Review

Preventive Epigenetic Mechanisms of Functional Foods for Type 2 Diabetes

Bilyaminu Abubakar [1,2], **Dawoud Usman** [2,3], **Kamaldeen Olalekan Sanusi** [2,3], **Nur Hanisah Azmi** [4] and **Mustapha Umar Imam** [2,5,*]

1 Department of Pharmacology and Toxicology, Usmanu Danfodiyo University, Sokoto P.M.B. 2346, Nigeria
2 Centre for Advanced Medical Research and Training, Usmanu Danfodiyo University, Sokoto P.M.B. 2346, Nigeria; sanusikamaldeen@yahoo.com (K.O.S.)
3 Department of Physiology, Usmanu Danfodiyo University, Sokoto P.M.B. 2346, Nigeria
4 Faculty of Food Science and Nutrition, Universiti Malaysia Sabah, Kota Kinabalu 88400, Malaysia
5 Department of Medical Biochemistry, Usmanu Danfodiyo University, Sokoto P.M.B. 2346, Nigeria
* Correspondence: mustyimam@gmail.com

Abstract: Type 2 diabetes (T2D) is a growing global health problem that requires new and effective prevention and management strategies. Recent research has highlighted the role of epigenetic changes in the development and progression of T2D, and the potential of functional foods as a complementary therapy for the disease. This review aims to provide an overview of the current state of knowledge on the preventive epigenetic mechanisms of functional foods in T2D. We provide background information on T2D and its current treatment approaches, an explanation of the concept of epigenetics, and an overview of the different functional foods with demonstrated preventive epigenetic effects in T2D. We also discuss the epigenetic mechanisms by which these functional foods prevent or manage T2D, and the studies that have investigated their preventive epigenetic effects. In addition, we revisit works on the beneficial influence of functional foods against the programming and complications of parentally-triggered offspring diabetes. We also suggest, albeit based on scarce data, that epigenetic inheritance mechanistically mediates the impacts of functional nutrition against the metabolic risk of diabetes in offspring. Finally, our review highlights the importance of considering the preventive epigenetic mechanisms of functional foods as a potential avenue for the development of new prevention and management strategies for T2D.

Keywords: diabetes; epigenetic inheritance; functional foods; intergenerational

1. Introduction

1.1. Background on Type 2 Diabetes and Its Treatment Approaches

Diabetes is the seventh-leading cause of global mortality, and has surpassed pandemic proportions. From less than 1 million deaths in the year 2000, the disease was responsible for almost 7 million deaths in 2021 [1]. Type 2 diabetes (T2D) is specifically characterised by high levels of glucose in the blood resulting from a combination of factors, including insulin resistance, a decrease in insulin secretion, and an increase in glucose production by the liver [2]. T2D causes significant morbidity and mortality worldwide, and is associated with a number of serious health complications, such as cardiovascular disease, kidney disease, and blindness [3,4].

Owing to the fact that a high consumption of unhealthy diets, and sedentary lifestyles have been greatly implicated, the current treatment approaches for T2D include lifestyle modifications (e.g., healthy diet and physical activity), oral medications, and insulin therapy [5,6]. Lifestyle modifications are considered the cornerstone of T2D management, and are often the first line of treatment for individuals with prediabetes or newly diagnosed T2D. In addition to lifestyle changes, oral medications, such as metformin, sulfonylureas,

and dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used to improve insulin sensitivity, increase insulin secretion, and decrease glucose production [7,8]. For individuals who require more intensive therapy, insulin therapy may be recommended.

While these traditional approaches have been effective in managing T2D, they have limitations, and may not be effective for all individuals. As such, there is a growing interest in developing alternative strategies for preventing and managing T2D, including the use of functional foods with demonstrated preventive epigenetic effects [9].

Even though the disease has no known cure, a combination of lifestyle modification and drug therapy in diagnosed individuals has shown great success in reducing mortality and increasing quality of life. More important, as advocated by the World Health Organisation, is the preventive narrative in reducing the global burden of the disease. Diet has been a cornerstone in the prevention of diabetes since the era of classical Greece, as declared in the tenet "Let food be thy medicine and medicine be thy food", by Hippocrates.

1.2. Dietary Lifestyle as a Risk Factor for Type 2 Diabetes

The risk of developing type 2 diabetes has been largely linked to either environmental, lifestyle, or genetic factors [10]. Concrete data have linked lifestyle factors such as diet [11], heavy smoking [12], opioid use [13], physical inactivity (sedentarism), obesity [14,15], and alcoholism [16,17] to type 2 diabetes. Individual diets (food) and some dietary combinations have the potential to differentially impact the risk of developing type 2 diabetes [18,19]. Numerous studies have shown that the type of food people consume could be associated with the development of diabetes. In a cross-sectional study, Shu et al. demonstrated an association between consuming a Western diet, and the risk of type 2 diabetes mellitus among middle-aged Chinese adults [20]. Moreover, several cohort and preclinical studies have highlighted diet as a contributory factor in the predisposition to type 2 diabetes mellitus [11,21–23]. A high-fibre diet, low glycaemic index diet, and high amylose diet have been associated with a lesser predisposition to type 2 diabetes, when compared to their counterparts [24–26]. Nuts have also been shown to be beneficial in preclusion to type 2 diabetes. On the other hand, refined grains and sugar-sweetened beverages tend to promote a predisposition to type 2 diabetes [27]. For instance, clinical trials of short- and medium-term durations on postprandial glucose excursion in normal patients, insulin sensitivity in obese patients, and glucose handling in diabetic patients confirmed the superiority of a whole-grain diet over refined grains in maintaining a near-euglycemic state [28]. Studies have also shown that people who consume fermented dairy products are less likely to develop type 2 diabetes than those who consume non-fermented ones [29,30].

1.3. The Concept of Epigenetics, and Its Role in Chronic Diseases

Epigenetics is the study of changes in gene function that occur without a change in the underlying DNA sequence [31]. These changes are caused by modifications to DNA and its associated proteins, such as histones, which play a crucial role in regulating gene expression. There are several different types of epigenetic modifications, including DNA methylation, histone modification, and non-coding RNA-mediated regulation, all of which can have a significant impact on gene expression [32]. Epigenetic changes can occur in response to a variety of environmental and lifestyle factors, such as diet, physical activity, and exposure to toxins. These changes can be transmitted from one generation to the next, and may play a key role in the development and progression of chronic diseases, including T2D [33].

Studies have demonstrated that epigenetic changes can lead to alterations in the expression of genes involved in glucose metabolism, insulin secretion, and inflammation, which are all important factors in the development and progression of T2D [34]. Additionally, epigenetic changes can increase the risk of T2D by altering the expression of genes involved in fat metabolism, which can lead to obesity and insulin resistance [35]. Epigenome-wide association studies have substantially linked DNA methylation to diabetes [35]. Using human pancreatic islets, Daneshpajooh et al. also demonstrated that diabetes and impaired

insulin secretion could result from epigenetic modifications that alter gene expression [36]. In addition, epidemiological findings in offspring born to Dutch Hunger Winter mothers during World War II have provided some evidence of the predisposition to diabetes due to intra-uterine perturbations [37]. On the other hand, several pieces of evidence also highlight the mechanistic role of epigenetics in the dietary mitigation of type 2 diabetes. For instance, Li et al. show that a diet high in folates reduces blood glucose levels and improves insulin sensitivity, by altering the DNA methylation patterns in the adipose tissues of genes associated with type 2 diabetes [38]. The role of epigenetics in chronic diseases such as T2D highlights the importance of environmental and lifestyle factors, such as diet, in disease prevention and management. Therefore, this review sought to summarise the current knowledge on the preventive epigenetic mechanisms of functional foods in T2D.

2. The Role of Epigenetics in T2D

2.1. Overview of Epigenetic Changes Associated with T2D

T2D is associated with epigenetic changes that can impact the expression of genes involved in glucose metabolism, insulin signaling, and inflammation. These epigenetic changes include the following:

i. DNA methylation: DNA methylation is a chemical modification that involves the addition of a methyl group to the DNA molecule. Methylated DNA in mammals is usually in the form of 5-methylcytosine. In lower organisms (*Drosophila melanogaster*, fungi, and bacteria), the majority of the methylated DNA is in the form of N6-methyladenine [39]. While N6-methyladenine has been associated with over-expression, 5-methylcytosine has been linked with gene repression [40,41]. In T2D, DNA methylation changes have been observed in genes involved in insulin secretion and glucose metabolism, leading to alterations in their expression and function [42]. Maternal high-fat diet consumption in mice during gestation and lactation has been demonstrated to cause insulin resistance and glucose intolerance in their F_1 offspring, through the promotion of *Irs2* DNA methylation, and a decrease in *Map2k* DNA methylation [43]. DNA methylation has been hypothesised to act by disrupting the binding of transcription factors to recognition elements (containing a CG nucleotide), leading to the silencing of gene expression [44]. These aberrations in DNA methylation (whether hypo- or hyper-methylations) are oftentimes secondary to DNA methyltransferases gene (DNMT1, DNMT3A, and DNMT3B) dysregulation/mutations.

ii. Histone modification: Histones are proteins that interact with DNA to help package it into a compact structure. Histone modifications include the phosphorylation, methylation, acetylation, and ubiquitination of histone molecules. This leads to conformational changes that remodel chromatin, thereby altering the activity and interactions of transcription factors, nuclear proteins, and histone molecules; this, in turn, affects gene transcription and its sequelae [45]. In T2D, changes in histone modification have been observed in genes involved in insulin sensitivity, glucose metabolism, and inflammation [46].

iii. Non-coding RNA-mediated regulation: Non-coding RNAs, such as microRNAs, are short RNA molecules that do not encode for proteins, but play a crucial role in regulating gene expression. For instance, the parental intake of five functional food oils has been shown to modulate miRNA expression in both the parent and offspring [47]. In addition, functional foods have also been shown to modulate the expression of lncRNA in parents and offspring [38,48–50]. Essentially, in T2D, changes in the expression of non-coding RNAs have been observed in genes involved in insulin secretion and glucose metabolism, leading to alterations in their function [51,52].

These epigenetic changes associated with T2D can also interact with other factors, such as obesity and physical inactivity, which are known to increase the risk of T2D [35]. The complex interplay between these factors highlights the importance of a holistic approach to the prevention and management of T2D, which takes into account both the genetic and environmental factors.

Furthermore, epigenetic changes in genes involved in insulin secretion and sensitivity, glucose metabolism, inflammation, and adipocyte differentiation and function can have

a profound impact on the development of type 2 diabetes (T2D). Insulin secretion and sensitivity can be decreased due to these epigenetic changes, leading to insulin resistance, which is a defining characteristic of T2D. Additionally, alterations in glucose metabolism can result in an increase in glucose production by the liver, and elevated blood-glucose levels, due to changes in glucose uptake, utilisation, and storage in peripheral tissues. Inflammation is also impacted by these epigenetic changes, resulting in a persistent state of low-grade inflammation that is associated with the progression of T2D. Moreover, changes in the differentiation and function of adipocytes can lead to altered lipid storage and an increased risk of obesity and insulin resistance. These various changes accumulate over time, resulting in a progressive decline in glucose metabolism and insulin sensitivity, which can increase the likelihood of developing T2D and its associated health complications.

2.2. Epigenetic Inheritance of T2D

Based on the sustainability of a conferred metabolic disease along subsequent generations of offspring, an epigenetic transfer may be termed transgenerational, intergenerational or multigenerational [53]. Such epigenetic change(s) could be important therapeutic target(s) for reducing diabetes, because of the typical epigenetic signature of being modifiable and reversible. Numerous clinical observations and in vivo laboratory experiments involving animals have proved beyond conjecture that there is a generational link of type 2 diabetes between parents and their subsequent descendants. Compelling animal studies involving embryo transfer experiments [54], and discordant human siblings born to parent before and after the development of maternal diabetes [55] have given credence to the association between gestational diabetes and the development of later-life type 2 diabetes. Later generational phenotypic expressions (e.g., type 2 diabetes) consequent on "developmental programming" due to early-life environmental insults, especially the over- and under-nutrition of specific nutrients, have demonstrated the risk of a generational diabetic link between offspring and their parents [56–58]. Crudo et al. demonstrated a transgenerational association between late-gestation glucocorticoid intervention in F1 pregnant guinea pigs, and global DNA methylation and the expression of crucial metabolic genes in subsequent generations of offspring [59]. In an earlier study, maternal under-nutrition had been associated with transgenerational increased neonatal adiposity in the offspring of exposed women [60]. Furthermore, using a mouse model, Pavlinkova and colleagues have demonstrated the association between paternal diabetes and sperm quality, and expression patterns in the offspring of later generations [57]. With the foregoing observations, and many more reports in the literature, it is almost impossible to rule out the transmission of type 2 diabetes from parents to their subsequent generational offspring.

Accordingly, the underlying mechanisms responsible for the transmission of type 2 diabetes have been explored since the early 1990s. Diets have been shown to programme type 2 diabetes, by altering the structural and functional metabolic systems in adipose tissues, muscles, and the pancreas and liver [61–63]. Epigenetics have evolved as the underlying molecular mechanisms through which these dietary disturbances during intra-uterine life are registered and "reminisced" during later generations as metabolic dysfunctions such as type 2 diabetes. These metabolic dysfunctions occur through upstream modifications in epigenetic signatures which influence gene expression without tampering with the DNA sequence. For example, studies have shown that diet influences the expression of intestinal fatty acid binding protein (IFABP) mRNA, which will in turn affect all downstream processes affected by its protein [64]. IFABP is known to be an expressed product of the FABP2 gene, which is responsible for a myriad of fatty acid trafficking processes across several metabolic pathways. This report indicates that diet can modify the epigenetic memory of specific genes, which in turn affects the expression of proteins responsible for the handling of specific metabolic pathways involving the homeostasis of blood glucose and body weight. This, in the long run, impacts the development of heritable type 2 diabetes mellitus.

Therefore, understanding the specifics of these changes is crucial for the development of new strategies for preventing and managing the disease, including the use of functional foods with preventive epigenetic effects.

3. Functional Foods and Their Epigenetic Effects

Since the 1970s, there has been an increased interest in diets that provide additional health benefits beyond the traditional macro- and micronutrients [65]. Diets with such properties have been termed "functional foods". Functional foods can be regarded as processed foods that are taken whole or enhanced (enriched or fortified) to provide some tertiary benefit on the body's physiology over and above the nutrition (primary) and sensory (secondary) benefits provided by conventional foods, when imbibed at efficacious levels as part of a varied diet on a regular basis [29,65]. In his perspective article, Temple opines that "Functional foods are novel foods that have been formulated so that they contain substances or live microorganisms that have a possible health-enhancing or disease-preventing value, and at a concentration that is both safe and sufficiently high to achieve the intended benefit" [66]. These foods are designed to deliver specific health benefits, and are often enriched with bioactive components such as vitamins, minerals, and phytochemicals.

The health benefits of functional foods can vary widely, depending on the type of food and the specific bioactive components it contains. Functional foods have been extensively studied in recent years for their potential in promoting overall health, and preventing various diseases. These foods have been shown to play a significant role in disease prevention, by exerting a variety of positive effects on the body. One such effect is improving the nutrient status of the body. By providing essential vitamins and minerals that may be lacking in the average diet, functional foods can help improve the overall nutrient status of the individual [67]. Another important effect of functional foods is their ability to modulate inflammation. Some functional foods contain bioactive components that can help regulate the immune system, and reduce chronic inflammation, which is associated with the development of many chronic diseases, including T2D [68].

Another key benefit of functional foods is their ability to regulate glucose metabolism. Some functional foods contain bioactive components that can help improve insulin sensitivity, and regulate glucose metabolism, which can be especially beneficial for individuals who are at risk of developing T2D [9]. Additionally, some functional foods contain components that can modify epigenetic marks, such as DNA methylation and histone modification. For instance, a recent study by Kusuyama et al. demonstrates the potential of parental exercise and diet to determine the development of offspring diabetes, by altering offspring histone methylation (an epigenetic change) [25]. Such epigenetic modifications may be responsible for the multigenerational transmission of impaired islet function [26,69].

3.1. Functional Foods in the Management of Type 2 Diabetes

Functional foods have been studied in clinical trials, and have shown numerous advantages in the management of patients with diabetes [70–72]. Specific functional foods, including whole grains, legumes, vegetables, soybeans, green tea (*Camellia sinensis*), probiotics, prebiotics, and spices such as turmeric, garlic, and ginger, have demonstrated positive effects on glycaemic control and cardiovascular health [70–72]. As a result, they are often recommended as complementary therapies to conventional drugs for managing type 2 diabetes (T2DM) and its associated complications [71].

Furthermore, functional foods can benefit individuals of all ages with chronic diabetes, but it is important to consider their individual dietary needs, preferences, and any comorbidities when implementing a functional-food-based approach. However, limitations, such as individual variability in response to functional foods, challenges with compliance and dietary adherence, and issues related to the availability and affordability of functional foods, should also be taken into account [73,74].

Therefore, a comprehensive approach that combines functional foods with other evidence-based strategies is essential for effective diabetes management. By considering

these factors, and tailoring the approach to each individual, the incorporation of functional foods can contribute to improved glycaemic control and overall health in patients with chronic diabetes.

3.2. Health Benefits of Functional Foods against Parentally-Triggered Offspring Type 2 Diabetes

A number of functional foods have been proven beneficial to offspring defense against an inherited predisposition to diabetes (see Table 1). These functional foods are categorised, below, into whole foods or enhanced foods:

3.2.1. Whole Foods

Whole foods, defined here, include diets that are largely unmodified, and re-discovered to confer tertiary health benefits (i.e., against parentally-triggered offspring diabetes) beyond the primary nutrition and secondary physicochemical benefits. These include milk fat, germinated brown rice, and camel milk. Milk fat is an important component of mammalian breast milk that serves as good source of milk-fat globule membrane (MFGM), a fraction that is rich in bioactive lipids and proteins [75]. Ye et al. demonstrated the ability of MFGM to mitigate glucose intolerance and insulin resistance in both male and female offspring of mice challenged with HFD during pregnancy and lactation [76]. Notably, this instance of neonatal protection was associated with sexually specific remodulation of the HFD-triggered gut dysbiosis. Similarly, studies by Mahmoud et al. [77] demonstrated that whole camel milk, rich in camel whey protein, prevents the reconstruction of diabetes and its related complications in the offspring of diabetic mothers. In addition, whole-grain-germinated brown rice, rich in gamma oryzanol, has been shown to raise adiponectin levels. This elevation in adiponectin promotes insulin sensitivity, and suppresses glucose output [78]. The anti-diabetic effect of the whole brown rice was conferred to susceptible offspring via modifications of DNA methyl marks and post-translational acetylation of histones H3 and H4 [79]. These represent good examples of the epigenetic impact of functional foods across generation.

3.2.2. Enhanced Foods

Enhanced functional foods may be enriched or fortified with functional ingredients, or may be formulations that exclude substances such as allergens, gluten, or lactose [29]. The high glucose levels predominant in diabetes have been reported to cause a surge in the levels of zinc in urine, by affecting urinary zinc absorption [80]. Investigations demonstrate that such a significant excretion of endogenous zinc by the offspring is prevented following the administration of poultry eggs enriched with vitamin E and omega-3 fatty acids [81]. Another study demonstrates that the intake of poultry egg enriched with macronutrients (vitamin C and E) and micronutrients (Cu, Zn, and Mn) by offspring of zinc-triggered diabetic parents reverses the risk of inheriting type 2 diabetes and its complications, such as oxidative damage [82]. This is particularly important because hyperglycaemia (of diabetes) propels the formation of free radicals of the oxygen species through glucose auto-oxidation and non-enzymatic glycations. Otherwise, an excess of these free radicals overcomes the antioxidant defenses, and results in damages such as lipid peroxidation [83]. Thus, food enrichment mitigates the lipid peroxidation status of offspring born to diabetic parents. Sometimes, the nutrients implicated (for enrichment) are essential components of enzymes, some of which play significant roles in the antioxidant defense system. Consequently, such functional foods may serve as dietary supplements to normalise the mineral status in offspring of diabetic parents, and may thus prevent oxidative stress amongst populations consuming foods with high Zn levels. Furthermore, the length of the chromosomal telomeres has been reported to shorten in diabetes, and is negatively correlated with glucose concentrations and glycated hemoglobin (HbA1c) levels [84,85]. A study revealed that foods fortified with omega-3 polyunsaturated fatty acids (*n*-3 PUFA) depress the hepatic telomere shortening, which was observed in the offspring of gestationally diabetic (GDM) rats [86]. The *n*-3 PUFA administered to the offspring of GDM rats significantly raised their

insulin levels, and reversed an impaired glucose tolerance that was observed to worsen with offspring age. In another instance, the low birth weight common to most famines is associated with the development of type 2 diabetes [87]. Studies show that modified poultry egg enriched with vitamin E and omega-3 fatty acids improve birth weight, and enhance offspring survival [81]. Though these enhanced functional foods reduce the risk of developing type 2 diabetes and its complications, demonstrations of the mechanistic bases behind their inherited benefits remain scarce.

3.3. Functional Foods with Preventive Epigenetic Effects in T2D

Several functional foods have been shown to have preventive epigenetic effects in T2D, including berries, cruciferous vegetables, green tea, omega-3 fatty acids, and spices.

i. Berries: Berries such as blueberries, blackberries, and strawberries contain bioactive compounds such as anthocyanins and ellagitannins, which have been linked to the prevention of T2D by improving insulin sensitivity, regulating glucose metabolism, and reducing inflammation. In a study by Ma et al. [88], blueberry supplementation was found to alter the DNA methylation patterns of genes involved in insulin signaling and inflammation in individuals with T2D, suggesting the potential role of blueberries in preventing T2D through epigenetic mechanisms.

ii. Cruciferous Vegetables: Cruciferous vegetables, such as broccoli, cauliflower, and cabbage contain bioactive compounds such as sulforaphane and indole-3-carbinol, which have been found to reduce inflammation and improve insulin sensitivity, hence preventing T2D [89]. Cruciferous vegetables have also been shown to alter the DNA methylation patterns of genes implicated in insulin signaling and inflammation in patients with T2D, implicating a possible role in T2D prevention via epigenetic processes [90].

iii. Green Tea: Green tea is rich in catechins, including epicatechin and epicatechin gallate, which have been shown to have preventive epigenetic effects in T2D, and have been referred to as epi-drugs [91]. These compounds have been shown to regulate glucose metabolism and improve insulin sensitivity through their interaction with specific epigenetic marks, such as histone modifications and DNA methylations [92,93]. Moreover, it has been shown that epigallocatechin gallate inhibits the neural-tube abnormalities caused by maternal diabetes, and limits the increased expression and activity of DNA methyltransferases, resulting in the suppression of DNA hypermethylation, and the restoration of neural-tube-closure-required gene expression [94]. These findings suggest a preventive and management role for green tea in T2D through epigenetic mechanisms.

iv. Omega-3 Fatty Acids: Omega-3 fatty acids, found in fatty fish such as salmon, and in flaxseeds, have been linked to the prevention of T2D through reducing inflammation and improving insulin sensitivity [95]. Moreover, studies have shown the possible link between omega-3 fatty acid supplementation and the methylation of inflammatory genes in T2D [96]. This implies a potential role of omega-3 fatty acids in preventing T2D through epigenetic mechanisms.

v. Spices: Spices such as turmeric and cinnamon contain bioactive compounds such as curcumin and cinnamaldehyde, which have been linked to the prevention of T2D through improving insulin sensitivity, and regulating glucose metabolism and inflammation. For instance, curcumin has been shown to regulate histone deacetylases, histone acetyltransferases, DNA methyltransferase I, and miRNAs [97]. Moreover, the study by Yun et al. [98] showed the potential of curcumin in T2D through histone modification. This study showed that high glucose levels trigger the NF-B signaling pathway, resulting in the activation of pro-inflammatory genes. However, the curcumin treatment of high glucose-induced cells stimulates HDAC activity, particularly HDAC2, while reducing HAT activity, particularly p300, resulting in the deacetylation of p65 NF-B and, as a result, the suppression of proinflammatory cytokine production. Therefore, the role of curcumin supplementation in the regulation of the DNA methylation, histone acetylation, and miRNAs of genes involved in insulin signaling and inflammation in individuals with T2D suggests a potential role for curcumin in preventing T2D through epigenetic mechanisms [99].

As perinatal perturbations (malnutrition and other metabolic insults) in parents (F0) have been demonstrated to predispose offspring (F1) to the development of later-life risk factors for diabetes, an appropriate functional food could prevent intergenerational epigenetic change(s) that could worsen the burden of diabetes (see Figure 1). This hypothesis is strengthened by the fact that supplementation of the nutritional factor in question during intra-uterine life prevents the development of diabetic risk factors in subsequent generations [100–103]. This scenario is underscored in low- and middle-income countries where malnutrition due to poverty and illiteracy, and other perinatal perturbations are endemic. A plethora of data in the literature have highlighted a number of diets with "functional" capability [65,104]. Germinated brown rice, fortified margarines, soya bean/soy, bitter melon, sea grape, and psyllium are among dietary components termed as functional foods based on animal studies and clinical trials [21,29,105–108]. The scientific evidence supporting these effects is growing, but more research is needed to fully understand the mechanisms underlying these effects, and to determine the optimal dose and duration of consumption.
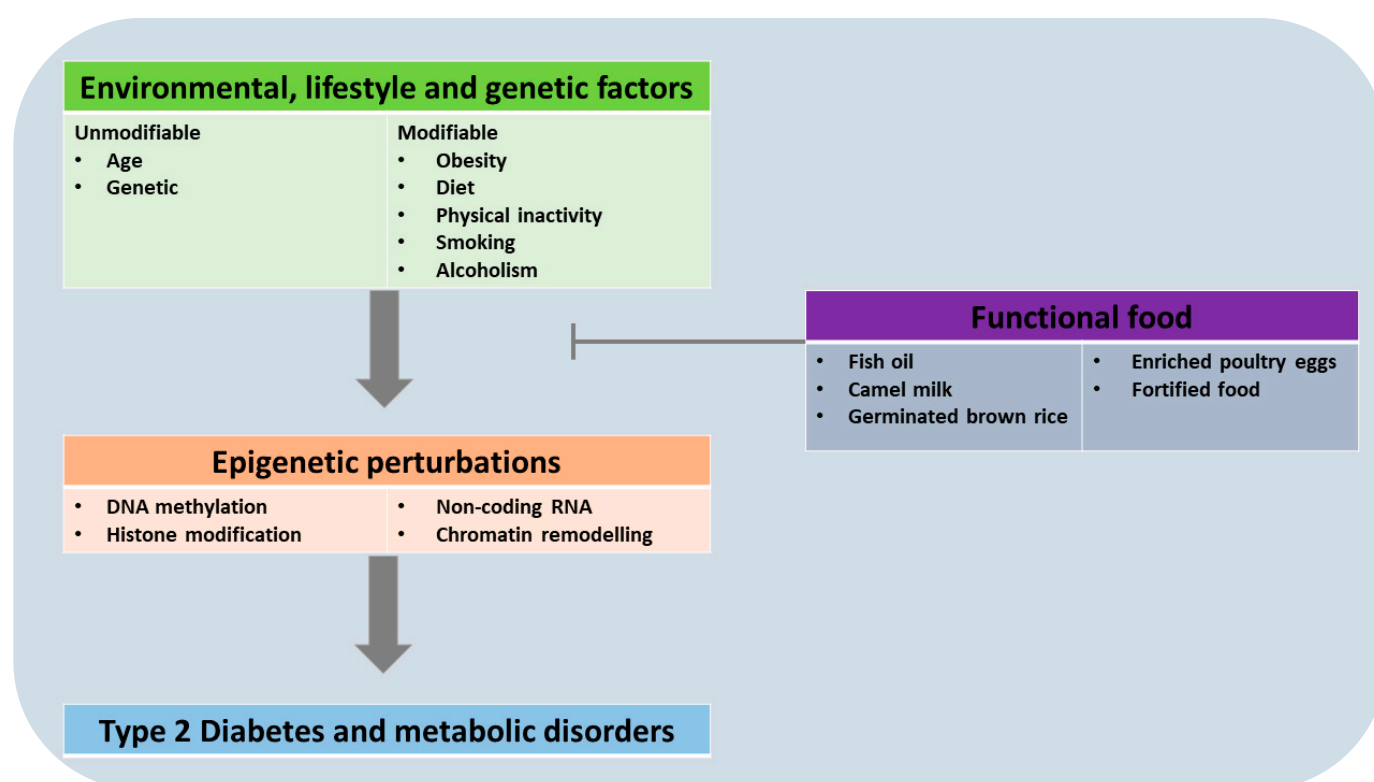
Environmental, lifestyle and genetic factors

Unmodifiable
- Age
- Genetic

Modifiable
- Obesity
- Diet
- Physical inactivity
- Smoking
- Alcoholism

Functional food

- Fish oil
- Camel milk
- Germinated brown rice
- Enriched poultry eggs
- Fortified food

Epigenetic perturbations

- DNA methylation
- Histone modification
- Non-coding RNA
- Chromatin remodelling

Type 2 Diabetes and metabolic disorders

Figure 1. Modifiable and unmodifiable factors leading to epigenetic perturbations in type 2 diabetes and metabolic disorders.

Table 1. Functional foods demonstrating defence against offspring diabetes.

Functional Food	Nature of Functional Food	Bioactive Phytochemical/Zoochemical	Study Model	Efficacious Levels	Methods	Nature of Antidiabetic Functionality	Mechanistic Basis	Conclusion	Ref.
Omega-3 enriched diet	Enriched	Omega-3 (ω3)	Offspring of Wistar rat	Efficacy of ω3-rich diet extends up to PND90	Dam; gestation and lactation [control (C: 19% of lipids and ω6: ω3 = 12), HF (HF: 33% lipids and ω6: ω3 = 21), or HF enriched with ω3 (HFω3: 33% lipids and ω6: ω3 = 9) diet]	The ω3 improved the glycaemic profile (insulin sensitivity, fasting glucose levels)	-	A ω3-rich diet attenuates or prevents the short-term metabolic disruption elicited by HFD in offspring	[109]
Fat diet	Factor out formulation	Perinatal fat restriction	Offspring of mice	Low-fat dietary intervention across gestation and lactation	Dam; gestation or lactation (low- and/or high-fat diet) Offspring; glucose tolerance and insulin sensitivity test at 12 and 70 weeks	Perinatal fat restriction provided adequate efficacy to restore insulin sensitivity in aging female progeny	-	Fat restriction ameliorates glucose dysmetabolism and prevents diabetes	[110]
Milk fat	Whole	Milk fat globule membrane (MFGM)	Offspring of C57BL/6 mice	1000 mg/kg BW/day MFGM	Dam; 3 weeks pre-gestation + gestation + lactation (high-fat diet (HFD) or a control diet) Pup; lactation (with or without 1000 mg/kg BW/day MFGM supplementation)	MFGM ameliorated metabolic disorder and improved glucose tolerance in offspring exposed to maternal HFD in a sex-specific manner	Sex-specific microbiota enrichment in offspring	MFGM is protective against transmitted glucose dysmetabolism	[76]
Fish oil food	Fortified food	*n*-3 PUFA	Offspring of C57BL6J mice	30 g FO/kg diet (equivalent to ~85–90 mg of FO per day for mice and 10 g per day for humans)	Dam; pre-gestation to lactation [HF diet (45% fat), HF + fish oil (FO—30 g/kg of diet) and low fat (LF; 10% fat)] F1: after weaning (HF or FO). LF weaned onto LF as control	FO lowered insulin resistance, reduced glucose intolerance, and improved insulin sensitivity	-	Fish oil improves glucose clearance and insulin sensitivity	[111]

Table 1. *Cont.*

Functional Food	Nature of Functional Food	Bioactive Phytochemi-cal/Zoochemical	Study Model	Efficacious Levels	Methods	Nature of Antidiabetic Functionality	Mechanistic Basis	Conclusion	Ref.
Fish oil food	Fortified food	*n*-3 PUFA	Offspring of C57BL/6 mice	12.58 g/kg diet [fish oil containing 70% (FA) DHA and 10% (FA) EPA in the form of triglyceride (DHA + EPA, 0.68% *w/w*)]	F0; pregnancy and lactation [control diet (AIN93G), *n*-3 PUFA-deficient diet and fish oil-contained *n*-3 PUFA rich diet (DHA + EPA, 0.68%, *w/w*)] F1; PD21 (high-fat diet or low-fat diet)	Deficiency in *n*-3 PUFA elicited glucose intolerance and insulin resistance in offspring. The *n*-3 PUFA helped to ameliorate glucose dysmetabolism	-	Glucose metabolism disorders could be potentially alleviated by *n*-3 PUFA, by its increasing of insulin sensitivity, inhibiting gluco-neogenesis, and promoting glycogenesis	[112]
Fish oil food	Fortified food	*n*-3 PUFA	Offspring of STZ-induced GDM Wistar rats	3rd month to 11th month of age	Dam; 6th day of gestation (STZ 30 mk/kg) Offspring of GDM rats: First phase, 3 months; standard diet (AIN-93, soybean oil). 2nd phase, 3–11 month; Group1- GDM offspring + AIN-93, soybean oil), Group2- GDM offspring + fish oil (60% *n*-3 PUFA), and Group3; GDM offspring + safflower oil (*n*-3 PUFA deficient) all versus control	The *n*-3 PUFA group had decreased oxidative stress, delayed hepatic telomere lengthening, inflammation, with reduced levels of diabetes-related metabolites, compared to the GDM group.	-	The long-term risk of developing diabetes is decreased by *n*-3 PUFA	[86]

Table 1. *Cont.*

Functional Food	Nature of Functional Food	Bioactive Phytochemical/Zoochemical	Study Model	Efficacious Levels	Methods	Nature of Antidiabetic Functionality	Mechanistic Basis	Conclusion	Ref.
Germinated brown rice	Whole germinated brown rice and oryzanol-rich extract	Oryzanol	Offspring of high-fat diet induced female Sprague Dawley rats	50% GBR and 100 and 200 mg/kg of oryzanol-rich extract	Pregnant female Sprague Dawley rats were fed with high-fat diet (HFD) alone, HFD + 50% germinated brown rice or HFD + oryzanol rich extract (100 or 200 mg/kg/day) throughout pregnancy and lactation. Their offspring were weaned at 4 weeks post-delivery and were followed up until 8 weeks	GBR and oryzanol produced metabolic outcomes (adiponectin, 8-Iso prostaglandin) that favoured insulin sensitivity better than HFD feeding in the dams and offspring	Altered global DNA methylation, and modulated H3 and H4 acetylation	GBR and oryzanol can ameliorate HFD-induced epigenetically-mediated insulin resistance	[79]
Margarine	Fortified	Vitamin A (retinol and β-carotene)	Human offspring (49 years)	Increased by 25% from; 4.2 µg/g of retinol and 3.6 µg/g of β-carotene (equivalent to 0.6% of the current RDA) to 6 µg/g of retinol and 3 µg/g of β-carotene (equivalent to 0.8% of the current RDA). β-carotene may be a precursor of retinol	Longitudinal follow-up on offspring of mothers who had been exposed to the extra vitamin A from margarine fortification (during pregnancy). As aftermath of a mandatory vitamin A fortification (of 25%) issued by the government of Denmark in 1962	Significantly more cases of T2DM in the offspring of less-exposed, compared to exposed	-	Foetal exposure to extra vitamin A from fortified margarine may lower the risk of developing T2DM in adulthood	[113]

Table 1. *Cont.*

Functional Food	Nature of Functional Food	Bioactive Phytochemical/Zoochemical	Study Model	Efficacious Levels	Methods	Nature of Antidiabetic Functionality	Mechanistic Basis	Conclusion	Ref.
Camel milk	Whole	Undenatured camel whey protein (CWP)	Diabetic offspring of STZ diabetic mouse dams (BALB/c)	100 mg/kg for month of parturition	Dam; preconceptionally diabetic (2 weeks), gestational/foetal exposure to CWP	In offspring at the third month postpartum, the CWP restored the expression of ATF-3, and the levels of ROS, pro-inflammatory cytokines. Additionally, it normalised glucose and insulin levels, compared to the diabetic control. Improved survival	-	Mitigates the tendency of the offspring to develop diabetes and related complications	[77]
Enriched normo-caloric diets (flaxseed)	Enriched	Alpha-linolenic acid	C57Bl6/J mice	94 g% fat-free chow diet + 6% ALA enrichment (47.9 mole % 18:2n-6)	Dam; 2 weeks pre-conception and during gestation and lactation [diet of 94 g% fat-free chow + 6% fat enriched in essential fatty acids (EFA): alpha-linolenic (ALA-18:3, n-3), linoleic (LA-18:2, n-6), or saturated fatty acids (SFA)]. HFD diet = 61.18 g% fat-free chow diet with 38 g% lard. Offspring; a 2-month post-weaning washing-out with normo-caloric diet (regular chow)	ALA lowered glucose, insulin, HOMA index, and stearoyl-CoA desaturase (SCD1) activity	-	ALA-enriched maternal normo-caloric diets potentially attenuate insulin resistance in adult offspring	[114]

Functional Food	Nature of Functional Food	Bioactive Phytochemical/Zoochemical	Study Model	Efficacious Levels	Methods	Nature of Antidiabetic Functionality	Mechanistic Basis	Conclusion	Ref.
Modified Poultry egg	Enriched	Optimised nutrients compared to conventional eggs (Lower; protein, CHO, total lipids, cholesterol, TG, Zn. Higher; Cu, Mg, Vitamin E, C and omega-3 fatty acid (linolenic acid)	Diabetic offspring of diabetic rats induced by synthetic diet rich in high zinc (80 mg/kg), high fat and refined sugar	For 30 days before mating	Three parental groups (both males and females); (1) control diet-105D, (2) diabetic diet-105D and (3) diabetic-egg mixed diet -75D+30D (105 days before mating). Subset of groups 1 and 3; offspring (120D of modified egg diet from ninth day after weaning)	Parental intake of modified egg protected against malformations, and improved offspring survival. Offspring (F1) of diabetic parents fed modified egg had reduced blood glucose, blood pressure, and lipid peroxidation, normal lipid profile, and improved enzyme activity	-	Though offspring of diabetic rats have a high tendency to become diabetic, modified egg reverses this risk and ameliorates complications such as oxidative stress, by normalising the mineral status	[82]
Modified poultry egg	Enriched	Vitamin E and omega-3 fatty acids	Diabetic offspring of NIDDM Wistar rats induced by synthetic diet rich in high zinc (40 or 80 mg/kg)		Parental groups (75 days before mating); (1) control 20 mg zinc (2) 40 mg/kg zinc (3) 80 mg/kg zinc. Administered EM (4 liquid eggs/kg) to parents (1 month before mating -weaning date PND21). Terminal assessment 18 days post-weaning	Enrichment enhanced survival and body weight, restored basal mineral levels, reduced the presence of trace elements in urine, prevented offspring abnormalities	-	Vitamin E and omega-3 fatty acids protect offspring from damaging effects of diabetes	[81]

ATF-3, activating transcription factor-3; CWP, camel whey protein; EM, egg mixed diet; GDM, gestational diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; PND, postnatal day; PUFA, polyunsaturated fatty acids; RDA, recommended dietary allowance; STZ, streptozotocin; T2DM, type 2 diabetes, TG, triglyceride; ZN, zinc.

4. Implication for the Development of New Prevention and Management Strategies for T2D

The understanding of the preventive epigenetic mechanisms of functional foods in T2D has important implications for the development of new prevention and management strategies for this disease. Some of the key implications are:

i. Personalised Nutrition: By using functional foods that target specific epigenetic changes associated with T2D, it may be possible to develop personalised nutrition plans for individuals with this disease, or those at risk of developing it.

ii. Complementary Therapy: Functional foods have the potential to complement conventional treatments for T2D, such as lifestyle changes and pharmaceuticals, by modifying the epigenetic landscape, and improving treatment outcomes.

iii. Disease Prevention: By targeting the epigenetic changes that contribute to the development and progression of T2D, functional foods have the potential to prevent the disease from developing in the first place.

iv. Reduced Dependence on Pharmaceuticals: By improving the efficacy of existing treatments, and reducing the need for higher doses of medication, functional foods may also reduce the financial burden of T2D on both patients and the healthcare system.

In essence, the preventive epigenetic mechanisms of functional foods in T2D are a promising area of research with important implications for the development of new, complementary therapies for this disease. The existing evidence suggests that functional foods have the potential to improve treatment outcomes, and prevent the disease from developing in the first place, but more research is needed to fully understand these mechanisms, and to confirm these effects in human-based trials.

5. Conclusions and Future Outlook

The problem of T2D has been a leading health concern for a long time. To address this epidemic, we propose the incorporation of functional foods into our diets, to not only prevent the onset of diabetes in offspring, but also improve the health of the parents, at minimal cost and with less medical consultation. We also noted that functional foods, taken at key developmental periods, may act via epigenetic means to positively impact offspring metabolic health, although the specific mechanisms, and the impact of maternal versus paternal intake, remain unclear, and require further research. The existing evidence provides promising results for the preventive epigenetic effects of functional foods in T2D. However, more rigorous and long-term clinical studies are needed in order to fully understand the potential of functional foods in the prevention and management of this disease. Further research is needed to confirm the preventive epigenetic effects of functional foods in T2D, through further clinical trials, to determine the optimal dosing and duration; understand specific epigenetic mechanisms through mechanistic studies; develop personalised nutrition plans based on individuals' epige-netic profiles and dietary habits through research; determine the efficacy of functional foods in reducing T2D incidence through interventional studies; and investigate the epigenetic effects of functional foods on other diabetes-related complications, such as cardiovascular disease and neuropathy. The overall aim of future research in this field should be to build upon the existing evidence, and provide a comprehensive under-standing of the preventive epigenetic effects of functional foods in T2D for the devel-opment of new, evidence-based prevention and management strategies.

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