

Review

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[Filomena Carvalho](#) , Filipa Branco , Radhia Aitfella Lahlou , Paula Pires , Manuel Salgado , [Luís R. Da Silva](#) *

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Review

Natural Functional Beverages as an Approach to Manage Diabetes

Filomena Carvalho ¹, Filipa Filipe ¹, Radhia Lahlou ¹, Paula Pires ¹, Manuel Salgado ¹
and Luís R. Silva ^{1,2,3,*}

¹ CPIRN-UDI/IPG—Centro de Potencial e Inovação em Recursos Naturais, Unidade de Investigação para o Desenvolvimento do Interior do Instituto Politécnico da Guarda, Guarda, Portugal.

² CICS-UBI—Health Sciences Research Center, University of Beira Interior, Covilhã, Portugal

³ University of Coimbra, CIEQPF, Department of Chemical Engineering, Rua Sílvio Lima, Pólo II—Pinhal de Marrocos, 3030-790 Coimbra, Portugal

* Correspondence: luisfarmacognosia@gmail.pt

Abstract: Diabetes mellitus is a chronic disease, commonly associated with unhealthy habits and obesity, and it is becoming a serious health issue worldwide. As a result, new approaches to treat diabetes are required, and a movement towards more natural ones is emerging. Consuming fruit and vegetables is advised to prevent diabetes since they contain several bioactive compounds. A simple and effective strategy to include them in the diets of diabetic and obese people is through beverages. This review aimed to report the anti-diabetic potential of different vegetable and fruit beverages. These functional beverages demonstrated *in vitro* potential to inhibit α -glucosidase and α -amylase enzymes, and to improve glucose uptake. *In vivo*, the beverage consumption showed a reduction of blood glucose, increase of insulin tolerance, improvement of lipid profile, control of obesity, and reduction of oxidative stress. This suggests the potential of vegetable and fruit-based functional beverages to be a natural innovative therapy for the management of diabetes.

Keywords: diabetes mellitus; functional beverages; fruits; vegetables; phenolic compounds; anti-diabetic activity

1. Introduction

Over the last few years, the market for functional foods has been growing and developing very quickly, due to the increased prevalence of lifestyle diseases and to the awareness of the importance of a healthy lifestyle by the general public [1].

Chronic diseases are long-lasting illnesses that can be caused by a combination of genetic, physiological, environmental, and behavioral factors; they include cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes [2]. Chronic diseases can be prevented and controlled but cannot be cured [3]. According to the World Health Organization (WHO), having a healthy diet throughout life helps to prevent these noncommunicable diseases, which are the world's biggest killers [4].

The prevalence of diabetes has shown a worldwide increase, from 4.7 in 1980 to 8.5% in 2014, with about 422 million people having the disease in that year [5]. As of 2021, more than half a billion people lived with diabetes [6]. The association between diet and chronic disease is well known; in particular, diets low in glycaemic index and carbohydrates and high in vegetables are associated with a more effective control of type 2 diabetes (T2D) [7].

The consumption of functional foods may be a good approach to promote healthy habits, due to their ready availability and disease-preventing characteristics [3]. There are many different types of functional foods on the market right now, including dairy foods, baked goods and cereals, baby foods, confectionary, meat products, snacks and ready meals, spreads, and beverages. The benefits of functional beverages include the ability to add desired bioactive components; reduced production

costs; simplicity in handling of the cold chain during storage, and a greatest acceptance by the consumers [8].

Fruits and vegetables, which can be part of those functional beverages, contain many bioactive compounds, including polyphenols, vitamins, minerals, and pectins, which stimulate insulin secretion and successfully reduce the blood level of glucose, being also able to inhibit carbohydrate absorption in the small intestine [9–12]. The United States Department of Agriculture (USDA) recommends five to nine servings per day; the WHO recommends at least 400 g of fruits and vegetables every day [13]. Functional beverages developed from different fruit and vegetable blends fit in well with consumer expectations for distinctive but nutritious products [14]. Therefore, the current work reviews the scientific advances made in the last 13 years, regarding the use of functional beverages made from fruits and vegetables against the long-term condition diabetes.

2. Diabetes

Diabetes is a serious public health problem with a negative impact on socioeconomic development, mortality, and disability on a global scale [15]. In line with the 2011 Political Declaration on the Prevention and Control of NCDs, diabetes is one of the top five noncommunicable illnesses (NCDs) that need to be controlled [16]. Diabetes is likely to have affected 537 million people worldwide in 2021, and 700 million people are predicted to have the disease by 2045 [17]. It is a chronic disease characterized by high levels of blood glucose (hyperglycaemia), which leads over time to serious damage to the heart, veins, eyes, kidneys, and nerves [5]. Insulin is responsible for the removal of glucose from the blood by cells of the liver and muscles, followed by glucogenesis [18]. Thus, this dangerous, chronic condition develops either when the pancreas does not produce enough insulin or when the body is unable to effectively use the insulin that is produced [19].

Type 1 diabetes (T1D) is characterized by deficient insulin production in the body. To control the level of glucose in their blood, people with T1D need to take insulin daily. They cannot live without it [5]. The destruction of the pancreatic β -cells is what leads to this deficit in insulin production, which may be acquired or epigenetic (autoimmunity/mutation) [20]. Aside from frequent urination and thirst, other symptoms include excessive hunger, weight loss, visual problems, and exhaustion [5]. The risk factors of this type include autoimmune, genetic and environmental factors, and there is no known way of prevention [21]. Children and teenagers are the most affected by T1D [5]. The European Region has the largest number of children and teenagers with T1D, totaling over 296,500 [22,23].

T2D is seen as a lifestyle disease because it is a result of obesity, poor eating habits, and stress and is accountable for more than 90% of the cases of diabetes [24]. T2D is also associated with a prolonged increase in blood glucose levels, which may have two causes: flaws in insulin secretion, because of impaired β -cell function, or in its receptor (insulin resistance) [25]. Exogenous insulin may be necessary for T2D patients even if they frequently do not need it, if diet and oral hypoglycaemic medicines are insufficient for controlling blood glucose levels. The symptoms of T2D are similar to those of type 1, however, they are frequently absent or milder, making the diagnosis more difficult [5]. According to WHO, the greater risk factor for developing T2D is being overweight or obese; a poor diet, inactivity, high blood pressure, and a family history of diabetes are also typical determinants of the disease [5]. Patients with T2D are prone to various types of immediate and long-term problems, including malignancies, microvascular disorders (retinopathy, nephropathy, and neuropathy), and macro-vascular diseases (hypertension, hyperlipidaemia, heart attacks, coronary artery disease, strokes, and peripheral vascular disease) [26].

Over the past few decades, there has been an increase in the prevalence of T2D worldwide, primarily as a result of sedentarism and a decrease in the nutritional value of diets, which leads to an increase in overweight and obesity [27]. Over 1 million deaths were brought on by this illness in 2017.

In the European Region, there are about 60 million people with diabetes, with about 10.3% of them being men and 9.6% women, aged 25 years and over [29]. In Portugal, there were more than 1 million diabetic people between the ages of 20 and 79 in 2018, indicating a prevalence of 13.6%.

The early diagnosis (with the measurement of HbA1C values, the fasting blood sugar, or the random blood sugar test, according to the Centers for Disease Control and Prevention (CDC) guidelines [30]) and control of blood sugar, blood pressure, and cholesterol management can prevent or delay the consequences linked to diabetes [21].

Patients with T2D must follow a low-calorie diet and regularly engage in physical activity, otherwise, pharmaceutical therapy might be needed [31]. In the current market, few therapeutic drugs have been introduced to regulate blood glucose metabolism to a normal state. The cost of treating diabetes and its complications is unpredictably high [32]. Particularly, the treatment plans used to try to manage diabetes are the use of hypoglycaemic medications, insulin injection, as well as surgical therapies (bariatric) [24]. However, synthetic medications such as metformin cause adverse effects such as nausea, vomiting, and gastrointestinal disorders [33]. Therefore, the development of affordable and effective diabetes therapies with fewer adverse side effects is a challenge and highly demanded [32].

3. Functional Beverages

People are now more recognizant of the value of their diet's nutritional content [34]. Functional beverages contain bioactive components that come from plants, animals, and microorganisms [35] and they include phenolic compounds, minerals, vitamins, amino acids, peptides, unsaturated fatty acids, and others [36]. To increase the favourable consumer perception of functional beverages, researchers are focusing on enhancing the stability of the active ingredients by encapsulation, emulsion, and high-pressure homogenization procedures.

3.1. Definition and Types

Currently, there is no universal or legislative definition for the term "functional food". Nevertheless, by Regulation (EC) No 1924/2006 of 20 December 2006, functional foods contain nutrients or other substances like vitamins, minerals, amino acids, essential fatty acids, fibre, or plants and herbal extracts that exert a nutritional or physiological effect on consumers [37].

Functional foods are categorically different from nutraceuticals, pharmafood, and nutritional supplements; as a result of their health-promoting properties, which are frequently disease-prevention rather than therapeutic qualities, they are categorized as food rather than pharmaceutical drugs [38]. In that regard, functional foods and beverages must be consumed in average portions as part of a "normal" diet, in order to have a beneficial effect [39].

In general, a functional food or beverage can be any of the following: a natural food or beverage; a food or beverage to which a component has been added; a food or beverage from which a component has been removed; a food or beverage whose composition has been altered; a food or beverage in which the bioavailability of an active agent has been modified; or any combination of all of the above [40]. Beverages are a convenient way to consume food and other substances, as well as a good method for dissolving active chemicals.

According to Corbo et al., functional beverages fall into three categories: sports and energy drinks, dairy-based beverages (including probiotics and minerals-enriched drinks), and beverages made from vegetables and fruits [8]. Fresh milk, fermented milk, and yoghurt drinks are the most popular dairy-based beverages, and they are excellent carriers of probiotics. Sports drinks are flavoured drinks that are meant to be consumed prior to or during exercise to hydrate the body, supply carbohydrates, electrolytes (such as sodium, potassium, calcium, and magnesium), and occasionally, vitamins or other minerals. The main ingredient in energy drinks is typically caffeine, which is intended to improve performance, concentration, and endurance [8]. This last group of beverages imposes a risk on human health, giving sports drinks' high amounts of sugar and acidic additives, which cause tooth erosion and decay. Also, the high amount of carbohydrates in these drinks causes gastrointestinal disorders, with water retention in the intestines, and causing obesity and damage to the liver. Energy drinks contain guarana and caffeine, which cause lipogenesis: the excess fat accelerates its accumulation in the liver, leading to insulin resistance [41]. Especially for

children and adolescents, the high caffeine levels in energy drinks may have several negative effects [42]. Thus, the consumption of this type of drinks must be moderated.

This review will focus on the properties of beverages made from vegetables and fruits, which have a high concentration of bioactive compounds that may be beneficial in several health issues [14].

3.2. Market of Functional Foods and Beverages

Functional foods have undoubtedly been identified as the top trend in the food industry, despite the lack of clarity for the data on global sales, resulting from the non-existence of a clear definition for them [43]. The market for functional foods and beverages was valued at \$240.20 billion in 2017, and from 2022 to 2027 it is estimated an increase of \$132.84 billion [44]. The global market for functional beverages is now dominated by enhanced water, dairy-based beverages, energy drinks, sports drinks and functional fruit juices (Figure 1A) [45]. The production and the consumption of functional beverages have significantly increased as a result of rising urbanization, middle-class population growth, an increase in dual-income households, growing health concerns, and significant contributions to disease prevention and health promotion [36]. The global functional beverage market was valued at \$131.47 billion in 2022, the Asia Pacific dominated the worldwide market (Figure 1B) [46]. The need for functional foods varies substantially from country to country in Europe. The market's growth has been comparably consistent and profitable, accounting for 16% of global sales. The largest source of income is the United Kingdom, which contributes 20% of total revenues [43].

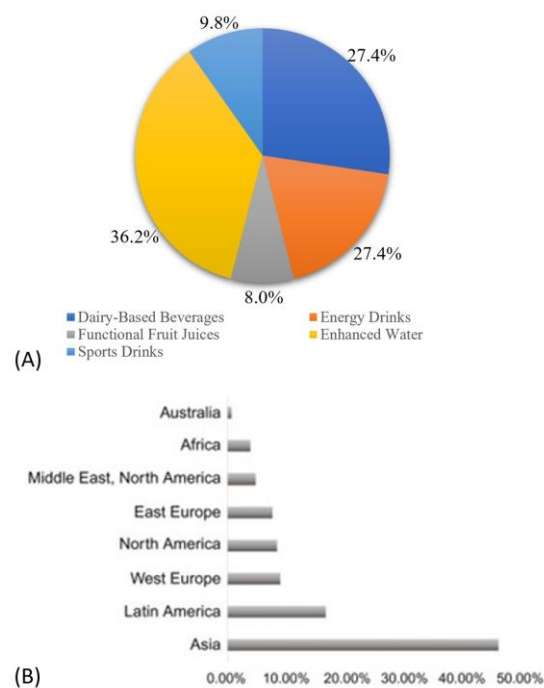


Figure 1. (A) Worldwide market of some selected popular beverages in 2019 [45]; (B) global beverage consumption forecast 2021 [46].

4. The Role of Fruit and Vegetable-Based Functional Foods and Beverages against Diabetes

Since functional foods are very rich in health-promoting bioactive compounds, particularly antioxidants, which actively participate in vivo in modulating disease development by inhibiting ROS-mediated reactions, they may help control diseases like cancer, coronary heart disease, and diabetes [3,54]. Increasing clinical evidence shows that regular consumption of foods that affect glycaemic control, blood pressure regulation, activation of antioxidant enzymes, gut microbiota, and suppress excessive production of pro-inflammatory cytokines during diabetes can prevent or delay T2D and its associated complications in high-risk individuals [48]. The use of functional foods as a

complementary therapy for the prevention and management of diseases has progressively grown over the past few decades as a strategy to boost health and psychological well-being. Additionally, this strategy has been used increasingly frequently by patients who want to get rid of the adverse effects of traditional medicine as well as the symptoms of chronic illnesses [49].

Fruits and vegetables are crucial components of a healthy diet, since they have a low-calorie density and help provide nutrients like vitamins, minerals, dietary fibre, and bioactive substances. They have attractive colours and flavours and are very hydrating and filling. Their consumption can help replace diets high in salt, sugar, or saturated fats, prevent chronic noncommunicable diseases like heart disease, cancer, diabetes, and obesity and address micronutrient deficiencies. FAO/WHO recommend a minimum population target of 400 g/day of fruit and vegetables (excluding tubers), or five servings of 80 grams each [50]. At all ages, they promote bodily functioning, development, and the physical, mental and social well-being. Besides lowering the risk of non-communicable diseases, they can prevent several types of malnutrition, including undernutrition, micronutrient deficiencies, overweight, and obesity. Together with malnutrition, unhealthy diets are among the top ten risk factors for disease globally [57,58].

Li et al. have found that an increment in the intake of fruits and green leafy vegetables, according to previous studies, is associated with a lower risk of developing T2D [53]. According to Anderson et al., fruits and vegetables have a preventive impact on diabetes because of antioxidants such as polyphenols [54]. The majority of secondary metabolites in plants are phenolic compounds, a diverse category of substances that includes simple flavonoids, phenolic acids, complex flavonoids, and coloured anthocyanins [61,62]. According to Survary et al., fruits and vegetables have a hypoglycaemic effect that is attributed to their insulin-like activity [57]; Jayaprakasam et al. and Wedick et al. suggest that this activity may also be due to the increase of insulin secretion by the bioactive compounds anthocyanins and anthocyanidins (insulin secretagogues) [64,65]. The phenolic antioxidants found in berries, in particular, have a significant potential to manage T2D by controlling hyperglycaemia and the microvascular problems associated with cellular oxidative damage, as well as macrovascular complications, such as hypertension [56].

The research on fruit- and vegetable-based functional beverages and their direct or indirect effects on diabetes, conducted since 2010, is reviewed in the sections that follow. The anti-diabetic effects of functional beverages described in these studies are summarized in Figure 2.

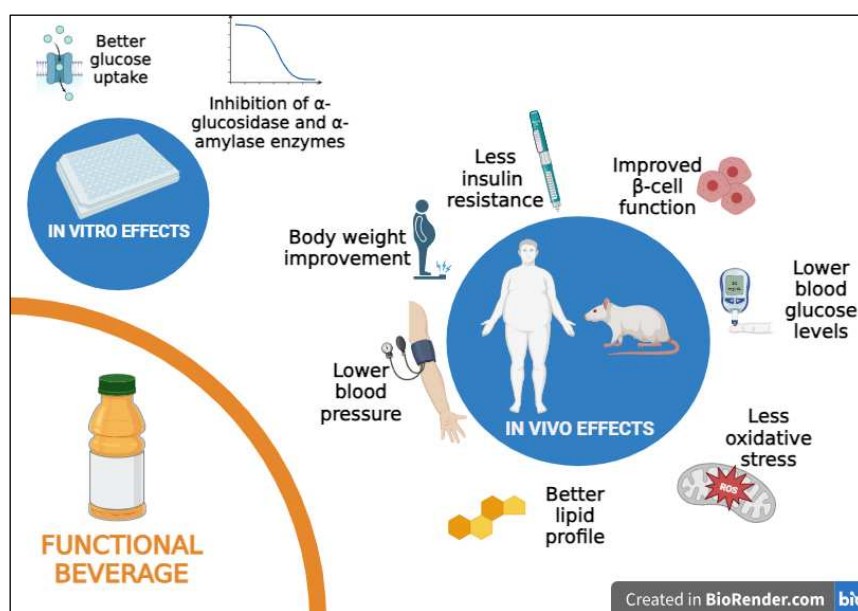


Figure 2. In vitro and in vivo diabetic effects of natural functional beverages.

4.1. In Vitro Studies with Functional Beverages and Diabetes

According to several authors, functional beverages could represent a cutting-edge strategy for managing diabetes. Table 1 summarizes studies that show natural functional beverages have an inhibitory effect on α -glucosidase and/or α -amylase enzymes. These enzymes break down polysaccharides into glucose [13]. Values of inhibition of α -glucosidase and α -amylase were reported in a range from 6.12 to 98.6% and 20.03 to 60.14%, respectively [13,66,67]. There are ranges for the IC₅₀ of 1 to 40.68 and 0.25 to 71.28 mg/mL [68–70]. These results vary depending on the concentration and administered amounts of the studied functional beverage. The small intestine's α -amylase enzyme is crucial for the breakdown of starch into glucose and maltose, increasing the postprandial glucose levels. According to Ujiroghene et al., blocking or lowering this enzyme's ability to digest starch may aid the management of diabetes [63]. However, excessive inhibition of α -amylase is not advised, since it could result in too much undigested carbohydrate in the colon, which could promote unfavourable bacterial fermentation and cause flatulence and diarrhoea [65]. α -Glucosidase is another key enzyme that catalyses the final step in the digestive process of carbohydrates, and its inhibition could similarly delay the digestion of oligosaccharides and disaccharides to monosaccharides, diminishing glucose absorption and hence reduce postprandial hyperglycaemia [66].

According to Badejo et al., the phenolics and flavonoids present in the beverages may be responsible for the inhibitory effect on these enzymes. Polyphenolic compounds may bind covalently to α -amylase and alter its activity, because they can form quinones or lactones that react with nucleophilic groups on the enzyme molecule [61].

Therefore, a viable therapeutic strategy for the treatment of diabetes is the regulated inhibition of the enzymes α -amylase and α -glucosidase by the chemicals included in these natural functional beverages.

The sea-buckthorn-based smoothies from Tkacz et al.'s study demonstrated inhibition of the pancreatic lipase, primarily due to polymeric procyanidins found in the buckthorn fruit. This inhibition was in addition to the inhibition of α -amylase and α -glucosidase enzymes [13]. The pancreatic lipase is an enzyme that breaks down triglycerides into bioavailable fatty acids and monoglyceride/glycerol molecules, and so its inhibition is responsible for the reduction of energy intake, which can facilitate the control of diabetes [67].

To examine the antidiabetic potential of fruit juices, Mahmoud et al. and Zhong et al. tested the glucose uptake after the consumption of a *Momordica charantia* juice and probiotics-fermented blueberry juices, respectively [70,74]. The glucose uptake assay is used to evaluate the antidiabetic activity of compounds that increase glucose uptake. The consequences of diabetes are caused by high blood glucose levels, which must be reduced to prevent them [69]. The *M. charantia* juice was able to stimulate the glucose uptake by diaphragms from diabetic rats, especially when combined with the administration of insulin; this may be related to the increase of the tissue's sensitivity to insulin, and the potentiation of its action, with charatin being the compound responsible for the diabetic potential of the fruit [68]. Probiotics-fermented blueberry juices also promoted glucose consumption of HepG2 cell lines, showing the potential of phenolic compounds to prevent the progression of obesity and hyperglycaemia [64]. It was discovered by Castro-Acosta et al. that apple and blackcurrant polyphenols decrease both sodium-dependent and -independent glucose uptake in Caco-2 cells, a model for human enterocytes [70]. The apple extract may have inhibited the glucose transport in the small intestine since in Caco-2 cells, a reliable in vitro model of the human enterocyte, the same extract dose-dependently decreased the total glucose absorption and sodium-independent glucose uptake.

This demonstrates the in vitro anti-diabetic effects of juices and drinks made from fruits and vegetables (Table 1). There is further work to be done in the areas of novel beverages, fruits and vegetables with anti-diabetic properties, and most critically, clinical trials to prove these claims. The existing in vivo research is covered in the following section.

Table 1. Reported in vitro assays for anti-diabetic properties of different fruit and vegetable-based functional drinks, since 2010.

Beverage	Assays	Results	Reference
Fermented bitter gourd juice	α -glucosidase inhibition (measured as glucose production reduction)	↓ glucose production = 14.5 - 19.2 %	[60]
<i>Prunus</i> fruit smoothies	α -amylase and α -glucosidase inhibition	IC ₅₀ amy = <1.00 - 8.03 mg/mL IC ₅₀ gluco = 1.20 - 6.94 mg/mL	[62]
Bitter gourd fruit juice	Glucose uptake by diaphragms from diabetic rats	Glucose uptake (absence of insulin): ↑ 1.40 mg/g tissue Glucose uptake (presence of insulin): ↑ 4.08 mg/g tissue	[68]
Apple and blackcurrant polyphenol-rich drinks	Glucose uptake by Caco-2 cells	↓ glucose uptake (apple polyphenols) = 46 - 51% IC ₅₀ (blackcurrant polyphenols) = 0.51 - 0.63 mg/mL	[70]
Fermented sprouted quinoa yoghurt beverages	α -amylase inhibition	IC ₅₀ amy (100 μ L) = 30.48 - 39.36 mg/mL IC ₅₀ amy (200 μ L) = 39.44 - 51.57 mg/mL IC ₅₀ amy (400 μ L) = 50.06 - 71.28 mg/mL	[63]
Tigernut beverages fortified with extracts of <i>Vernonia amygdalina</i> and <i>Momordica charantia</i>	α -amylase and α -glucosidase inhibition	Inhibition amy = 20.59 - 60.14 % Inhibition gluco = 38.82 - 75.54 %	[61]
Probiotics-fermented blueberry juices	α -amylase and α -glucosidase inhibition Glucose uptake by HepG2 cells	IC ₅₀ amy = 0.25 - 2.67 mg/mL IC ₅₀ gluco = 1 - 40.68 mg/mL ↑ glucose uptake \approx 1 mmol/L	[64]
Sea-buckthorn based smoothies	α -amylase, α -glucosidase and pancreatic lipase inhibition	Inhibition amy = 20.03 - 49.82 % Inhibition gluco = 6.12 - 98.61 % Inhibition lipase = 50.80 - 96.31 %	[13]

Amy = α -amylase; gluco = α -glucosidase.; IC₅₀ = half-maximal inhibitory concentration; ↑ = increase; ↓ = decrease

4.2. In Vivo Studies and Clinical Trials with Functional Beverages and Diabetes

Some in vivo research has been done for the anti-diabetic properties of functional beverages (Table 2). Rats are a suitable animal model used to understand the mechanisms of diabetes, with streptozotocin and alloxan being the most common chemical agents applied for the induction of diabetes in rats [71]. Several studies have examined the effectiveness of various functional beverages in preventing diabetes in streptozotocin or alloxan-induced diabetic rats. Other studies have also induced obesity in rats, with the administration of a high-fat diet, to test the vegetable and fruits' effect on the development of diabetes in obese mice.

Diabetes is characterized by increased fasting blood glucose, hyperinsulinemia, and insulin resistance [72]. Diabetes is indicated by a fasting plasma glucose level >126 mg/dL, or casual plasma glucose >200 mg/dl [73]. In these investigations, the fruit juices' capacity to lower hyperglycaemia was frequently reported as a reduction in the fasting blood, plasma, or serum glucose levels. For instance, Ariviani et al. showed the hypoglycaemic effect of a pigeon pea beverage in diabetic rats, due to the antioxidant compounds that possess the ability to scavenge free radicals, which improves insulin secretion and, as a result, decreases blood glucose levels [74]. According to Mahmoud et al.'s hypothesis, the *M. charantia* in the fruit juice has the ability to decrease the blood glucose in diabetic rats by stimulating the surviving β -cells to release more insulin [68].

Insulin resistance is defined by compensatory hyperinsulinemia, due to a decreased sensitivity of target tissues such as skeletal muscle, the liver, and adipose tissue to insulin [75]. In an attempt to counteract hyperglycaemia, increased insulin production results in hyperinsulinemia [76]. Some functional drinks mentioned in Table 2 have the ability to reduce insulin resistance [74,82-85]. A tomato and vinegar beverage improved postprandial glucose levels with decreased plasma insulin levels, demonstrating the reduction of insulin resistance. This was attributed to the reduction of free fatty acid concentration in obese rats, which induces hepatic fat accumulation, leading to a decrease

in insulin sensitivity and the production of glucose. Numerous secondary disorders, such as obesity, cardiovascular problems, hypertension, hypertriglyceridemia, and atherosclerosis, are mostly attributed to insulin resistance [80]. To prevent diabetes and the associated metabolic disorders, treatments that can boost insulin sensitivity and reduce endogenous insulin levels are suitable approaches [81].

In diabetics, the body loses the ability to produce insulin, which is caused by pancreatic β -cell apoptosis or insulin resistance [82]. Some of the functional beverages under study increased insulin synthesis in diabetic rats, which may be useful for identifying a solution to the insulin deficiency issue [74,83,89–91].

In Diabetes mellitus, hyperglycaemia and dyslipidaemia coexist. Diabetes can benefit from a medication that also regulates abnormal lipid levels [84]. A high consumption of fruits and vegetables has been linked to decreased plasma lipid levels [86]. Several studies with fruit/vegetable juices have demonstrated an improvement in the lipid profile of diabetic rats. In a study performed by Swami et al. a fermented *Syzygium cumini* stem beverage decreased the total, LDL, and VLDL cholesterol, as well as serum triglycerides, with an increase in HDL cholesterol [85]. This effect may be related to the beverage's proanthocyanins and flavonols composition, which have been shown to regulate cholesterol levels, and quercetin, which lowers triglyceride levels. According to Mahmoud et al., *M. charantia* fruit juice has lipid-lowering properties [68]. In this study, the juice was able to significantly reduce the total cholesterol and serum triglyceride levels, while elevating the levels of serum HDL cholesterol. This hypolipidemic effect may be due to the control of hydrolysis of certain lipoproteins, and the selective uptake and metabolism by different tissues. Additionally, insulin inhibits adipose tissue hormone-sensitive lipase, which slows lipolysis and prevents the mobilization of peripheral depots. It is possible that this fruit mimics the action of insulin/have a synergistic effect, explaining this anti-hyperlipidaemic effect. A method to modify blood lipids is necessary to lessen the risk of problems and the progression of diabetes, since high levels of total cholesterol and triglycerides may lead to cardiovascular complications.

Obesity is a very common metabolic condition that is brought on by an abnormal buildup of adipose tissue in the body. As obesity progresses, T2D and the associated health problems [87]. As shown by several authors [82–84,94], several functional beverages have helped obese rat models lose body weight. In the study assessed by Seo et al., the decreased body weight was explained by a significant decrease in triglyceride excretion in the group that consumed tomato vinegar beverages [78]. On the other hand, weight loss from the degeneration of adipocytes and muscular tissues to make up for the body's energy loss caused by frequent urination and excessive glucose transferred from glycogen, is a crucial aspect of managing Diabetes mellitus. A few studies have shown a control of body weight loss in diabetic rats by different fruit/vegetable drinks [36,80,85,95,96].

Diabetes and its complications are thought to be caused by oxidative stress, which can be a mediator of insulin resistance and its progression to glucose intolerance [91]. Malondialdehyde (MDA) is a biomarker for oxidative stress in Diabetes mellitus, linked to lipid peroxidation; a high plasma level of this marker indicates low antioxidant status [74]. The *M. charantia* fruit juices of Mahmoud et al. and Gao et al. were able to mitigate oxidative stress, as shown by the reduction of MDA levels [74,85]. Ariviani et al. found that giving diabetic-hypercholesterolemic rats a pigeon pea beverage reduced their MDA levels [74].

Other important factors involved in diabetes development can be regulated by the consumption of these functional beverages. For example, some studies in rat models have described decreases in the blood pressure [82,98] and glycated haemoglobin (HbA1c) levels [76]; an increase in glucokinase (GCK) activity [84,90], and β -cell function [68]. HbA1c levels reflect the average blood glucose concentration over the past few weeks [5]. Reduced GCK activity has been associated with poor pancreatic β -cells insulin production and glucose tolerance [77].

In a different approach, Leow et al. investigated the molecular mechanisms of the anti-diabetic effects of palm fruit juice [93]. The treatment of T2D-induced rats with this juice led to the downregulation of genes involved in insulin signalling, which leads to the down-regulation of enzymes related to the development of insulin resistance. This is encouraging, because this route

could be a target for modifying ageing and chronic diseases [93]. According to Iwansyah et al., drinking fruit juice from *Physalis angulata* L. increases the expression of the GLUT-4 gene in diabetic rats [90]. GLUT-4 mediates the circulation, glucose reduction, and the body homeostasis, and its inappropriate translocation is caused by damaged insulin responders/signalling [100,101].

As the next step, a few clinical studies have been performed to assess the effect of functional beverages in diabetic patients. Banihani et al. reported a decrease in fasting serum glucose and ~~in~~ insulin resistance in patients with T2D, 3 hours after the consumption of fresh pomegranate juice, at 1.5 mL/kg of body weight. In addition, they reported an increase in β -cell function. The main compounds responsible for the antidiabetic activity of this beverage are aglycones and other phenolic compounds originated from the degradation of glycosidic momordicoside [96]. In a clinical study performed by Devaki & Premavalli, 6 months of daily consumption of 45 mL of a bitter gourd fermented beverage (equivalent to a dose of 18 mg of phenols, 129 mg of quinine and small quantities of 5 different vitamins every day) in diabetic subjects led to an improvement of diabetes' symptoms. There was a with a significant reduction of fasting blood glucose, postprandial blood glucose, and HbA1c levels [97]. The blood lipid profile remained the same. The authors claim that bitter gourd contains a lectin with activity similar to insulin, contributing to its hypoglycaemic effect. It also contains polypeptide-P, an insulin-like substance that decreases blood sugar levels.

A clinical trial with the daily consumption of a beverage enriched with 333 mg of polyphenols from cranberry and strawberry, for 6 weeks, on 116 insulin-resistant individuals, revealed an improvement in insulin sensitivity; however, the beverage did not affect the lipid profile or markers for oxidative stress and inflammation [98]. According to the author's results and research, doses of polyphenols lower than 800 mg have metabolic benefits. Kim et al. tested the modulation of lipid and glucose metabolism, and of oxidative stress and inflammation by a beverage made with açai, which is rich in anthocyanins like cyanidin 3-O-rutinoside and cyanidin 3-O-glucoside. 37 individuals with metabolic syndrome were randomized and drank 325 mL of the beverage with 1.139 mg/L gallic acid equivalents of total polyphenolics (or a placebo control), twice a day for 12 weeks. At the end of the study, the plasma level of interferon-gamma (IFN- γ) and urinary level of 8-isoprostane (inflammatory response and oxidative stress biomarkers, respectively) were significantly decreased, which contributes to reduce the risk of developing chronic diseases. However, glucose and lipid-metabolism biomarkers were not affected [99]. According to a case report stated by Aktan et al., the daily consumption of *Vaccinium corymbosum* juice for 2 years by a 75-year-old pre-diabetic patient induced profound hypoglycaemia. The serum glucose values were at a level of 30 mg/dl after the episode, and the patient had drunk up to 500 mL of the juice 1-2 hours before. After discontinuing the consumption of the beverage for 6 months, the levels were upped to 105 mg/dl [100]. This suggests the important role of the *V. corymbosum* juice in lowering the serum glucose levels. Hasniyati et al. reported that functional yogurt containing bengkuang and tape ketan hitam was able to decrease the MDA levels of T2D patients, after 2 weeks of daily consumption by a group of 46 people, but had no impact on fasting blood glucose levels [101]. Lastly, drinks rich in apple and blackcurrant polyphenols had a diabetic-preventing effect, by lowering postprandial plasma glucose levels, C-peptide, GIP, and insulin in 25 healthy men and women, 30 minutes after the daily dose of 1200 mg apple polyphenols or 600 mg apple polyphenols + 600 mg blackcurrant anthocyanins drinks. The apple component of the beverages was rich in phlorizin (151 and 76 mg in the first and second drinks, respectively). The triglyceride levels stayed the same) [70].

Up to date, not enough clinical trials have been performed to infer about a specific dose of a compound necessary to have a specific anti-diabetic effect. Adding to that, complex polyphenol combinations present in fruit extracts may be responsible for these effects, due to additive or synergistic actions [70]. A study demonstrated that a daily dose of 320 mg of anthocyanins has positive effects in dyslipidemia and insulin resistance in diabetic patients [102]. However no specific dose is yet clearly defined, and there is a need for further research.

Table 2. Reported in vivo assays for anti-diabetic properties of different fruit and vegetable-based functional drinks, since 2010.

Beverage	Administration	Relevant results	Reference
<i>Emblica officinalis</i> fruit juice	1 ml/kg, daily, 8 weeks in STZ-DR	↓ serum glucose, FBG, TAG, TC, VLDL-C ↑ serum insulin, FBI, HDL-C, LDL-C	[83]
Fermented noni fruit juice	1.5 µL/kg, 2xday, 12 weeks in HFD-OR	↓ body weight, FBG, insulin resistance ↑ insulin, glucose tolerance	[77]
<i>Musa sapientum</i> lyophilized stem juice	50 mg/kg, daily, 2 weeks in STZ-DR	↓ FPG, PPG, HbA1c, TC, LDL-C, VLDL-C, TAG, G6P, HMG-CoA ↑ insulin, HDL-C, GCK activity	[84]
Processed tomato-vinegar beverage	14 ml/kg, daily, 6 weeks in HFD-OR	↓ TAG, body weight, insulin resistance ↑ glucose tolerance, HDL-C, GCK activity	[78]
Fresh pomegranate juice	1.5 mL/kg, once, in T2D patients	↑ β-cell function ↓ FPG, insulin resistance	[96]
Bittergourd fermented beverage	45 ml, daily, for 1 and 6 months in diabetic patients	↓ FBG and PPBS (1 month) ↓ FBG and PPBS, = blood lipid profile, ↑ HbA1c (6 months)	[97]
Grapefruit sweetened juices	2-3 ml, daily, for 2 weeks in HFD-OR	↓ body weight, FBG, FSI, liver TAG	[88]
<i>Vaccinium corymbosum</i> infusion	Cup of juice, daily, for 2 years, in a pre-diabetic	↓ serum glucose, HbA1c, insulin resistance	[100]
Palm fruit juice	170-720 mg GAE/kg, daily, for 4-36 weeks in CS-DR	↓ blood glucose, TAG, TC, liver lipids = body weight	[89]
Palm fruit juice	HC diet + 5.4 g GAE/kg, 4 weeks in DR	upregulation of 71 genes (HDL apolipoproteins hepatic detoxification) downregulation of 108 genes (insulin signalling and fibrosis)	[93]
Apple and blackcurrant polyphenol-rich drinks	200 g, once, in healthy patients	↓ PPG, insulin, C-peptide, GIP = TAG	[70]
Fermented <i>Syzygium cumini</i> stem	4ml/kg, daily, for 30 days in STZ-DR	↓ FBG, TC, LDL-C, serum TAG, AI, VLDL-C ↑ serum insulin, HDL-C	[85]
<i>Momordica charantia</i> fruit juice	10 ml/kg, 14 days before diabetes and 21 days after, in STZ-DR	↓ serum glucose, insulin resistance, serum TC, TAG, pancreatic MDA ↑ serum insulin, β-cell function, HDL-C, TAOC, pancreatic GSH	[68]
Strawberry and cranberry polyphenols beverage	333 mg polyphenols, daily, for 6 weeks, in insulin-resistant patients	↑ insulin sensitivity = lipids and markers of inflammation and oxidative stress	[98]
Cowpea juice, tomato juice and green apple juices combined	Combinations, daily, for 28 days in ALL-DR	↓ FBG	[33]
Pigeon pea beverage diluted in water	2.7 g/kg, daily, for 2 weeks in DHR	↓ plasma glucose, TC, MDA = body weight	[74]
Açaí beverage	2x325 mL, daily, for 12 weeks, in patients with metabolic syndrome	↓ IFN-γ plasma level, 8-isoprostane = lipid and glucose metabolism markers	[99]
Fermented <i>Momordica charantia</i> juice	10 mL/kg, daily, for 4 weeks in STZ-DR	↓ body weight loss, blood glucose, FBG, serum insulin, insulin resistance, TC, LDL-C, TAG, MDA ↑ HDL-C	[79]
Fermented jackfruit leaf beverage	1.5 mL/kg, daily, for 28 days in STZ-DR	↓ FBG, body weight loss, relative organ weights	[32]
<i>Emblica officinalis</i> fruit juice	2 ml/kg, daily, for 42 days in DR; for 4 weeks in HF-DR	↓ body weight, FBG, insulin resistance, HbA1c, TAG, blood pressure; TC = HDL-C	[76]

Citrus concentrate enriched with b-cryptoxanthin, hesperidin and pectin	2 mL, daily, for 8 weeks in HF-PDR	↑ glucose tolerance ↓ plasma glucose, plasma insulin, TAG, LDL-C, VLDL-C, blood pressure = TC, HDL-C	[92]
<i>P. angulata</i> fruit extract	1 and 2 mL/kg, daily, for 2 weeks in STZ-DR	↓ FBG, upregulation of GLUT-4, restoration of damaged organs = body weight	[90]
Yogurt bengkung tape ketan hitam	200 mL, daily, for 2 weeks in T2D patients	= FBG ↓ plasma MDA	[101]

T2D = type 2 Diabetes; PD = pre-diabetic; GAE = gallic acid equivalents; FBG = fasting blood glucose; FPG = fasting plasma glucose; PPG = postprandial plasma glucose; FSI = fasting serum insulin; TAG = triglycerides; DHR = diabetic-hypercholesterolemia rats; IFN = interferon-gamma; MDA = malondialdehyde; GIP = Gastric inhibitory polypeptide; AI = atherogenicity; TAOC = total antioxidant capacity; GSH = reduced glutathione; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol; GCK = glucokinase; G6P = glucose-6-phosphatase; HMG-CoA = HMG-CoA reductase; ↑ = increase; ↓ = decrease; = means maintenance of levels.

An interesting aspect to consider is the positive effect of some studied fermented beverages. A protective effect of alcoholic beverages has been found against diabetes, when the consumption is light to moderate [103]. According to Conigrave and Rimm, the consumption of a small amount of alcohol may even be beneficial in the control of cardiac complications of diabetes, as long as it is done in low doses, in order to avoid hypoglycemia or poor glycemic control [104]. This highlights the potential of functional beverages to exert beneficial health effects, even if they have alcohol in their composition, provided the consumption levels are controlled.

The carbohydrate content of different fruit and vegetable juices may be an important factor in the effects of their consumption. Fruit juice composition varies depending on the species or variety of fruit, its maturity, and the environmental and climatic factors of the growing season [105]. Fruit juices with sorbitol and a fructose-to-glucose ratio greater than 1 are more likely to result in carbohydrate malabsorption, which can induce diarrhea and stomach pain [106]. For example, white grape juice has an almost equal amount of glucose and fructose and does not contain sorbitol, the same for orange juice; for pear and apple juices, they have a higher concentration of fructose than glucose, and contain sorbitol. The carbohydrate composition of the first-mentioned juices favours carbohydrate absorption [106]. This is an important aspect to consider when choosing the type of foods used to produce functional beverages, when directed to the control of diabetes.

Despite the interesting results from our study, we need to take into account the disadvantages of consuming juices instead of whole fruits and vegetables. Unlike fresh fruit, fruit juices are not a good source of fibers, are less satiating and usually have a high sugar content [107], therefore, their consumption should not substitute the consumption of fresh fruit and vegetables, but should be used as an extra means of ensuring a healthy and balanced diet [108]. Also, the safety of the consumption of these types of foods must be guaranteed with the use of preservation methods that increase the stability of their shelf life [43].

5. Conclusions and Future Perspectives

Diabetes mellitus is a common metabolic disorder with many complications, and it has been increasing worldwide with lifestyle trends, mainly poor eating habits that cause obesity. The current options for the treatment of diabetes have undesired side effects; more natural and safer alternatives are becoming popular among the community for the control of this and other diseases.

Fruit and vegetables consumption is beneficial for health and highly advised by health organizations. Beverages like juices and smoothies are an easy and pleasant way to include these foods in our diet, and they have bioactive compounds, mainly polyphenols, that enhance health properties. Therefore, this review has been done regarding the effect of fruit and vegetable-based natural functional beverages on the management of diabetes. Several natural juices have been tested for anti-diabetic properties, both *in vitro* and *in vivo*. From the *in vitro* perspective, they have shown

properties such as the ability to inhibit α -glucosidase and α -amylase enzymes, and improvement of the glucose uptake by different organs. In vivo studies have evidenced many interesting anti-diabetic effects, such as the reduction of blood glucose, increase of insulin tolerance, improvement of lipid profiles, control of obesity and reduction of oxidative stress. This highlights the potential of natural beverages, even when alcoholic, as novel anti-diabetic agents. In order to control these issues, it could be interesting to introduce this type of product into the diets of diabetics or even obese people who are at risk for the disease.

In the future, new beverages need to be developed and tested, with focus on foods that are rich in bioactive compounds and anti-diabetic properties. However, the safety of the regular consumption of these products needs to be assessed and well-defined beforehand. More clinical trials need to be done to test the actual effects in humans. It would also be interesting to evaluate the use of these functional beverages as a complement for the existent diabetes treatments, with the need to assess possible synergistic (or antagonistic) effects between other medications and these foods. From the perspective of the circular economy, making beverages from fruits and vegetables that are too unattractive to sell and typically end up in the trash would be a smart move to reduce food waste while also increasing cost efficiency.

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