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Diabetes mellitus: Strategies to delay the onset and its management options

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ABSTRACT: **Background:** Diabetes mellitus is a chronic disease caused by inherited and /or acquired deficiency in the production of insulin or ineffectiveness of the insulin. This life-long disease has been a source of concern since it affects mostly individuals in their reproductive age (45-64 years) and high risk of cardiovascular disease, blindness, kidney failure, lower limb amputation, nerve disease and fetal organ damage during pregnancy. Although, several agents are available for managing diabetes, there is absence of adequate information on the strategies for preventing, managing and treating the disease. **Discussion:** Herein, we gave an account of different strategies that can be adopted to prevent and manage diabetes mellitus. We indicated that strategies for preventing and managing diabetes include life style modifications, antioxidants, phytotherapy, pharmacological approach, reducing inflammatory mediators, targeting key carbohydrate metabolizing enzymes and gene therapy.**Conclusion:** These strategies can be adopted to reduce the high prevalence of diabetes and associated complications.

Keywords: Diabetes mellitus, Strategies, Prevention, Management options

Background:

Diabetes refers to a metabolic disorder characterized by relative or absolute deficiency of insulin secretion and/or insulin resistance [1]. The disorder is a worldwide public health problem and one of the main chronic syndromes currently affecting mankind, regardless of socioeconomic status and geographic location [2]. In almost all high-income countries, diabetes is a leading cause of cardiovascular disease (cardiomyopathy)**,** blindness (retinopathy)**,** kidney failure (nephropathy)**,** hepatopathy, nerve damage (neuropathy), blood vessel disease leading to heart attack or stroke and lower limb amputation [3, 4]**.** In addition, people with diabetes also have a higher risk of developing infections. Diabetes is also known to be one of the foremost causes of mortality and morbidity in the world [5]. The symptoms of diabetes mellitus include excessive thirst (polydipsia) and excessive hunger (polyphagia), frequent urination (polyuria), tiredness, drowsiness or fatigue, dry itchy skin, weight loss, slow healing of wounds and blurred vision. The prevalence of diabetes is increasing at a very alarming rate worldwide. In 2019, the global estimate was 463 million adults living with diabetes [4]. This has been projected to increase to 700

million by 2045. In Africa, a 2019 estimate of prevalence of diabetes puts it at 19.4 million and is projected to increase to 47 million by 2045. In Nigeria, the prevalence of diabetes in 2019 was put at over 2.7 million cases (20-79 years old) and this has been projected to double by 2045 [4]. Furthermore, one in 11 adults has diabetes in 2019 while in 2045, it is being projected to be one in 10 adults; one in two adults are living with diabetes that is yet to be diagnosed. Every 6 seconds, 1 person dies from diabetes mellitus that accounted for 5.0 million deaths in 2019 [4].

Diabetes mellitus is categorized into two major types, namely; insulin dependent diabetes mellitus (IDDM) or type I diabetes mellitus, which results from the body's failure to produce insulin [6], and non-insulin dependent diabetes mellitus (NIDDM) or type II diabetes mellitus, which results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with relative insulin deficiency [7-9]. Furthermore, gestational diabetes (due to insulin blocking hormones during pregnancy) develops in some women when they are pregnant. Most of the time, this type of diabetes goes away after the baby is born. However, gestational diabetes have a greater chance of developing into type 2 diabetes later in life. Less common types include monogenic diabetes, which is an inherited form of diabetes, and cystic fibrosis-related diabetes.

Diets with high carbohydrate content have been implicated as one of the major factors of that account for the high prevalence of diabetes mellitus. Other causes are genetic factors, obesity, auto-immune destruction of beta cells of the pancreas.

With this alarming prevalence and the consequences of the diseases, attempts at documenting information on various strategies that can be used to reduce not only the incidence of the disease, but also diabetes associated mortality cannot be over emphasized. The main goal of diabetes prevention, management and treatment is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, several strategies are employed to curtail diabetes and prevent or treat many complications that can result from diabetes and/or from its treatment. These strategies include:

(a) Life style modifications
(b) Antioxidant
(c) Phytotherapy
(d) Pharmacologic approach
(e) Targeting key carbohydrate metabolizing enzymes
(f) Reducing inflammatory mediators
(g) Gene therapy

Prevention Strategies

(a) Lifestyle modifications

Lifestyle modification involves altering long-term habits, typically of eating or physical activity, and maintaining the new behaviour for months or years. Lifestyle modification can be used to treat a range of diseases, including obesity and diabetes mellitus. There are essentially seven key self-preservation behaviors in patients with diabetes that predict healthy outcomes, namely: eating well, being physically active, monitoring blood sugar regularly, compliance and adherence to the medications prescribed, good problem-solving skills, healthy coping skills and risk-reduction behaviors. All these seven behaviors have proven to show a positive correlation with good glycemic control, reduction of complications and improvement in quality of life of diabetic patients. Individuals with diabetes have been shown to make a drastic impact on the advancement and development of their disease by partaking in their own care. Despite this fact, when looking at a longer-term change in individuals, compliance and adherence to these activities is incredibly low.

One of the essential focuses of preventing diabetes is the “ABCs” of diabetes management: A1c, blood pressure and cholesterol. Maintaining an A1c (test that indicates the average level of blood sugar over the past 2 to 3 months) level of about 7%, keeping the blood pressure <140/90mmHg, and

maintaining Low-Density Lipoprotein (LDL) at <100mg/dL (with no cardiovascular disease) and an LDL of <70mg/dL with any type of cardiovascular complications, are key proponents of diabetes prevention strategies, which is not only the responsibility of the healthcare provider and the medications prescribed to maintain, but the individual themselves. To achieve any of these goals, however, it is important to maintain an active lifestyle and to eat properly throughout the day. Evidence-based medicine and research has shown a strong trend towards patients taking control of the disease state in their own hands, but that means changing a mindset. Medication on its own will help, but without pursuing a balanced lifestyle, complications will continue to arise and the progression of the disease will go on. Maintaining an active lifestyle can be achieved through the following:

i. **Weight loss**: improves insulin resistance and reduces hypertension. People who are overweight or obese should therefore be encouraged to achieve and maintain a healthy body weight.

ii. **Physical activity (Exercise):** is one of the main pillars in the prevention of diabetes. Increased physical activity is important in maintaining weight loss and is linked to reduced blood pressure, reduced resting heart rate, increased insulin sensitivity, improved body composition and psychological well-being. Sedentary lifestyle is a powerful but modifiable risk factor for type 2 diabetes mellitus; therefore, moderate exercise is of utmost benefit in patients with diabetes since it facilitates glucose uptake into peripheral tissues for energy utilization [10, 11]. There are a few ways that exercise lowers blood glucose:

    - Insulin sensitivity is increased and the cells are better able to use any available insulin to take up glucose during and after the physical activity.
    - The contraction and relaxation of muscles during the physical activity will stimulate another mechanism that is completely separate of insulin. This mechanism allows the cells to take up glucose and use it for energy whether insulin is available or not.
    - When exercise is done on regular basis, it has the tendency to lower the Glycated hemoglobin (A1cs).

The goal here when adopting exercise as a preventive strategy for diabetes is to undertake at least 30 minutes of activity that makes the body sweat and the individual breathe a little harder most days of the week.

iii. **Balanced and Nutritious Diet:** Eating well is crucial for preventing diabetes since it is essential for health. No foods are strictly off-limits. Focus on eating only as much as the body needs. It is advisable to always eat plenty of vegetables, fruits, and whole grains. Choose non-fat dairy and lean meats. Limit foods that are high in sugar and fat and keep it about the same from meal to meal. In addition, dietary modifications can also be used to manage diabetes most especially Type 2. For Type 1 diabetics, there will always be a need for insulin injections throughout their life. However, both Type 1 and Type 2 diabetics can see dramatic effects on their blood sugars through controlling their diet, and some Type 2 diabetics can fully control the disease by dietary modification [12]. As diabetes can lead to many other complications, it is critical to maintain blood sugars as close to normal as possible and diet is the leading factor in this level of control [13]. Recent research shows that the first step in diabetes management should be for patients to be put on a low carbohydrate diet. Patients that are put on a high carbohydrate diet find it very difficult to maintain normal blood glucose levels. Patients that are put on a low carbohydrate or restricted carbohydrate diet, manage to maintain near normal blood glucose levels and Glycated hemoglobin (A1cs) [14]. Feeding pattern should include foods high in fruits, vegetables, low-fat dairy, whole grains, poultry, fish, nuts, low in

saturated fat, red meat, sweets, sugar-containing beverages, sodium as well as foods high in protein [15, 16].

iv. **Smoking**: This is a well-established risk factor for many chronic diseases, including diabetes and its complications. As well as other harmful effects, smoking increases abdominal fat accumulation, insulin resistance and makes it harder to undertake exercise. As a preventive strategy for diabetes, all smokers should be encouraged to quit smoking. However, weight gain is common when quitting smoking and therefore dietary advice on avoiding weight gain should also be given (e.g. managing cravings and withdrawal symptoms by using short bouts of physical activity as a stress-relief activity, rather than eating snacks).

v. **Stress and depression**: There is evidence of a link between depression and both diabetes and cardiovascular disease. When the body is stressed, the blood sugar level rises. As a preventive strategy, the individual should avoid stress, should not be too anxious as it is possible to forget to exercise, eat right or take the prescribed medications. Stress can be managed or relieved by taking deep breath, and /or engage in hobbies that will bring about relaxation of the body.

vi. **Sleeping patterns**: Both short (<6h) and long (>9h) sleep durations may be associated with a higher risk of developing type 2 diabetes. Sleep deprivation may impair the balance of hormones regulating food intake and energy balance. Long sleep durations may be a sign of sleep-disordered breathing or depression and should be treated appropriately.

vii. **Avoid alcohol consumption:** Avoiding excess alcohol may make it easier to control the blood sugar level of individuals. The American Diabetes Association advises that women who drink alcohol have no more than one drink a day and men who drink have no more than two.

viii. **Regular check-ups:** As a preventive strategy of diabetes, it is advisable to undertake regular check-ups at least twice a year to check up the levels of A1c (average blood sugar over 3 months), cholesterol and blood pressure. The individual should always go for full examination every year. Visit a foot doctor to check for problems like foot ulcers and nerve damage.

Finally, at present, type 1 diabetes cannot be prevented. Environmental factors and exposure to some viral infections have also been linked to the risk of developing type 1 diabetes. However, there is a lot of evidence that lifestyle changes (achieving a healthy body weight and moderate physical activity) can help prevent the development of type 2 diabetes.

Management Options
(b) Antioxidant Strategy

i. Oxidative Stress in Diabetes Mellitus

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the terms collectively used to describe free radicals and other non-radical reactive derivatives. Biological free radicals are highly unstable molecules which are products of normal cellular metabolism. They have electrons available to react with various organic substrates such as lipids, proteins and deoxyribonucleic acid (DNA) [17]. Numerous experimental evidences have highlighted a direct link between oxidative stress and diabetes through the measurement of oxidative stress biomarkers in both diabetic patient and rodents [18, 19]. A hyperglycemic state can lead to an increase in the levels of oxidative DNA damage markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG); lipid-peroxidation products measured as thiobarbituric acid-reactive substances (TBARS); protein oxidation products such as nitrotyrosine and carbonyl levels and also lower the activity of antioxidant enzymes. Cell

culture studies using pancreatic beta cells, aortic smooth muscle cells and endothelial cells have also provided evidence for an increase in ROS production in diabetes [20, 21].

Free radical formation in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress [18]. Free radical and oxidative stress induced complications from diabetes mellitus include coronary artery disease, Neuropathy, nephropathy, retinopathy [22] and stroke [23]. *In vivo* studies support the role of hyperglycemia in the generation of oxidative stress leading to endothelial dysfunction in blood vessels of diabetic patients [24]. Increase in the levels of glucose and insulin along with dyslipidemia in patients suffering from diabetes develops macroangiopathies that cause oxidative stress leading to atherosclerosis [25].

ROS level elevation in diabetes may be due to decrease in destruction or/and increase in the production by catalase (CAT-enzymatic/non-enzymatic), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) antioxidants. The variation in the levels of these enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications [26]. Therefore, a management strategy for diabetes would be to boost the antioxidant enzymatic/non-enzymatic defense system of the body of individuals. Antioxidants have already shown to be prospective in the treatment of diabetes both type 1 and type 2. Superoxide dismutase provides first line defense against ROS mediated cell injury by catalyzing the proportion of superoxide, the primary ROS in oxygen metabolism, to molecular oxygen and peroxide whereas catalase regulates hydrogen peroxide metabolism that can, in excess, cause serious damage to lipids, RNA and DNA. CAT converts H_2O_2 catalytically into water and oxygen and thus neutralizes it. Furthermore, glutathione peroxidase and glutathione reductase metabolizes peroxide (an oxidant) to water and converting glutathione disulfide back into glutathione [18].

ii. Pathways of Free Radical Generation in Diabetes Mellitus and its Complications

In diabetes, ROS is thought to be generated through increased polyol pathway [27], increased formation of advanced-glycation end products (AGEs) [28] and protein kinase C (PKC) activation [20] resulting in damage to macromolecules and organ malfunction.

Aldose Reductase Pathway

Aldose reductase is the rate limiting enzyme of the polyol pathway. This nicotinamide adenine dinucleotide phosphate NADPH-requiring aldose reductase, catalyses the reduction of glucose to sorbitol followed by the oxidation of sorbitol to fructose by NAD^+ dependent sorbitol dehydrogenase. At normal blood glucose concentration (5.5 mM), aldose reductase catalyzed reaction represents less than 3% of total glucose utilization [29]. However, hyperglycemia results in saturation of hexokinase and more than 30% of glucose is directed into the polyol pathway [30]. In a diabetic state, polyol pathway increases in tissues such as retina, kidney, peripheral nerves and blood vessels that do not require insulin for cellular glucose uptake [31].

The overall reaction of the polyol pathway leads to a reductive imbalance of NADPH and NADH due to a shortage of intracellular NADPH and a surplus of NADH. Increased NADH generation during conversion of sorbitol to fructose provides the substrate for NADH oxidase to generate ROS [32]. NADH serves as a source of electrons in complex 1 of the electron transport chain resulting in increased mitochondrial generation of superoxide radical. In diabetic cells, oxidative phosphorylation in mitochondria is enhanced due to increase flux of electron donors into the electron transport chain. This drives the inner mitochondrial membrane potential upward causing blockage of electron transfer within the complex III [33]. Electrons back up to coenzyme Q results and these electrons are transferred one at a time to molecular oxygen, generating superoxide. DNA damage by superoxide and peroxynitrite results in the activation of poly (ADP-ribose) polymerase (PARP), a DNA repair enzyme. PARP reduces the activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (an enzyme of the glycolytic pathway which catalyses the conversion of glyceraldehyde-3-phosphate to 1,3-biphosphoglycerate) by ADP-ribosylation [34, 35].

The polyol pathway also results in reduction in the bioavailability of NADPH. The reduced bioavailability of NADPH negatively affects the antioxidant defence system by depleting glutathione (GSH) a very important antioxidant. The polyol pathway serves as a main source of ROS generation in the retina [36]. In addition, sorbitol accumulation has been implicated in osmotic swelling of the eye lens and cataractogenesis [37].

In summary, aldose reductase normally reduces aldehydes generated by reactive oxygen species to inactive alcohol. When glucose concentration in the cell becomes too high, aldose reductase reduces that glucose to sorbitol. Sorbitol dehydrogenase then oxidises sorbitol to fructose. The buildup of sorbitol has damaging effects in cells, including osmotic damage, cataract formation and diabetic retinopathy. Therefore, the strategy to manage diabetes and its complications including formation of cataract and diabetic retinopathy would be to prevent the accumulation of fructose and sorbitol in the lens by way of reducing or inhibiting the activities of the first and the second enzymes of the polyol pathway, the aldose reductase and sorbitol dehydrogenase respectively. Aldose reductase inhibitors (ARI) comprise a variety of structurally different compounds like plant extracts, animal tissues or specific small molecules. In diabetic rats, plant flavonoids, such as quercetin or the isoflavone genistein, have delayed diabetic cataract formation [38, 39]. Flavonoids, such as those harboring 3-O-alpha-l-rhamnopyranosyl-(1-->6)-beta-d-glucopyranoside groups in their C rings, including kaempferol 3-O-alpha-l-rhamnopyranosyl-(1-->6)-beta-d-glucopyranoside and isorhamnetin 3-O-alpha-l-rhamnopyranosyl-(1-->6)-beta-d-glucopyranoside have been reported to exhibit the highest degree of rat lens aldose reductase inhibitory activity *in vitro* [40]. Examples of natural products with known AR inhibitory activity are extracts from indigenous plants like *Ocimum sanctum*, *Withania somnifera*, Curcuma longa, and *Azadirachta indica* [41]. Nonsteroidal anti-inflammatory drugs, such as sulindac, aspirin or naproxen have been reported to delay cataract in diabetic rats through a weak AR inhibitory activity [42-44].

Advanced Glycation End Products (AGEs) Formation Pathway

Glucose can react spontaneously with free amino groups of protein to form Schiff bases. These Schiff bases through complex reactions such as Amadori rearrangement, dehydration and condensation forms cross-linked heterogeneous fluorescent derivatives called advanced glycation
end products (AGEs). Advanced glycation end products constitute a heterogeneous group of molecules formed by non-enzymatic reactions of reducing sugars, ascorbate and other carbohydrates with amino acids, lipids and nucleic acids [45, 46]. Glycation end product adducts such as pyraline, pentosidine and N-Carboxy- methyl lysine are found to be elevated in diabetic tissues [47-49].

The mechanism by which glycation alters the cell functions include (i) denaturation and functional decline of the target protein and lipid, (ii) organopathy due to accumulation of AGEs in tissue, (iii) activation of receptor-mediated signal pathway in cells, (iv) generation of oxidative stress and carbonyl stress [50]. Protein glycation and formation of advanced glycation end products (AGEs) play an important role in the pathogenesis of diabetic complications like retinopathy, nephropathy, neuropathy, cardiomyopathy along with some other diseases such as rheumatoid arthritis, osteoporosis and aging. Increased renal AGE in diabetic animals and patients have been linked to structural abnormality observed in diabetic nephropathy such as mesangial expansion, glomerular basement membrane thickening glomerulosclerosis and tubulointerstitial fibrosis [51].

Advanced Glycation End Products level is increased with decreased renal function in type 1 diabetic patients [52]. Evidence from clinical studies indicates a correlation between progression of diabetic retinopathy and the level of AGE in serum and retinal blood vessels of diabetic patients [53]. High levels of serum AGEs have been documented in patients with type 2 diabetes mellitus and coronary heart disease [54]. Glycation increases susceptibility of low density lipoprotein (LDL) to oxidative modification which is considered a critical step in its atherogenicity [55].

Finally, the inhibition of AGEs formation is another mode for diabetes treatment, which is not dependent on the control of blood glucose, and would be useful in the prevention of certain diabetic complications [56].

Protein Kinase C (PKC) Activation Pathway

PKC activation is related to vasoconstriction, proliferation and overgrowth of smooth muscle cells as well as accelerated synthesis of extracellular matrix proteins, and thus plays significant roles in the onset and progression of vascular cell dysfunction in diabetes mellitus [57-59]. Two major pathways implicated in the activation of PKC in hyperglycemia are (a) persistent and excessive activation of several PKC isoforms result primarily from enhanced *de novo* synthesis of diacylglycerol (DAG) from glucose via increase in triose phosphate availability [35, 60-62] and (b) interaction between AGEs and their cell-surface receptors resulting in enhanced activity of PKC isoforms [63, 64].

PKC likely regulates diabetic complications on multiple levels such as activation of endothelial nitric oxide synthase (eNOS), NAD(P)H oxidase, phospholipase A2 (PLA2), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and by activating NF-KB [65].

Although, treatments for diabetic retinopathy have involved good metabolic control, laser photocoagulation and vitrectomy, the absence of satisfactory visual results have necessitated the exploit on the protein kinase c. Inhibitors of PKC such as Ruboxistaurin, an orally PKCβ inhibitor has demonstrated *in vitro* and *in vivo* benefits in diminishing cell and blood flow alterations related to hyperglycemia and has a potential use as a therapy for diabetic retinopathy with both anatomic and functional benefits. The ability of Ruboxistaurin in reducing visual loss in patients with diabetic retinopathy has also been demonstrated [66].

Antioxidants as Therapeutic Agents in the Management of Diabetes Mellitus

ROS has been implicated as a major cause of the metabolic memory after glucose normalization due to the chains of reactions leading to cell damage and loss of cellular function. The ability of ROS to directly oxidize and damage DNA, proteins, and lipids has implicated oxidative stress as a major 'player' in the onset and progression of late-diabetic complications [67]. In the absence of an appropriate condensation by antioxidant defense network, increased oxidative stress leads to activation of stress-sensitive intracellular signaling pathways and the formation of gene products that cause cellular damage and contribute to late diabetic complications [68-71]. Due to the implication of hyperglycemia-induced oxidative stress in diabetes, these patients should in theory benefit from antioxidant supplementation.

Therefore, the inhibition of intracellular free radical formation through the provision of antioxidants would provide a therapeutic strategy to prevent oxidative stress and related diabetic vascular complications. Antioxidants may act at different levels, inhibiting the formation of ROS and RNS or scavenge free radicals, or increase the antioxidants defense enzyme capabilities. Supplementation with antioxidants and/or factors essential to nitric oxide (NO) production may potentially improve endothelial dysfunction in T2DM by re-coupling eNOS and mitochondrial function, as well as decreasing vascular NAD(P)H oxidase activity [72]. However, for macrovascular/microvascular complications, the antioxidant therapy would be beneficial if both the blood pressure and optimal glucose level are controlled and there is adequate management of dyslipidemia [73].

Generally, antioxidants can be classified into enzymatic antioxidants and non-enzymatic antioxidant while the antioxidant therapy can be classified as antioxidant enzyme and substrates, biogenic elements, combined drugs, synthetic antioxidants, and drugs with antioxidant activity. The enzymatic antioxidant systems, such as copper, zinc, manganese superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase may remove the ROS directly or sequentially, preventing their excessive accumulation and consequent adverse effects while the non-enzymatic antioxidant systems consisting of glutathione, ubichinol, and uric acid or derivatives of the diet such as vitamins C and E, carotenoids, lipoic acid, selenium scavenge molecules that are endogenously produced [74]. Furthermore, exogenous antioxidants can compensate for the lower plasma antioxidant levels often observed in type 2 diabetes mellitus and in pre-diabetic individuals, whether their diabetes is primarily genetic in origin or due to obesity and a sedentary lifestyle [75]. In diabetes, the clinical benefits of Vitamin C (ascorbic acid) and vitamin E (tocopherol) lies in the ability of vitamin C to interact with glucose transporters and alter glucose homeostasis while vitamin D improve insulin sensitivity in animals [76]. Vegetables and fruits

have in their natural composition other substances besides these antioxidant vitamins, which guarantees health benefits associated with its consumption. These compounds are widespread in virtually all plant foods, often at high levels, and include phenols, phenolic acids, and flavonoids [77]. Flavonoids have been implicated to play positive roles in maintaining blood glucose levels, glucose uptake and insulin secretion and modulating immune function to prevent specific type of diabetes mellitus [78].

(c) Phytotherapy

Although, several anti-diabetic drugs are commercially available for treating diabetes mellitus, many of them are out of reach for a significant proportion of the population and are beset with some adverse effects [79]. The limitations and side effect of these conventional anti-diabetic drugs necessitate the search for alternative or complementary medicine that can enrich the therapeutic arsenal of diabetes mellitus. The use of medicinal plants and their phytochemicals for treating diabetes is not just a search for safer alternatives to pharmaceuticals, which transiently lower the blood glucose, preventing heart disease and high blood pressure, but also enhances the antioxidant system, insulin action and secretion [80].

Most of these plants have been found to contain secondary metabolites like glycosides, alkaloids, terpenoids, and flavonoids among others that are confer anti-diabetic activity on the botanicals. Different mechanisms of action have been identified for the beneficial effects of these plants in diabetes (Table 1). These include (i) rejuvenation of beta cells and stimulation of insulin secretion and insulin release from beta cells of islets, (ii) reduction in insulin resistance, (iii) blood glucose lowering effect, (iv) anti-oxidant activity and (v) anti-inflammatory action. The different types of secondary metabolites confer antidiabetic activity to the plants in various ways. Specifically, saponins stimulate insulin release from the pancreas while flavonoids are known to regenerate the damaged beta cells in the diabetic rats and acts as insulin secretagogues [81]. Furthermore, alkaloids exert anti-hyperglycemic activity by an extrapancreatic mechanism independent of insulin secretion [82]. Tannins have also been implicated to exhibit anti-diabetic activity through its glucose transport-stimulatory property [83].

(d) Pharmacological Approach

Insulin Therapy

Insulin is a peptide hormone secreted from the β-cells of pancreas in response to hyperglycemic condition [101]. Insulin is made up of two amino acid chains, A (acidic) and B (basic), joined by disulfide linkages. Insulin is a protein and is degraded in the gastro-intestinal tract; therefore insulin cannot be administered orally. It is administered subcutaneously in most cases and is the mainstay of therapy for individuals with type-1-diabetes [102]. Insulin is classified based on differences in molecular structures as rapid-acting, short acting, intermediate-acting or long-acting. Most diabetic patients require a combination of a shorter acting insulin to cover increased glucose levels after a meal and longer acting insulin to maintain a basal level. This is usually accomplished by giving twice-daily doses of intermediate-acting insulin combined with a rapid- or short acting insulin before breakfast and the evening meal [103].

Alternatively, a dose of long acting insulin is administered in the evening and doses of rapid acting or short-acting insulin are given before each meal. Insulin requirements change because of stress, infection, illness, emotional disturbances and pregnancy [102]. Adults should keep their blood glucose levels between 80 and 140 mg/dL before meals and at bedtime [104].

The injection site should be rotated frequently to prevent lipodystrophy which looks like lumps or small dents in the skin surface. Insulin is best absorbed from the abdomen, then the arms and legs and last the buttocks [102]. Rotating the injection sites within one body region for a period of time versus injecting in a different area of the body each day will decrease the variability in insulin absorption [105]. There is always a risk of hypoglycemia (low blood glucose) with insulin therapy [102].

Table 1: Selected Medicinal Plants with Scientifically Validated Anti-diabetic Activity

Botanical name	Family	Active constituents	Anti-diabetic Effects	References
Cochlospermum planchonii	Cochlospermaceae	Saponins	Reduces alloxan-induced hyperglycemia and metabolic disorders associated with diabetes	Yakubu *et al.* [84]
Leonotis leonurus	Lamiaceae	Total phenolics and falvonoids	Reduces streptozotocin-induced elevated blood glucose and dyslipidemia; potentiate insulin secretion	Oyedemi *et al.* [85]
Zingiber officinale	Zingiberaceae	Free and bound polyphenol	Ameliorated liver disorders caused by streptozotocin; has antiglycation and hypolipidemic and ameliorated pancreatic and renal derangement	Kazeem *et al.* [86]; Kazeem *et al.* [87]; Kazeem *et al.* [88]
Eugenia jambolana	Myrtaceae	Kaempferol, isoquercetin	Hypoglycemic, anti-hyperlipidemic, antioxidant effect	Rizvi and Mishra [89]
Ocimum sanctum L.	Lamiaceae	Tannins, saponins, terpenoids	Stimulates insulin secretion, anti-hyperglycemic	Pattanayak *et al.* [90]
Ficus exasperate	Moraceae	Saponins, flavonoids and alkaloids	Has antidiabetic activity and could be used to control metabolic disorders that characterize diabetes	Yakubu *et al.* [91]
Nigella sativa	Ranunculaceae	Alkaloids, thymoquinone	Anti-hyperglycemic, decreases oxidative stress and preserves pancreatic beta-cell integrity	Mathur *et al.* [92]
Fadogia agrestis	Rubiaceae	Saponins, alkaloids and flavonoids	Has antidiabetic activity and can be used to manage complications arising from diabetes	Yakubu and Ogunro [93]

Botanical name	**Family**	**Active constituents**	**Anti-diabetic Effects**	**References**
Senna fistula	Leguminosae	Alkaloids, flavonoids, saponins, terpenoids and fibres	Has anti-hyperglycemic activity and is effective in controlling some metabolic disturbances associated with diabetes	Ayinla *et al.* [94]
Senna alata	Fabaceae	Flavonoids, alkaloids, saponins, phenolics and tannins	Has anti-diabetic activity and enhanced the activity of hexokinase	Yakubu *et al.* [95]
Allium sativum	Amaryllidaceae	Allicin, allixin, ajoene	Improvement in insulin sensitivity, anti-hyperglycemic, anti-hyperlipidemic and antioxidant effect	Kavishankar *et al*. [96]
Gymnema sylvestre	Asclepiadaceae	Gymnemic acid, flavones	Anti-hyperglycemic, anti-inflammatory and hypolipidemic effect	Kanetkar *et al.* [97]
Tinospora cordifolia	Menispermaceae	Alkaloids, steroids, cardiac glycosides	Antioxidant activity, promotes insulin secretion, inhibition of gluconeogenesis and glycogenolysis	Saha and Ghosh [98]
Alarngium lamackii	Alangiaceae	-	Has anti-diabetic activity and antioxidant activity	Kumar *et al.* [99]
Andrographis paniculata	Acanthaceae	Andrographolide	Posses anti-diabetic activity and was effective in restoring the disturbed metabolic profile associated with diabetes	Akhtar *et al.* [100]

Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds, orienting across the cell membrane as a heterodimer ϖ It is oriented across the cell membrane as a heterodimer. The α subunits carry insulin binding sites, while the β subunits have tyrosine kinase activity. Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter GLUT4 to the plasma membrane. The second messenger PIP3 and certain tyrosine phosphorylated guanine nucleotide exchange proteins play crucial roles in the insulin sensitive translocation of GLUT4 from cytosol to the plasma membrane, especially in the skeletal muscles and adipose tissue. Over a period of time insulin also promotes expression of the genes directing synthesis of GLUT4. Genes for a large number of enzymes and carriers are regulated by insulin through Ras/Raf and MAP-Kinase as well as through the phosphorylation cascade.

Pramlintide

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is U.S. Food and-Drug Administration (FDA-approved for use in adults with type 1 diabetes. It has been shown to induce weight loss and lower insulin doses. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia [106].

Pancreas and Islet Transplantation

Pancreas and islet transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immuno-suppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management [106, 107]. Islet transplantation remains investigational. Auto-islet transplantation may be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis [106].

α-Glucosidase Inhibitors

Alpha-glucosidase inhibitors are oral antidiabetic drugs used for type 2 diabetes mellitus that work by preventing the digestion of carbohydrates (disaccharides to monosaccharide) [108]. Alpha-glucosidase inhibitors, such as acarbose and miglitol, are indicated in combination with sulfonylureas for the management of type 2 diabetes [109, 110]. These drugs do not target a specific pathophysiologic aspect of diabetes. This class of oral hyperglycemic agents competitively inhibits enzymes in the small intestinal brush border that are responsible for the breakdown of oligosaccharides and disaccharides into monosaccharides suitable for absorption [111]. It works primarily on α-glucosidase, which is found predominantly in the proximal half of the small intestine. The intestinal absorption of carbohydrates is therefore delayed and shifted to more distal parts of the small intestine and colon. This retards glucose entry into the systemic circulation and lowers postprandial glucose levels. Alpha-glucosidase inhibitors act locally at the intestinal brush border and are not absorbed. They are excreted in feces. The main side effects of α-glucosidase inhibitors are gastrointestinal; specifically, bloating, abdominal discomfort, diarrhoea and flatulence occur in about 20% of patients [110, 111].

Insulin Sensitizers (Thiazolidinediones)

Thiazolidinediones are a class of medications used in the treatment of type 2 diabetes mellitus [112]. They function as ligands for the peroxisome proliferator-activated receptor gamma (PPARγ), which is most highly expressed in adipocytes. These nuclear receptors, which are ligand-activated transcription

factors, play an integral part in the regulation of the expression of a variety of genes involved in carbohydrate and lipid metabolism [111].

Thiazolidinediones improve insulin sensitivity, particularly in the peripheral tissues. Although unproven, this appears to be mainly mediated through an effect on adipocytes, since there are fewer PPARγ receptors in muscle tissue. In the adipocyte, differentiation is enhanced, lipolysis is reduced, and levels of circulating adipocytokines or "adipokines" are altered, namely a decrease in tumour necrosis factor-α and leptin and an increase in adiponectin. All these effects decreased tumour necrosis factor-α and free fatty acid levels and increased adiponectin levels are expected to enhance insulin sensitivity [113].

Direct comparisons of thiazolidinediones with metformin and sulfonylureas also demonstrate similar efficacy. Preliminary data suggest that thiazolidinediones may have beneficial effects beyond that of glycemic control. These include reduced urinary albumin excretion, increased levels of high-density lipoprotein cholesterol and reduced triglyceride levels, lower blood pressure and reduced levels of plasminogen activator inhibitor-1 [112].

Biguanides

Biguanides are a class of drugs that function as oral antihyperglycemic drugs used for the management of type 2 diabetes mellitus or pre-diabetes treatment [114]. Over 30 years ago, various biguanides (e.g., metformin, phenformin, buformin) were used in different countries for the treatment of diabetes.

Metformin is the first-line medication for the treatment of type 2 diabetes. It works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues. The mechanisms by which metformin exerts its antihyperglycemic effects are still not entirely clear. Its major action on patients with diabetes is to decrease hepatic glucose output, primarily by decreasing gluconeogenesis, but it may also, as a lesser effect, increase glucose uptake by skeletal muscles [114]. Zhou *et al.* [115] discovered that metformin activates hepatic and muscle adenosine monophosphate-activated protein kinase (AMPK), an enzyme normally activated by adenosine monophosphate, the breakdown product of adenosine triphosphate and a cellular signal for increased energy requirements. Activation of hepatic AMPK results in the phosphorylation and inhibition of acetyl-coenzyme A carboxylase, which catalyzes the rate-limiting step of lipogenesis. This block in fatty acid synthesis promotes fatty acid oxidation.

Insulin Secretagogues

Insulin secretagogues are compounds that help the pancreas to synthesize and release (or secrete) insulin [116]. Insulin secretagogues can be divided into two subclasses: sulfonylureas and non-sulfonylureas.

Sulfonylureas are a class of organic compounds widely used in the management of type 2 diabetes. They act by increasing insulin release from the beta cells of the pancreas [117]. Sulfonylureas that are currently available are gliclazide, glimepiride, glyburide, and the older agents, chloropropamide and tolbutamide. The last two are now rarely used. Sulfonylureas bind to the sulfonylurea receptor on the surface of pancreatic β-cells. The sulfonylurea receptor is intimately involved with subunits of an adenosine triphosphate sensitive potassium channel (kir6.2). The binding of a sulfonylurea to the sulfonylurea receptor–kir6.2 complex results in closure of the potassium channels and inhibition of the efflux of potassium ions from the resting β-cell. This results in depolarization of the cell membrane and, in turn, the opening of voltage-dependent calcium channels. The influx of calcium causes microtubules to contract and the exocytosis of insulin from vesicles [111].

Sulfonylureas do not directly affect insulin sensitivity. The increase in insulin sensitivity seen after treatment with these drugs is secondary to improved metabolic control. Sulfonylureas are predominantly metabolized by the liver and cleared by the kidneys. Several metabolites of glyburide are partially active, so that if clearance is impaired in the kidney, the accumulating metabolites can have a significant hypoglycemic effect [117].

Non-sulfonylureas are involved in inhibition of the amount of glucose produced by the liver and increase the insulin-receptor binding as well as stimulate tissue uptake of glucose [118]. This relatively new class of medications is currently represented by nateglinide and repaglinide [118]. Repaglinide is a benzoic acid derivative, and nateglinide is a phenylalanine derivative [119]. The mechanism of action of these drugs is similar to that of the sulfonylureas (closure of the potassium-adenosine triphosphate channel, leading to calcium-dependent insulin secretion). However, they bind to the sulfonylurea receptor at a different site and with different kinetics than the sulfonylureas. Thus, the onset of action is faster and the half-life is shorter, which results in a brief stimulation of insulin release [119]. These compounds are metabolized in the liver through the cytochrome P_{450} system into inactive biliary products [119].

The efficacy of repaglinide appears to be similar to that of sulfonylureas; postprandial hyperglycemia is well controlled [118]. These medications can be used either as monotherapy or in combination with other OHAs (but not sulfonylureas) [111]. Figure 1 shows the causes of hyperglycemia and sites of action of oral hyperglycemic drugs.

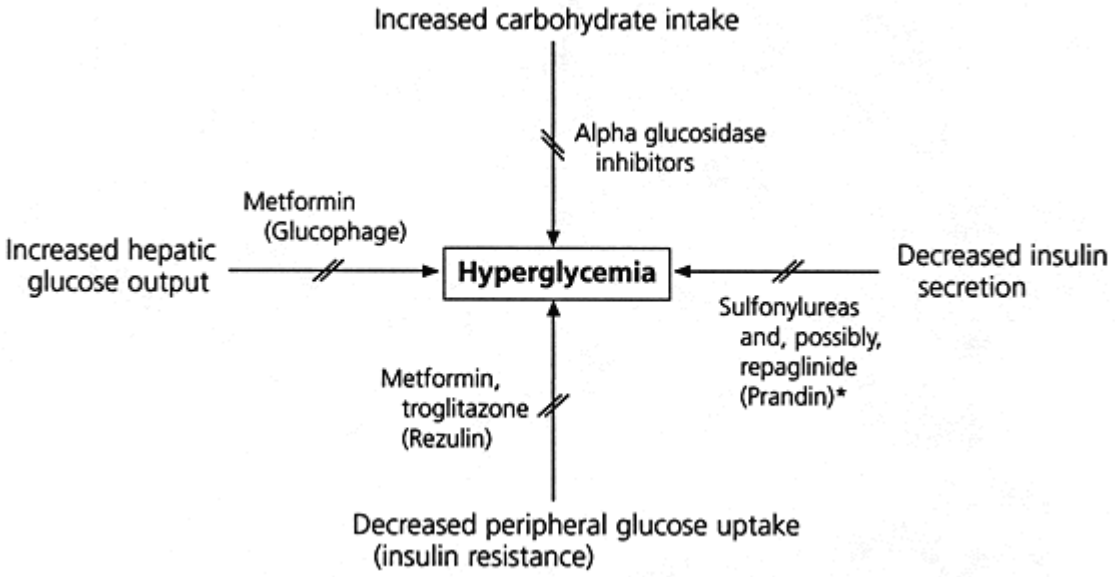

Figure 1: Causes of hyperglycemia and sites of action of oral antihyperglycaemic drugs
Source: Florence and Yeager [109]

Sodium-Glucose Co-transporter 2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in type 2 diabetes. There are three FDA-approved agents for patients with type 2 diabetes, but none are FDA-approved for the treatment of patients with type 1 diabetes [2]. The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic diabetic ketoacidosis) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis [120].

(e) Targeting key carbohydrate metabolizing enzymes
Reduction of Glucose-6-phosphate dehydrogenase inhibition

Glucose-6-phosphate dehydrogenase (G6PD) is the first and rate-limiting enzyme of the pentose phosphate pathway, which results in the production of ribose-5-phosphate and nicotinamide adenine

dinucleotide phosphate-reduced (NADPH). The entire antioxidant system as well as other reductant-requiring process, relies on adequate supply of NADPH because it is the principal intracellular reductant for all cells [121]. Several authors have also reported that G^PD is the principal source of NADPH and therefore, any decrease in the activity of G6PD will consequently lead to decreased NADPH and make cells very sensitive to oxidative damage [121, 122]. In addition, any changes in G6PD activity will alter NADPH levels and impact the antioxidant system [123]. Xu *et al.* [121] in their conclusion suggested that chronic hyperglycemia leads to a decrease of G6PD activity in the kidney cortex, which leads to increased oxidative stress. This acquired inhibition in diabetic kidneys may partly be due to decreased expression and increased phosphorylation of G6PD caused by the activation of protein kinase A (PKA). Therefore, a strategy for the prevention of diabetic complication most especially nephropathy would be to explore agents that can enhance the activity of G6PD which will reduce the oxidative stress that eventually leads to diabetic complications in animals.

Inhibition of a-amylase activity

Carbohydrates are the major constituents of the human diet and mainly play a role in the energy supply. These complex components of dietary carbohydrates are broken down to monosaccharides by the α-amylase and glucosidases since it is only in this form that they can be absorbed from intestinal lumen and transported into blood circulation [124]. Alpha-amylases constitute a family of endoamylases that catalyze the cleavages of α-D-(1-4) glycosidic bonds hydrolyzing carbohydrates into glucose and thus elevating the level of glucose in diabetic patients [125]. Retardation of carbohydrate digestion by inhibition of enzymes such as α-amylase would lead to reduction in the level of blood glucose and hence could be considered as a therapeutic strategy for the treatment of diabetes. Alpha-amylase inhibitors therefore have a therapeutic role in the management of diabetes. The inhibition of pancreatic alpha-amylase is one of the therapeutic targets for delaying oligosaccharide digestion to absorbable monosaccharides in the intestinal brush border, resulting in reduced postprandial hyperglycemia [126]. Alpha-amylase inhibitors currently in clinical use to reduce or delay the digestion of carbohydrates and provide short-term glycemic control include acarbose and miglitol. The shortcoming associated with these α-amylase inhibitors is their non-specificity in targeting different glycosidases and have also been reported to produce serious side effects such as hypoglycemia, diarrhea, flatulence, and bowel bloating that limit their use as a therapeutic drug [111].

Inhibition of glucokinase activity

Glucokinase is a unique isoform of the hexokinase enzymes, which are known to phosphorylate D-glucose and other hexoses. Glucokinase (hexokinase IV) has a major role in the control of blood glucose homeostasis because it is the predominant hexokinase expressed in the liver and also has a very high control strength on hepatic glucose disposal [127]. It serves as a glucose sensor of the insulin-producing pancreatic islet β-cells, controls the conversion of glucose to glycogen in the liver and regulates hepatic glucose production [128]. Glucokinase is currently considered a strong candidate target for antihyperglycemic drugs for type 2 diabetes [128]. This is supported by the impact of mutations in the glucokinase gene on blood glucose concentration in humans. Inactivating mutations that lower the enzyme affinity for glucose or compromise glucokinase expression cause diabetes (maturity onset diabetes of the young type 2), whereas activating mutations lower blood glucose [128]. Pharmacological activators of glucokinase (GKAs) that mimic the effect of activating mutations represent a potential novel strategy for antihyperglycemic therapy [128, 129].

Fructose-1,6-bisphosphatase activity

Fructose-1,6-bisphosphatase is an enzyme that converts fructose-1,6-bisphosphate to fructose-6-phosphate in gluconeogenesis and the Calvin cycle which are both anabolic pathways. Overproduction of glucose via gluconeogenesis is a principal cause of the high blood glucose levels found in patients with type 2 diabetes, and is inadequately controlled by currently available medications. The enzyme fructose-

1,6-bisphosphatase (FBPase), a major control point in the pathway of gluconeogenesis, is recognized as an attractive target for pharmacological intervention [130]. The strategy here is to explore the activator of the enzyme, fructose-1,6-bisphosphatase which will enhance the rate of clearance of glucose, the causative agent of diabetes mellitus.

(f) Inflammatory mediators

Inflammation is considered to be a key regulator of the pathogenesis of type 2 diabetes mellitus, but what triggers this inflammation still unknown [131]. However, it is possible that obesity might be a contributory factor. Obesity is associated with enlargement of adipose tissue and consequently increases the number of adipose tissue macrophages [132]. These macrophages are responsible for almost all adipose tissue tumor necrosis factor-α (TNF-α) expression, significant amounts of interleukin-6 (IL-6), and other acute-phase response markers and mediators of inflammation [133]. Many pro-inflammatory cytokines play a central role in inflammatory reaction and have been reported to increase the risk of type 2 diabetes [134]. These pro-inflammatory cytokines can enhance insulin resistance directly in adipocytes, muscle and hepatic cells, leading to systemic disruption of insulin sensitivity and impaired glucose homeostasis. Increased levels of these pro-inflammatory cytokines can also lead to hepatic production and secretion of acute-phase proteins such as C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), amyloid-A, 1-acid glycoprotein, and haptoglobin which have been reported to appear in the early stages of type 2 diabetes, and their circulating concentrations increase as the disease progresses [131, 134]. TNF-α, secreted by adipose tissue, may play a critical role in insulin resistance and the pathogenesis of type 2 diabetes. The strategy here would be explore anti-inflammatory agents through multiple mechanisms that may include inhibiting the activation of NF-κB signaling pathway, as target in the management of diabetes.

(g) Gene therapy

Gene therapy is an experimental technique that uses gene to treat or control prevent diseases. Technology for gene therapy is advancing rapidly such that there are multiple pathways possible to support endocrine function, with potential to practically cure diabetes [135, 136]. Gene therapy can be used to manufacture insulin directly. An oral medication, consisting of viral vectors containing the insulin sequence is digested and delivers its genes to the upper intestines. Those intestinal cells will then behave like any viral infected cell, and will reproduce the insulin protein. The virus can be controlled to infect only the cells which respond to the presence of glucose, such that insulin is produced only in the presence of high glucose levels. Due to the limited numbers of vectors delivered, very few intestinal cells would actually be impacted and would die off naturally in a few days. Therefore, by varying the amount of oral medication used, the amount of insulin created by gene therapy can be increased or decreased as needed. As the insulin-producing intestinal cells die off, they are boosted by additional oral medications [135, 137].

Gene therapy might eventually be used to cure the cause of beta cell destruction, thereby curing the new diabetes patient before the beta cell destruction is complete and irreversible [138]. Gene therapy can be used to turn duodenum cells and duodenum adult stem cells into beta cells which produce insulin and amylin naturally. By delivering beta cell DNA to the intestine cells in the duodenum, a few intestine cells will turn into beta cells, and subsequently adult stem cells will develop into beta cells [137]. This makes the supply of beta cells in the duodenum self replenishing, and the beta cells will produce insulin in proportional response to carbohydrates consumed [139].

Conclusion

Diabetes is a high rising disease with its attendant consequences that include weight loss, organ dysfunction, other complications and mortality. As a result, efforts should be geared at arresting this deadly disease by preventing the onset and adequate management strategies that include life style modifications, use of antioxidants, phytotherapy (the use of medicinal plants), pharmacologic approach, targeting key carbohydrate metabolizing enzymes, reducing the generation of inflammatory mediators and gene therapy.

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EAB conceived the manuscript, ADM wrote the first draft, MTY finalized the draft, EAB proofread the manuscript. All authors participated in the writing of the report and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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