influenza*, *Pseudomonas* spp., *Staphylococcus aureus*	Community-acquired pneumonia/hospital-acquired pneumonia	Initial outpatient treatment: Combination therapy with amoxicillin/clavulanic acid/cephalosporin and macrolide/doxycycline or monotherapy with respiratory fluoroquinolone. Severe in-patient pneumonia: β lactam + macrolide or β lactam + fluoroquinolone.	[108–110]
Infective endocarditis	*Streptococcus viridans*, *Staphylococcus aureus* and *Enterococcus* species	Acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock	Ampicillin with flucloxacillin, oxacillin with gentamicin, or vancomycin with gentamicin and rifampicin.	[111,112]
Emphysematous cholecystitis	*Clostridium perfringens* and *E. coli*	Biliary tract infection	Surgical removal of the gallbladder and broad-spectrum antimicrobial therapy.	[113]
Liver	*Klebsiella pneumoniae*	Pyogenic liver abscess	Combined antibiotic therapy with carbapenems.	[114,115]
Urinary tract	*E. coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and Enterococci	Cystitis, pyelonephritis, severe urosepsis, renal abscesses and renal papillary necrosis	Ertapenem, nitrofurantoin, ciprofloxacin, ofloxacin, trimethoprim–sulfamethoxazole, cefuroxime, and gentamicin.	[116–118]
Foot infections in diabetes	*Pseudomonas aeruginosa*, MRSA	Foot ulcer	β-lactamase inhibitor-amoxicillin/clavulanate; trimethoprim–sulfamethoxazole; carbapenem; aminoglycoside, colistin, and fluoroquinolone; amputation	[119]
Fournier's gangrene	Polymicrobial infections by aerobes and anaerobes	Necrotizing fasciitis of the perineal, genital, or perianal regions	Broad-spectrum antibiotics and surgical debridement.	[120,121]
Necrotizing fasciitis	*Klebsiella pneumoniae*	Extensive necrosis of subcutaneous tissue and fascia	Surgery, oxacillin, and a third-generation cephalosporin.	[122]

MRSA: methicillin-resistant *Staphylococcus aureus*.

Compounds from plants can yield valuable results in the treatment of bacterial infections, such as juice extracted from cranberries [123]. It was found that active compounds in

this juice are potent inhibitors of bacterial adherence to cells in the urogenital epithelium. The use of plants as a complementary treatment for diabetes and the bacteria that occur in T2DM is supported by several studies. Plants present different bioactive effects, such as anti-inflammatory, antioxidant, bactericidal, and fungicidal activity [124]. In the next section, we discuss the use of plants that can help to treat T2DM and associated infections.

4. Overview of Medical Plant Compounds for the Treatment of T2DM

As previously described, hyperglycemia secondary to T2DM is a condition that can alter the immune system through multiple pathways. In addition, the wounds in these patients have the characteristic that they can take more time to heal, are difficult to manage, and can cause ulcers, infections, and even amputations if not suitably treated [125–127]. If hyperglycemia is controlled, the susceptibility of these patients to generate infections should decrease [82,127,128]. Currently, the treatment for infections is pharmacological; however, the use of antibiotics can generate adverse effects, such as hepatotoxicity and nephrotoxicity [124]. In addition, bacteria are known to generate multidrug resistance over time; therefore, non-pharmacological alternatives are sought for the treatment of infections in diabetic patients. Metabolites such as polyphenols, flavonoids and alkaloids act as important antimicrobial agents due to their efficiency in treating bacterial infections and preventing resistance [129,130].

This work suggests the use of plants in two different ways. The first one is to use plants as a direct factor, which means to use certain ingredients as antibacterial agents, and the second one is to use plants as an indirect factor, which means to use hypoglycemic plant ingredients that will decrease the susceptibility to infections. In this way, plants become a non-pharmacological alternative for treating infections in patients with T2DM.

4.1. Mechanism of Action of Natural Products in the Treatment of T2DM and Associated Infections

4.1.1. Antibacterial Activity of Plants

As outlined in Section 3, infections in patients with diabetes are rather common, especially stemming from bacteria such as *Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes*, and *Proteus mirabilis*. To evaluate alternative treatments against infections, ethanolic extracts of shrubs such as *Brachylaena ilicifolia* and *Brachylaena elliptica* were tested against the bacteria mentioned before under laboratory conditions. The results showed that phytochemicals such as proanthocyanidins, alkaloids, flavonoids, and polyphenols and *B. ilicifolia* extracts inhibited the growth of *Pseudomonas aeruginosa*, thus serving as potent antibacterial agents [131].

Urinary tract infections are a common part of these conditions, and the use of antibiotics has caused bacterial resistance. This is why urine samples were taken from volunteers with urinary tract infections (UTIs) to isolate multidrug-resistant *Escherichia coli* bacteria. Subsequently, the synergistic effect of the antibacterial activity of the aqueous and methanolic extracts of *Prunella vulgaris*, commonly known as the "heal all" or "self-heal" plant, was evaluated with the following antibiotics: cefixime, ciprofloxacin, tobramycin and ofloxacin. The results that were significant were those of the cefixime + *P. vulgaris* aqueous extract group, which had a synergistic effect, and the ciprofloxacin + *P. vulgaris* (aqueous and ethanolic extract) group, which had no synergistic effect. This means that concomitant antibiotic use with *Prunella vulgaris* aqueous extract serves to generate a synergistic effect against multidrug-resistant bacteria [132].

As mentioned above, cranberry is commonly used as a prophylactic treatment against UTIs. To discover its biological functioning, a clinical study was carried out using "NutriCan" capsules in healthy men and women. The results showed a higher decrease in bacterial adhesion in men than in women, which was correlated with a time-dependent increase in the Tamm–Horsfall protein (THP). The THP is a high-mannose glycoprotein (from the innate immune system), which is of vital importance because on the surface of the type 1 fimbriated uropathogenic *Escherichia coli* (UPEC), there is uroplakin that is anchored with the conserved mannose moieties of the THP. This prevents attachment to uroepithelial

cells, which are found in the nephron of the kidney, especially tubular cells in the region of the loop of Henle, thus preventing infections [133].

Another condition secondary to UTIs is cystitis (bladder inflammation). In a clinical study in which women with uncomplicated cystitis were evaluated, it was shown that the use of trimethoprim–sulfamethoxazole with green tea had a synergistic effect on decreasing the prevalence of cystitis. The antibacterial activity of green tea is attributed to its phytochemicals, such as polyphenols and catechins [134].

In infections, we can find those of the nosocomial type (hospital-acquired infections), and *Klebsiella pneumoniae* is part of those most commonly found, being mainly present in blood, urinary and respiratory infections. The antibacterial activity against *Klebsiella pneumoniae* of glycolic extracts from *Juglans regia* L., which is commonly known as Persian walnut or English walnut, *Pfaffia paniculata* K., which is commonly known as ginseng, and *Rosmarius officinalis* L., which is commonly known as rosemary, was evaluated. *J. regia* and *R. officinalis* contain monoterpenes that can change the membrane permeability and kill the bacteria, whereas the antibacterial effect of *P. paniculata* is attributed to pfameric acid, which is a triterpene [135].

Currently, many microorganisms have become multidrug-resistant (MDR) (at least to three different antibiotics). The effects of methanolic extracts of the following plants, *Oxalis corniculata*, *Cinnamomum tamala, Ageratina adenophora,* and *Artemisa vulgaris*, which are commonly known as creeping woodsorrel, Indian Cassia, crofton weed, and mugwort, respectively, were tested against different MDR bacteria. The plants that showed antibacterial activity against *E. coli* were *O. corniculate* and *A. vulgaris*; against *S. aureus* were *C. tamala, A. adenophora* and *A. vulgaris*; and against *S. typhi* were *A. adenophora* and *O. corniculate*. The only plant that showed antibacterial activity against *C. koseri* and *K. pneumoniae* was *O. curniculate*. This activity was attributed to phytochemicals such as terpenoids, alkaloids, tannins, and flavonoids [136].

As part of the other nosocomial infections, *Staphylococcus aureus* is also part of the main ones. The antibacterial effect of *Arbutus pavarii*, known locally in Libya as Schmar, methanolic extracts and fractions (ethyl acetate, hexane, chloroform, butanol) was evaluated against methicillin-resistant *S. aureus*. The methicillin-resistant *Staphylococcus aureus* were isolated from a nasal swab from a student from Putra University of Malaysia, the MRSA KCCM 12255 was obtained from the Korean Culture Center of Microorganisms and the MRSA ATCC was obtained from the American Type Culture Collection. Various phytochemicals involved in antibacterial activity were identified, such as gallic acid, catechins, epigallocatechin gallate, epicatechin gallate, quercetin, flavonoids, phenolic acids and arbutin. Catechins damage the membrane of bacteria by causing a potassium leak, which causes a rupture of the membrane and the death of the bacteria; other phytochemicals can block the synthesis of amino acids [137].

4.1.2. Hypoglycemic and Hypolipidemic Plants

An indirect way to decrease susceptibility to infections in patients with T2DM is to decrease hyperglycemia in general to maintain the proper functioning of the immune system [82]. It has been seen that curcumin-enriched yogurt with insulin in diabetic Wistar rats induced by streptozotocin (STZ) maintained normal blood glucose levels and decreased oxidative stress and dyslipidemia. These effects are due to the increased translocation of GLUT-4 via the phosphorylation of AKT. Curcumin per se has the ability to scavenge ROS, to increase the activity of delta-aminolevulinic dehydratase, superoxide dismutase (SOD) and catalase (CAT) as well as to decrease thiobarbituric acid reactive substances (TBARS) [138].

The ethanolic extract from leaves of *Avicennia marina*, commonly known as gray mangrove plant, has proved to be a suitable hypoglycemic agent in a diabetic Swiss Webster mouse model induced by streptozotocin (STZ), in addition to acting as an antioxidant agent, increasing CAT and glutathione (GSH) levels, as well as decreasing toxins such as H_2O_2, malondialdehyde (MDA) and nitric oxide (NO) and protecting organs such as the kidney

and liver in order to avoid comorbidities [139]. Another study used the same plants, *Avicennia marina* and *Rhizophora mucronata*, and the aqueous extract (also from leaves) in a diabetic Wistar rat model induced by STZ. They proved to be useful hypoglycemic agents stimulating insulin secretion, which led to comments that phytochemicals such as flavonoids from the plants could prevent pancreatic β-cell apoptosis. In addition, these plants decreased MDA and lipid peroxidation, and both have the ability to be antioxidants per se [140].

Another effect that is sought in the use of plants against T2DM is the hypolipidemic effect, in addition to the hypoglycemic one. The hydroalcoholic extracts of *Eryngium caucasicum* roots showed this effect in a diabetic Wistar rat model induced by STZ and nicotinamide (NA), raising serum insulin levels and decreasing blood glucose. It is worth mentioning that carotenes and flavonoids could be responsible for reducing oxidative stress. This treatment also led to a decreased homeostasis model assessment (HOMA), which is a method for measuring fasting insulin and glucose in blood and is useful in determining insulin resistance and the functioning of pancreatic β-cells. Saponins suppress cholesterol absorption while increasing bile secretion, alkaloids inhibit cholesterol synthesis, and both natural products cause the elevation of high-density lipoproteins (HDL) and the decrease of very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL). *E. caucasicum* also demonstrated hepatoprotection by decreasing serum glutamic pyruvic transaminase (SGPT) and glutamic oxaloacetic transaminase (SGOT), therefore protecting the structural integrity of the liver. The insulin increase can inhibit lipase, which means that processes such as the stimulation of fatty acids in phospholipids for later cholesterol and plasma release are slowed down [141].

T2DM can also be combated using beverages from plants that are consumed worldwide, such as coffee. In a diabetic Wistar rat model (STZ + high fat diet), *Coffea arabica* aqueous extract proved to be a hypolipidemic and hypoglycemic agent. It also ameliorated insulin resistance. These effects are attributed to chlorogenic acid present in *Coffea arabica*, which has been reported to decrease adipocyte numbers in the abdominal area. It can modulate transport proteins that consequently decrease renal lipid peroxidation, renal triglycerides, and oxidative stress. The chlorogenic acid promotes the expression of antioxidant proteins by modifying the mRNA levels of antioxidant genes encoding glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) [142].

There are other types of plants that are not commonly used; however, they exert antidiabetic effects, such as *Datura stramonium L.*, commonly known as Jimsonweed or thorn apple. The hydro-methanolic root extract of this plant has improved glucose metabolism through insulin secretion, inhibiting α-amylase and α-glucosidase, blocking gluconeogenesis, protecting pancreatic β cells from inflammation and oxidative stress, improving glucose transporters GLUT-2 and GLUT-4 through flavonoids and polyphenols, and also reducing serum triglyceride, as was tested in a Swiss albino diabetic mice induced by STZ [143].

There are ornamental plants that have medicinal uses, such as *Enhydra fluctuans*, commonly known as Harkuch or Helencha. Aqueous alcohol *Enhydra fluctuans* extracts administered to Long Evans rats in which diabetic conditions were induced by STZ exerted anti-dyslipidemic and hypoglycemic effects by improving insulin sensitivity and the utilization of glucose at the peripheral level, decreasing glycogenolysis, decreasing fasting blood glucose, decreasing the ratio of TG/HDL-cholesterol, and inhibiting protein carbonylation and lipid peroxidation [144].

Fruit plants, in addition to serving as food, can also be effective antidiabetic agents when other parts of the plant, such as mango leaves, are utilized. Hydro-alcoholic extracts of *Mangifera indica L.* leaves exerted hypoglycemic effects via polyphenols that inhibited postprandial fat utilization and glucose, inhibited alpha-glucosidase, increased insulin sensitivity, blocked pancreatic lipase activities, induced GLUT-4 and decreased LDL levels in a Swiss albino diabetic mouse model, which was experimentally induced via administration of alloxan monohydrate [145].

This work proposes the use of plants as a complementary treatment for T2DM (Figure 4). As described above, the plants that can be used range from the best known (e.g., consumed in beverages such as coffee) to the not so commonly known plants. The antidiabetic effects of plants are attributed to the presence of phytochemicals such as polyphenols, flavonoids, catechins, and alkaloids, among others. Plants can be antidiabetic in two ways, acting as direct agents, lowering blood lipids and glucose, acting as antioxidant agents, or increasing antioxidant enzymes, increasing insulin sensitivity, improving glucose transport by transporters such as GLUT-4 or decreasing lipid peroxidation, or they may act as indirect agents, attacking the infections to which people with T2DM are more susceptible, thereby indirectly preserving the immune system and blocking hyperglycemia. Table 3 shows the different types of plants that can be used directly or indirectly to treat infections, their origin, and their mechanism of action.

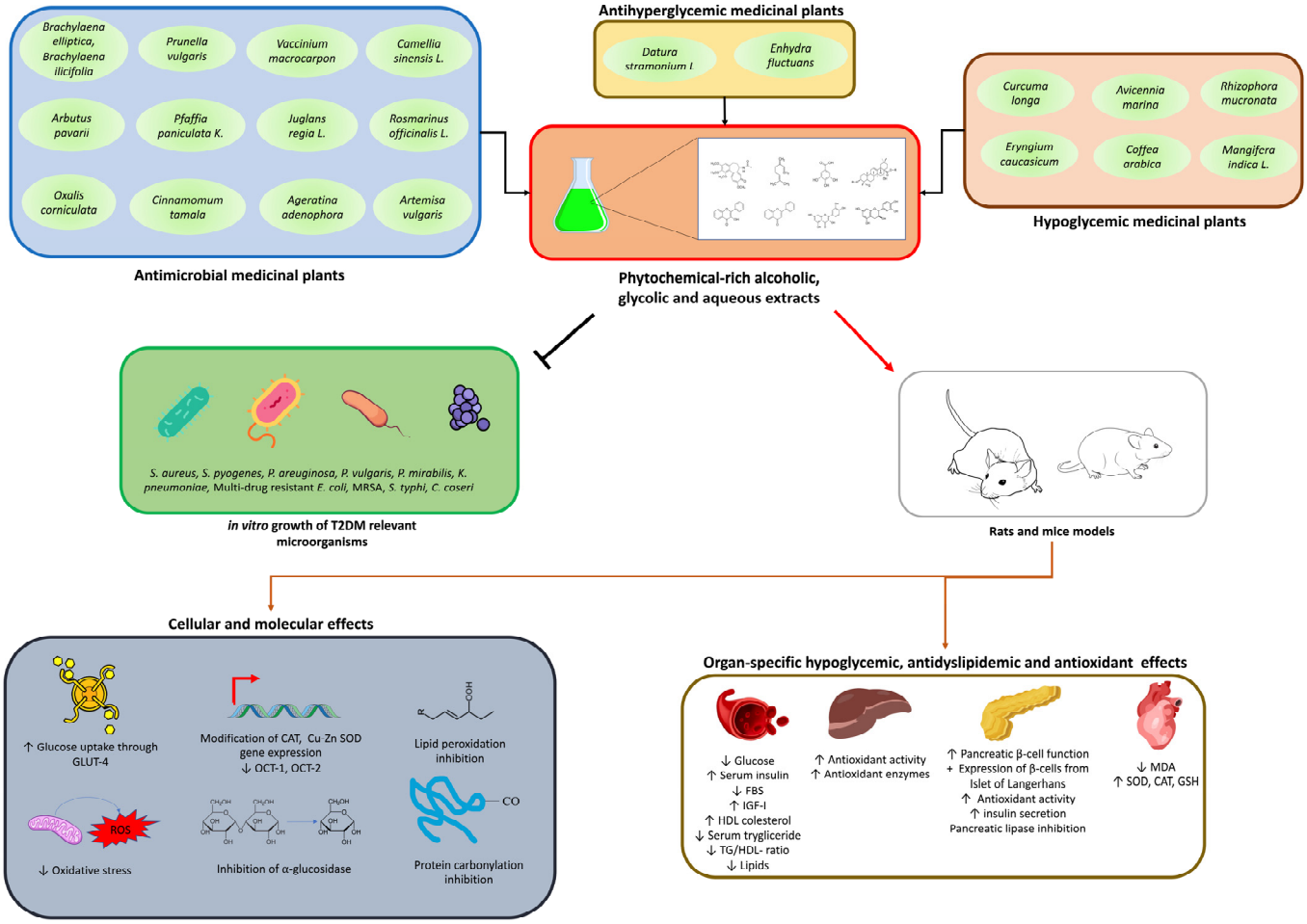

Figure 4. Alternative herbal treatments for T2DM, alongside the effects found in the literature. AUC: acute uncomplicated cystitis; THP: Tamm–Horsfall protein; FBS: fasting blood glucose; GLUT-4: glucose transporter type 4; GSH: glutathione; HDL: high-density lipoprotein; IGF-I: insulin-like growth factor I; LDL: low-density lipoprotein; MDA: malondialdehyde; NA: nicotinamide; OCT-1: organic cation transporter; MRSA: methicillin-resistant *Staphylococcus aureus;* T2DM: Type 2 diabetes mellitus; CAT: catalase; TG: triglycerides; *S. aureus: Staphylococcus aureus; S. pyogenes: Streptococcus pyogenes; P. aeruginosa: Pseudomonas aeruginosa; P. vulgaris: Proteus vulgaris; P. mirabilis: Proteus mirabilis; K. pneumoniae: Klebsiella pneumoniae*.

Table 3. Alternative herbal treatments for T2DM.

Plant	Origin/ Region	Extract/ Compounds	Model of Study	Mechanism of Action	Diabetes Effect	Reference
Brachylaena elliptica and *Brachylaena ilicifolia*	Africa	Alcoholic extract of the plant leaves	In vitro *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Proteus mirabilis* + alcoholic extracts	Bioactive compounds such as saponins, phenols, flavonols, and alkaloids inhibited the bacterial growth	Antibacterial activity	[131]
Prunella vulgaris	Africa	Aqueous and ethanolic extract	Multidrug-resistant *Escherichia coli* collected from the patient's urine	Phytochemicals inhibited the bacterial growth	Antibacterial activity	[132]
Vaccinium macrocarpon	America	Cranberry dry extract capsules "NutriCan"	Healthy men and women volunteers	Antiadhesive activity against *Escherichia coli* by THP	Antibacterial activity	[133]
Camellia sinensis L.	Asia	Capsules of spray-dried aqueous extract of green tea (green tea group)	Women with acute uncomplicated cystitis (*Escherichia coli*) + green tea + trimethoprim–sulfamethoxazole	Catechins antimicrobial effect	Antibacterial activity	[134]
Pfaffia paniculata K., *Junglans regia* L., *Rosmarinus officinalis* L.	*Pfaffia paniculata* K. America, *Junglans regia* L. Europe, *Rosmarinus officinalis* L. Mediterranean region	Glycolic extracts	Extract + *Klebsiella pneumoniae*	Phytochemicals against bacteria, such as monoterpenes, triterpenes, pfameric acid. Monoterpenes change the membrane permeability causing the death of the bacteria	Antibacterial activity	[135]
Oxalis corniculata, *Cinnamomum tamala*, *Ageratina adenophora*, *Artemisa vulgaris*	*Oxalis corniculata* Asia, *Cinnamomum tamala* Asia, *Ageratina adenophora* Mexico, *Artemisa vulgaris* Europe and Asia	Methanolic extracts from the leaves, except *Artemisa vulgaris*, that use aerial parts	Extract + *Escherichia coli*, *Staphylococcus aureus*, *Salmonella Typhi*, *Pseudomonas aeruginosa*, *Citrobacter koseri*, *Klebsiella pneumoniae*	Phytochemicals with antibacterial activity, such as terpenoids, alkaloids, tannins, flavonoids, coumarins, phenylpropanoids and sterols	Antibacterial activity	[136]

Table 3. *Cont.*

Plant	Origin/ Region	Extract/ Compounds	Model of Study	Mechanism of Action	Diabetes Effect	Reference
Arbutus pavarii	Africa	Methanolic extracts from leaf and stem bark	Methicillin-resistant *Staphylococcus aureus* + methanolic extracts	Phytochemicals such as gallic acid, catechins, epigallocatechin gallate, epicatechin gallate, quercetin, flavonoids, phenolic acids and arbutin	Antibacterial activity	[137]
Curcuma longa	Asia	Curcumin	Wistar rats + STZ	Increase antioxidants from liver and decrease lipids and glucose levels in blood	Hypoglycemic, hypolipidemic effect and antioxidant activity	[138]
Avicennia marina	Africa	Alcoholic leaf extract	Swiss Webster mice + STZ	Decrease glucose in blood, increase liver antioxidant enzymes and decrease oxidative stress	Hypoglycemic effect and antioxidant activity	[139]
Rhizophora mucronata	Asia	Aqueous leaf extract	Wistar rats + STZ	Decrease glucose in blood, increase serum insulin, increase function of pancreatic β cells, decrease MDA levels in heart, increase SOD, CAT and GSH levels in heart, reduce muscle MDA levels, strong positive immunohistochemical expression of β cells from the islets of Langerhans	Hypoglycemic, decrease oxidative damage, insulin-releasing activity	[140]
Eryngium caucasicum	Asia	Root hydro-alcoholic extract	Wistar rats + NA-STZ	Decrease FBS, improve insulin secretion and, therefore, glucose uptake through GLUT-4, increase antioxidant capacity to enhance β pancreatic cells, decrease blood glucose levels, favorable effects on QUICKI, increase IGF-I serum concentrations	Hypoglycemic, improve β cells, prebiotic, antioxidant activity	[141]

Table 3. *Cont.*

Plant	Origin/ Region	Extract/ Compounds	Model of Study	Mechanism of Action	Diabetes Effect	Reference
Coffea arabica	Africa	Pulp aqueous extract	Wistar rat + STZ + high fat diet	Decrease oxidative stress through the modification of the expression of mRNA antioxidant genes such as catalase and Cu-Zn SOD	Hypoglycemic, decrease triglycerides, improve insulin resistance, antifat deposition effect, antioxidant effect	[142]
Datura stramonium L.	Africa	Hydromethanolic root extract	Swiss albino mice + STZ	Enhance body weight, improve glucose intake, increase HDL cholesterol, decrease serum triglyceride	Antihyperglycemic effect, regeneration and proliferation of β pancreatic cells, antioxidant activity	[143]
Enhydra fluctuans	Asia	Aqueous alcohol whole plant extract	Long Evans rats + STZ	Decrease fasting blood glucose, decrease ratio of TG/HDL-cholesterol, inhibit protein carbonylation and lipid peroxidation	Antidyslipidemic and antihyperglycemic effect, improve insulin sensitivity, antioxidant effect	[144]
Mangifera indica L.	Asia	Hydro-alcoholic extract of the plant leaves	Swiss albino mice + alloxan monohydrate	Inhibit alpha-glucosidase activity, increase insulin sensitivity, polyphenols inhibit postprandial fat utilization and glucose, decrease LDL levels, induce GLUT-4, block pancreatic lipase activities and alpha glucosidase	Hypoglycemic, regeneration of β pancreatic cells, decrease hyperlipidemia, antioxidant activity	[145]

CAT: catalase; FBS: fasting blood glucose; GLUT-4: glucose transporter type 4; GSH: glutathione; HDL: high-density lipoprotein; IGF-I: insulin-like growth factor I; LDL: low-density lipoprotein; MDA: malondialdehyde; NA: nicotinamide; OCT-1: organic cation transporter; QUICKI: quantitative insulin sensitivity check index; SOD: superoxide dismutase; STZ: streptozotocin; TG: triglycerides; THP: Tamm–Horsfall protein.

5. Conclusions

Changes in the lifestyle of the population have increased chronic diseases worldwide. T2DM is a multifactorial metabolic disease, and new risk factors for it have been identified. The denominator of T2DM-related pathologies is a persistent state of hyperglycemia and dysregulation of other metabolites, such as lipids. Current drugs for treatment disclose various mechanisms of action, including enzymatic inhibitors, blockers of receptors, and stimulants of the release of insulin, among others. Infections are a common and severe sequel to diabetes and increase both morbidity and mortality in patients. The hyperglycemic environment causes immune system dysfunction in diabetic individuals. There are numerous synthetic compounds that help to control blood glucose levels and secondary infections. Examples of resistance to both antibiotics and insulin have been documented. Since ancient times, natural products have been utilized to exert therapeutic effects, and their structures can imitate or block the action of natural mediators in the human body. Recently, more attention has been given to validating natural compounds that can be added for the management of the hyperglycemic state. Diabetes is a metabolic disease that does not have a cure and is an irreversible condition, which is why more research in this field is urgently needed to understand the cellular and molecular mechanisms of its pathology and to propose new and effective ways to manage it. Future medications should be capable of providing multifaceted improvements to high blood glucose levels and to better control secondary infections attributed to immune system depression. However, even the most effective advances in therapy will not prove to be effective if people are unable to adapt to more healthy lifestyles. Overall, the traditional treatment of bacterial infections is the use of antibiotics; however, this can cause adverse effects and long-term bacterial resistance. In this work, effective alternatives have been presented to treat T2DM using medical plants. T2DM-associated infections can be indirectly prevented by reducing the state of hyperglycemia and, therefore, decreasing the susceptibility to infections using antidiabetic plants, and directly by utilizing antibacterial plants against bacterial infections.

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