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Beetroot for managing diabetes and its associated gut dysbiosis: Current findings and challenges

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ABSTRACT

There is strong evidence that diabetes is closely linked with gut dysbiosis such that insults to the gut microbiota can lead to diabetes. Meanwhile, since diabetes can be caused by a variety of tissue dysfunction, it would be ideal to develop single therapeutic strategies that aim at mitigating the condition and modulating the gut microbiota towards a healthy state. However, as it is difficult to define what a healthy gut microbiota is, the strategies would need to result in a healthy functional change in the microbiota. Recently, the use of functional foods for promoting health and modulating the gut microbiota is on the rise and colored vegetables such as beetroot have shown promising results. Meanwhile, the possible mechanism by which beetroot consumption combats diabetes through gut microbiota modulation is not established. Therefore, in this work, we discuss our current knowledge about the possible mechanism by which beetroot exerts antidiabetic effects as well as the challenges and future perspectives in this field of research.

1. Introduction

High blood sugar levels, insulin resistance, and dyslipidemia are the hallmarks of type 2 diabetes mellitus (T2DM), a chronic condition that also causes damaged pancreatic beta cells and insulin resistance (Bellary et al., 2021). With approximately 8% of the world's population affected by T2DM, this disease is of particular significance to global health care systems (Khan et al., 2020). Uncontrolled hyperglycemia is closely associated with the overproduction of reactive oxygen species (ROS), which causes oxidative stress and is a key component of T2DM pathophysiology (Bhatti et al., 2022).

In fact, diabetes is a risk factor for nephropathy (Chun & Park, 2020), cognitive dysfunction (Dao et al., 2023), cardiovascular events as well as micro- and macrovascular diseases (Mannucci et al., 2012). The body produces more dipeptidyl peptidase-IV (DPP-IV) as a result of T2DM, which inhibits the incretin system that regulates glucose homeostasis (Kasina & Baradhi, 2021). As a result, glycemic control has emerged as a crucial therapeutic approach for T2DM management. In the gut, pancreatic and intestinal glucosidases hydrolyze dietary carbohydrates to release glucose, which when absorbed, raises blood sugar levels (Liu et al., 2023).

The gut microbiota has been linked to diabetes pathogenesis as it has been found to play a crucial role in host glucose metabolism (Amabebe et al., 2020). This was evident in a study involving men with insulin resistance who experienced improved insulin sensitivity after receiving the gut microbiota of non-diabetic donors (Kootte et al., 2017). Since dietary glucose is a major contributor to hyperglycemia, delaying dietary carbohydrate hydrolysis by inhibiting α-amylase and α-glucosidase activities has emerged as an effective therapeutic approach for the management of diabetes (DiNicolantonio et al., 2015). Meanwhile, liver problems, asthenia, nausea, and gastrointestinal discomfort have all been associated with the use of pharmacological therapeutics that block carbohydrate-digesting enzymes (DiNicolantonio et al., 2015).

The prevalence of diabetes coupled with the side effects of existing antidiabetic drugs makes the search and development of safe non-pharmacological therapeutics for managing diabetes imperative. Considering that diabetes can be triggered by pancreatic problems and insulin resistance in the fat, liver and muscle cells, it is essential to develop therapeutic strategies that aim at mitigating the condition and modulating the gut microbiota towards a healthy state. However, as it is difficult to define what a healthy gut microbiota is, the strategies would need to result in a healthy functional change in the microbiota.

Interestingly, plants and their metabolites have remained invaluable therapeutic sources for health promotion and modulation of the gut

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microbial composition. Indeed, phytochemicals such as carotenoids, anthocyanins and betalains found in vegetables such as red beetroot (*Beta vulgaris* subsp. vulgaris) have potential antioxidant and glycemic control effects (Azizah et al., 2022; Li et al., 2022) and can therefore be used for combating the disease. Red beetroot (herein referred to as beetroot) is a vegetable high in nitrates, dietary fiber (Cava et al., 2012; Kale et al., 2018) and betalains which have anti-inflammatory, antioxidant and antidiabetic effects (Aliahmadi et al., 2021; Karimzadeh et al., 2022). It also has a strong ability to modulate the gut microbiota (Wang et al., 2023).

Despite the antidiabetic potential of the vegetable, the possible mechanisms by which it mitigates diabetes is not clearly understood. Therefore, in this work, we discuss our current knowledge about the antidiabetic potential of beetroot, the possible mechanisms by which it modulates the gut microbiota for diabetes remission and the future perspectives of its use as an antidiabetic functional food.

2. Different bioactive compounds in beetroot and their functions

High amounts of polyphenols, betalains, flavonoids, ascorbic acid, carotenoids, saponins and nitrate are present in beetroot (Chhikara et al., 2019) and the bioactive potentials of the vegetable has been reported (Bangar et al., 2022). This section will further elaborate on some of the important bioactive components in red beetroot and their impact on the gut microbiota.

2.1. Phenolic compounds and flavonoids

Beetroot is a rich source of flavonoids and phenolic compounds (Fig. 1). A recent study reported that the total phenolic acids content in beetroot was 30.81 mg gallic acid equivalent/g dry weight (DW) (Desseva et al., 2020) while other studies report relatively lower levels (Vasconcellos et al., 2016; Wootton-Beard & Ryan, 2011). Beetroot peels also have very high levels of phenolic acids such as rutin, epicatechin, catechin hydrate, vanillic, protocatechuic, *p*-coumaric, syringic acids and caffeic acid (Maraie et al., 2014). A study showed that 100 g of DW of beetroot pomace extract contained 132.52 mg of ferulic acid, 5.12 mg vanillic acid, 1.13 mg *p*-hydroxybenzoic acid, 7.11 mg caffeic acid, 5.42 mg Protocatechuic acid, 37.96 mg catechin, 0.39 mg epicatechin and 0.25 mg rutin (Vulić et al., 2014). Some studies have shown that cooked beetroot and beetroot juice have higher phenolic contents than beetroot powder and chips due to loss during the drying process (Mella et al., 2022; Vasconcellos et al., 2016). Four main groups of flavonoids namely betavulgarin, cochliophilin A, betagarin, and dihydroisorhamnetin have been identified in beetroot (Vulić et al., 2014) and potential anticancer flavanones such as betagarin and betavulgarin are present in beetroot leaves (Tan & Hamid, 2021). Other flavonoids in beetroots include 5-hydroxy-6,7-methylenedioxyflavone, 3,5-dihydroxy- 6,7-methylenedioxyflavanone, 2,5-dihydroxy-6, and 7-methylenedioxyisoflavone (Lim, 2012; Rana et al., 2022). Most phenolic compounds are not readily absorbed in the upper gastrointestinal tract after consumption and they therefore reach the large intestine where they interact with gut microbiota (Quatrin et al., 2020). These phenolic compound promote the growth of gut bacteria such as *Parabacteroides distasonis*, *Bifidobacterium* sp., *Prevotella* sp., *Bacteroides cellulosilyticus* and *Akkermansia muciniphila* which play critical roles in host energy metabolism (Han et al., 2009; Liu et al., 2019).

2.2. Carotenoids

Carotenoids are abundant in beetroot and act as potent antioxidant, oxygen radical scavengers (Lim et al., 2023), anticarcinogens (Vrdoljak, 2022) and immune stimulants (Riley et al., 2023) (Fig. 1). Beetroot flesh contains about 1.9 mg/100 g beta carotene (Rebecca, et al., 2014) and 22 μg/100 g alpha carotene (Ceclu & Nistor, 2020) while beetroot leaves contain 11.64 μg/100 g beta carotene and 3.5 μg/100 g alpha carotene (Ceclu & Nistor, 2020). Beta carotene consumption has been shown to prevent oxidative stress and DNA strand breakage (Riso et al., 1999) and therefore promote health. Although beta carotene consumption may not significantly alter gut microbial α-diversity (Honarbakhsh et al., 2022; Li et al., 2021), β-carotene may increase the abundance of *Roseburia,* Lachnospiraceae *and Parasutterella* but decrease the populations of *Dialister, Enterobacter* and *Collinsella* in the gut. β-carotene can also promote the production of acetic acid, propionic acid and lactic acid by gut microbes which can reduce inflammatory biomarkers (Li et al., 2023).

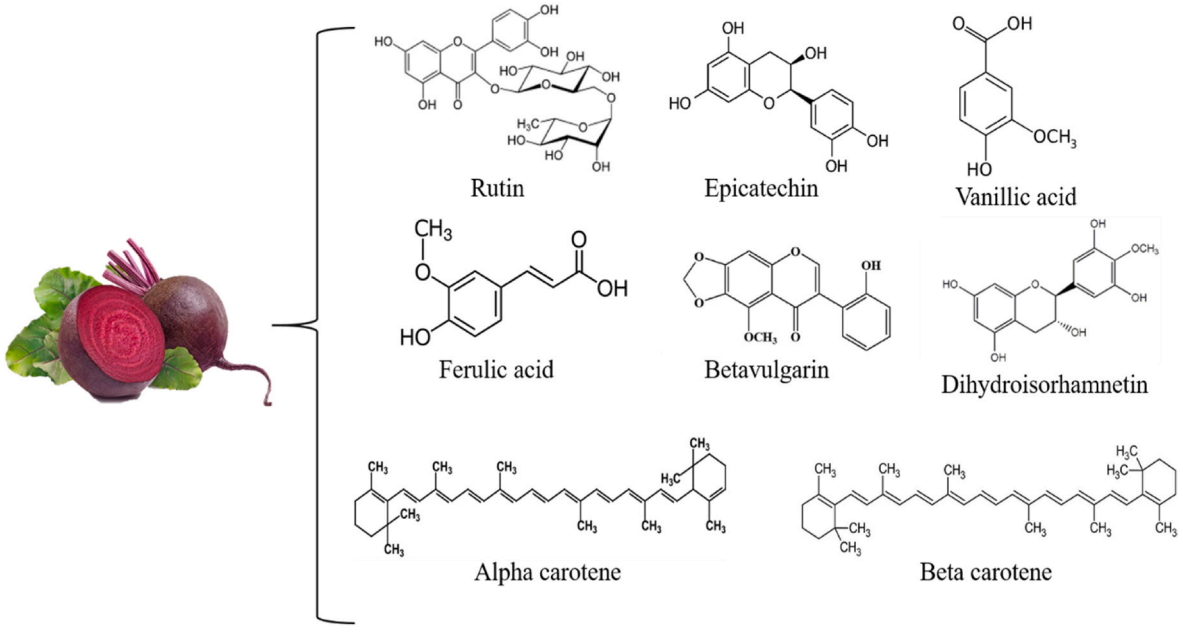

Fig. 1. Major phenolic and flavonoid compounds in red beetroot that have potential anti-diabetic activity.

2.3. Betalains

Based on their chemical structure and composition, betalains, can be classified as betaxanthin (yellow pigment) and betacyanin (red pigment) (Fig. 2). Betaxanthin can be subdivided into vulgaxanthin-I and vulgaxanthin-II (Ravichandran et al., 2013). Betacyanins such as prebetanin, betanin, isobetanin, and neobetanin have been identified in beetroot peel (Nemzer et al., 2011). Previous studies showed that dried beetroot extracts contained 20.75 mg/g of betacyanins and 19.01 mg/g of betaxanthins. Another study showed that betanin was the most abundant pigment in red beetroot juice (312.47 mg/100 g DW) followed by vulgaxanthin I (104.08 mg/100 g DW), isobetanin (71.28 mg/100 g DW), betanidin (18.2 mg/100 g DW) and isobetanidin (4.6 mg/100 g DW) (Slavov et al., 2013). Using eutectic solvents for betacyanin extraction from red beetroot can yield about 400 mg/100 g of the dye (Hernández-Aguirre et al., 2021). Interestingly, consumption of betalains may promote the growth of *Akkermansia* sp. which have beneficial effects against metabolic disorders such as insulin resistance and diabetes (Song et al., 2016). More so, betalains suppress *Staphylococcus aureus* and *Pseudomonas aeruginosa* attachment proliferation and proliferation by inhibiting their biofilm production (Yong et al., 2019).

3. Summary of recent clinical experiments on beetroot to control diabetes, and possible methods of improving the antidiabetic potentials of the vegetable

3.1. Antidiabetic abilities of beetroot consumption

The interest in using beetroot as a functional food for managing diabetes is fascinating due to the results observed in animal studies. In fact, several studies have demonstrated the antidiabetic potential of beetroot *in vitro* and in animal studies though a few positive outcomes have been observed in human studies. In diabetic rat models, for example, an ethanolic extract of red beetroot reduced fasting blood glucose, increased insulin levels, hepatic cholesterol levels, triglycerides, and serum low-density lipoproteins (Al-Harbi et al., 2021). Similarly, in a single-blind cross-over controlled study, consumption of a beetroot juice significantly lowered postprandial glycemic and insulin response relative to volunteers who consumed a control beverage (Wootton-Beard et al., 2014). Only several clinical trial studies have investigated the effects of beetroot supplementation on glycemic control and lipid profile in T2DM patients and they have yielded mixed outcomes (Table 1). Such outcomes could be due to the inter-individual variations in gut microbiota, metabotypes as well as genetics (Daliri et al., 2021; Surono et al., 2022).

3.2. Strategies for improving the antidiabetic effects of beetroot

Most studies about the antidiabetic potential of beetroot have focused on fresh beetroot (Aliahmadi et al., 2021; Karimzadeh et al., 2022) but not much is known about the potential anti-diabetic activities of fermented beetroot. Meanwhile, it is well established that fermentation with lactic acid bacteria and yeast can bioactivate, biotransform, and increase the release of bound bioactive compounds from the food matrix to augment their health promoting effects (Zhao et al., 2021). Recently, we recorded a significant increase in the antioxidant activity, DPP-IV inhibitory potential and inhibition of carbohydrate hydrolyzing enzyme activities when beetroot was fermented with *Latilactobacillus curvatus* PN39MY (Daliri, Balnionytė, et al., 2023; Daliri, Ofosu, Chelliah, & Oh, 2023). During fermentation, components of beetroot such as betanin (the main red-violet component in beetroot) can be converted by microbial deglucosylation into aglycones such as betanidin and isobetanidin (Czyżowska et al., 2006). Such aglycones produced after cutting-off the β-D-glucosyl residues of betanin demonstrate improved potential health benefits than the parent compounds (Wybraniec et al., 2011). Although fermentation also produces other metabolites besides aglycone molecules, the levels of aglycones can be increased drastically when certain specific bacteria are used for the fermentation process. *Bacteroides thetaiotaomicron* (Wardman et al., 2022), *L. casei, L. plantarum, Streptococcus thermophilus, L. acidophilus, L. delbrueckii* ssp. *bulgaricus, L. fermentum* and several *Bifidobacterium* species possess active β-D-glycosidases (β-D-glucoside glucohydrolase, E.C. 3.2.1.21) (Ko et al., 2022; Michlmayr & Kneifel, 2014) and may be useful for generating aglycones of betalains (Fig. 3). *Saccharomyces cerevisiae* also have β-D-glycosidases (Tang et al., 2013) which could produce aglycones during fermentation. Other metabolites of bioactive relevance such as neobetanin may also be generated during fermentation by microbial dehydrogenases (Qin et al., 2022). Most of the metabolites produced after the fermentation process are usually readily absorbed through the gut epithelium via passive diffusion (Xiao, 2017), thereby increasing their bioavailability. It is therefore essential to identify beneficial microbes that can be used for the development of antidiabetic functional foods (see Fig. 4).

Apart from using bacteria as cell factories for generating bioactive

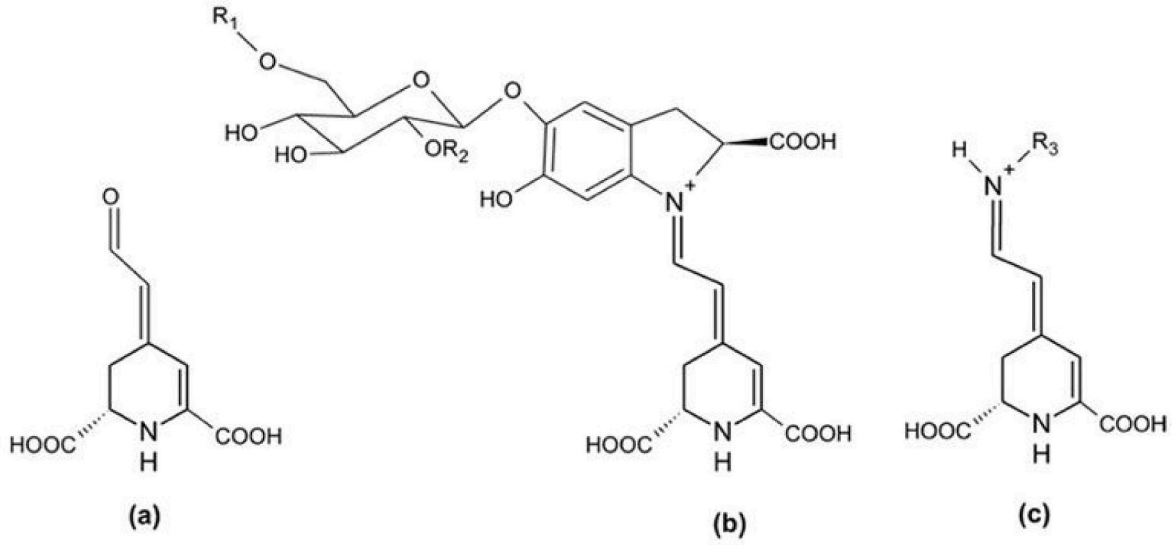

Fig. 2. General structures of betalamic acid (a), betacyanins (b) and betaxanthins (c) Betanin: R1═R2═H. R3 = amine or amino acid group. Adapted from Baião et al. (Baião et al., 2017).

Table 1
Effects of beetroot consumption on T2DM patients and healthy volunteers.

Group	Study	Population	Method	Dose	Duration	Outcome
Type 2 diabetes patients	Karimzadeh et al. (2022)	45 patients (31 males), 53.99 ± 9 years. Duration of disease = 6.43 ± 3.31 years	Stratified block randomized control trials	12 ml of concentrated beet root juice, twice daily	12 weeks	Compared with the control group, beetroot juice reduced IL-6 (−0.1 vs.0.83, P = 0.001), TNF-α (−1.28 vs. 5.51, P = 0.001), and NF-κB (−0.03 vs. 0.36, P = 0.005)
	Karimzadeh et al. (2023)	38 patients (n = 19 in beetroot group and n = 19 in placebo group), 54 ± 9 years. Duration of disease = 6.43 ± 3.3 years	Simply randomized, parallel-group, controlled, and open-label trial	24 ml of concentrated beetroot juice, once per day	12 weeks	Compared with the baseline, significant reductions in plasma insulin (14.55 ± 7.85 vs. 10.62 ± 6.96, P = 0.014) and homeostasis model assessment of β-cell function (HOMA-B) (3.96 ± 0.83 vs. 3.63 ± 0.75, P = 0.038)
	Bahadoran, Norouzirad, et al. (2021)	64 patients (n = 35 in beetroot group and n = 29 in placebo group), 54.0 ± 8.5 years (47.9% were male), Duration of disease = 8.5 ± 6.1 years	Randomized double-blind placebo controlled trial	5 g of beetroot powder, once per day	24 weeks	No effect on metabolic parameters
	Gilchrist et al. (2013)	27 patients (18 males), 67.2 ± 4.9 years, Duration of disease = 13.6 ± 8.1 years	Double-blind, randomized, placebo-controlled crossover trial	250 ml of beetroot juice, once per day	2 weeks	No improvement in insulin sensitivity
	Aliahmadi et al. (2021)	44 patients (10 males), 57 ± 4.5 years. Duration of disease ≥5 years	Quasi-experimental study	100 g of raw beetroot powder, once per day	8 weeks	Reduction in fasting blood sugar levels (−13.53 mg/dL), glycosylated hemoglobin (−0.34%), apolipoproteinB100 (−8.25 mg/dL), aspartate aminotransferase (−1.75 U/L), alanine aminotransferase (−3.7 U/L), homocysteine (−7.88 μmoL/l), and a significant increase in total antioxidant capacity
	Bahadoran, Norouzirad, et al. (2021)	9 healthy adults and nine T2DM patients	Randomized crossover study	270 ml of beetroot juice, once per day	Once	Reduced blood glucose levels significantly after consuming white bread
Healthy volunteers	Olumese and Oboh (2016)	30 subjects (18 males) aged 19–29 years, (FBS ≤2 5.6 mmol/L) and BMI less than 25 kg/m^2	Not reported	10% beetroot juice, once per day	6 weeks	Reduced blood glucose levels from 76.1 mg/dL to 49.8 mg/dL, decrease the values of insulin obtained during the intervention period from 9.42 μ IU/ml to 1.16 μ IU/ml
	Wootton-Beard et al. (2014)	16 subjects (6 males), 27 ± 5 years, 23·3 ± 2.8 kg/m^2	Randomized, single-blind, cross-over design	225 ml of concentrated beetroot juice, once per day	Once	Significant lowering of the postprandial insulin response
	Shepherd et al. (2016)	16 young adults (26.6 ± 6 year), BMI = 24.6 ± 3.1 kg/m^2 15 adults (59.2 ± 6 year), BMI = 26.36 ± 3.8 kg/m^2	Double-blind, placebo-controlled, randomized control trial	140 ml concentrated beetroot juice, once per day	Once	No effect on plasma glucose, C-peptide, or incretin concentration No effect on plasma glucose, C-peptide, or incretin concentration
	Chang et al. (2018)	10 volunteers (1 male and 9 females), aged 20–24 years and BMI ranging from 16·7–26·8 kg/m^2	Randomized crossover study	270 ml of concentrated beetroot juice, once per day	Once	Reduced blood glucose levels significantly after consuming white bread

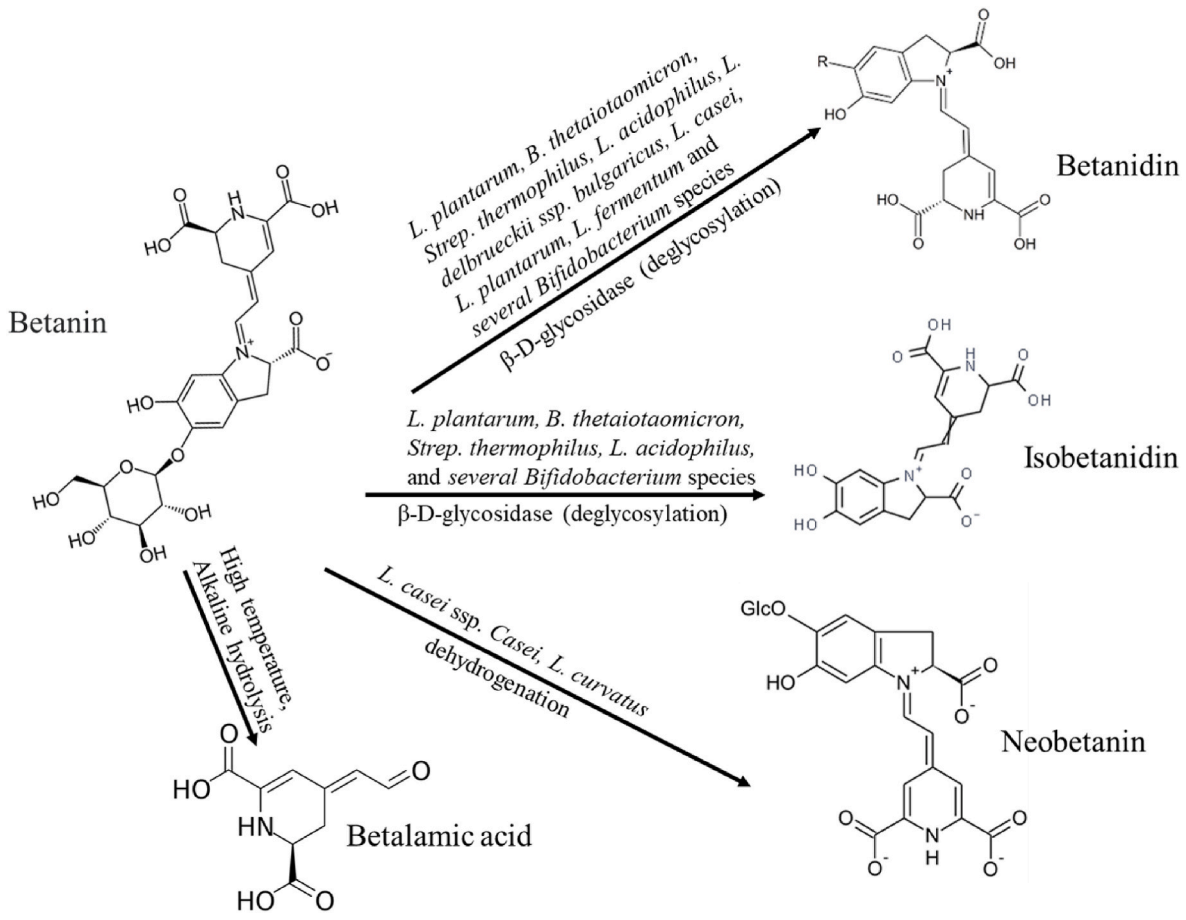

Fig. 3. Bioconversion of betanin into various metabolites with improved biological activities. The reactions by which the metabolites are produces are indicated below the list of bacteria.

components in beetroot, treatment of beetroot with specific β-D-glycosidases under controlled temperature and pH could yield aglycones. Indeed, a combination of high temperature and fermentation could further improve the bioactivity of beetroot products since microbial transformation and thermal degradation could generate new compounds (Daliri, Balnionytė, et al., 2023; Daliri, Ofosu, et al., 2023). Similarly, treating beetroot with appropriate imidases under the right conditions could yield betalamic acid (a strong antioxidant compound). Betalamic acid can also be obtained by high temperature treatment of beetroot (Xu et al., 2023) and by alkaline hydrolysis (Miguel, 2018).

4. Diabetes-associated gut dysbiosis and the impact of beetroot on gut microbial ecology

4.1. Diabetes-associated gut dysbiosis

Accumulating evidence show that the gut microbiota of diabetics and non-diabetics are different (Larsen et al., 2010). To understand the causality between gut microbiota and diabetes, Cani et al. (Cani et al., 2008) fed mice with high-fat diet (HFD) to alter their gut microbiota. The HFD-fed mice exhibited dramatic changes in the gut microbiota (a decrease in the levels of *Lactobacillus* spp., Bifidobacterium spp. and *Bacteroides-Prevotella* spp.), high plasma lipopolysaccharide concentrations (an indicator of metabolic endotoxemia), inflammation, intestinal permeability and high bold glucose levels compared to control mice. Treating the mice with ampicillin and neomycin however altered their gut microbiota, reduced metabolic endotoxemia to a level similar to that of the control mice, significantly reduced cecal endotoxin contents, reduced blood glucose and restored gut membrane permeability. In a similar study, administration of vancomycin and polymyxin B was shown to drastically reduce the levels of lithocholic acid (LCA) and deoxycholic acid (DCA) producers such as *Clostridium* cluster XI, *Clostridium* cluster XIVa and *B. fragilis* and their metabolites (LCA and DCA). This resulted in altered liver glycogen metabolism, bile acid and cholesterol biosynthesis and reduced blood glucose levels (Kuno et al., 2018). This is because, microbial LCA and DCA are farnesoid X receptor agonists which suppress gluconeogenesis, lipogenesis and fatty acid synthesis (Han et al., 2021). These studies provide evidence that gut dysbiosis can cause diabetes. Similar to animal studies, gut microbial dysbiosis is also well documented in diabetic patients (Karlsson et al., 2013). In a recent literature review of forty-two human studies reporting the relationship between diabetes and gut microbiota, the populations of *Akkermansia, Bifidobacterium, Faecalibacterium, Bacteroides* and *Roseburia* genera were significantly reduced in T2DM, while the genera of *Fusobacterium*, *Blautia* and *Ruminococcus* genera were significantly increased in T2DM patients (Gurung et al., 2020).

The introduction of a complete and stable bacteria community in the gut to repair or replace the altered native microbiota has yielded some promising outcomes (Ng et al., 2022). For instance, in a randomized, double-blind controlled study of insulin-resistant men, patients received the gut microbiota from lean body mass donors. Analysis of the experimental results demonstrated that fecal microbiota transplantation (FMT) improved insulin sensitivity and also increased the number of butyrate-producing gut bacteria (Vrieze et al., 2012). Although an increase or restoration in the levels of butyrate-producing bacteria is thought to be responsible for the disease remission after FMT (Capper et al., 2020; Ng et al., 2022; Vrieze et al., 2012), the specific bacteria that need to be restored for the remission are yet to be established.

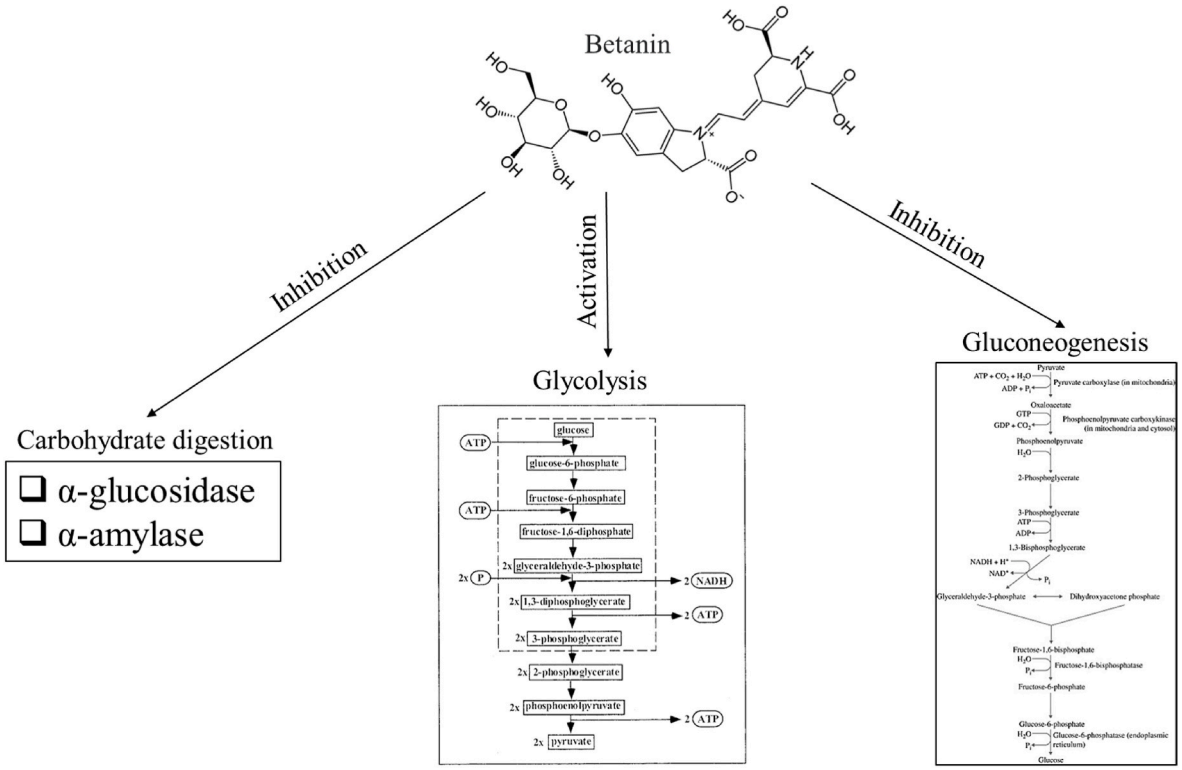

Fig. 4. Possible mechanism by which betanin directly inhibit carbohydrate digestion and glucose metabolism to mitigate diabetes.

Furthermore, the functional changes that occur in the microbial community following the treatment of diabetic patients with FMT are still unclear. This is particularly important because the gut microbial profile of the recipient tend to differ from the donor's gut microbiota over time, due to host immunity (Littmann et al., 2021) and diet (Lee et al., 2017) although the health effect may remain. However, as the gut microbiota is directly involved in diabetes and its management, strategies aimed at modulating the gut microbiota and its functions remain imperative.

4.2. *Beetroot modulation of microbial structure and function in diabetes-associated dysbiosis*

The modulatory effects of beetroot on the gut microbiota have been attributed to its constituents (de Oliveira et al., 2021) as they can promote the growth of microbes that can metabolize them while inhibiting others. This is particularly true because the ability of resident bacteria to utilize dietary components for growth directly influences their abundance in the gut (Agans et al., 2018). For instance, recent studies with healthy volunteers demonstrated that beetroot consumption can increase the population of *Akkermansia muciniphila* (a known butyrate producer) and decrease the abundance *Bacteroides fragilis* (Wang et al., 2023). Researchers reported that beetroot consumers had high levels of fecal butyrate which was associated with the high levels of betacyanin catabolites in beetroot (Wang et al., 2023). In general, betalains are poorly absorbed in the upper gastrointestinal tract (Clifford et al., 2017; Sawicki et al., 2018) and can therefore reach the large intestine to modulate the gut microbiota. This was demonstrated in a study in which consumption of betacyanin promoted the growth of *Akkermansia, Mucispirilum,* and *Anaerotruncus* species in diabetic mice (Henning et al., 2017). The antimicrobial activity of betalains against gram-positive bacteria is also well established (Velićanski et al., 2011; Vulić et al., 2013; Yong et al. 2017, 2018) and this may likely play a role in the ability of beetroot consumption to alter the gut microbial profile.

Beetroot components not only selectively promote the growth of gut microorganisms but can also modulate their functions by upregulating (Agans et al., 2018; McIntosh et al., 2012) or downregulating microbial gene expression which can influence host physiology. Since gut microorganisms contribute to the digestion of complex carbohydrates, proteins and fats in the host by expressing enzymes required for the hydrolysis of these compounds (Oliphant & Allen-Vercoe, 2019), the ability to modulate their functions would be critical for gut health. In a recent study, consumption of fermented beetroot was found to inhibit the growth of Enterobacteriaceae, suppress their β-glucosidase production and inhibit the overall β-glucosidase activity in the gut (Klewicka et al., 2009). In fact, gut bacteria belonging to the Enterobacteriaceae family (Klewicka et al., 2009) and *Bacteroides* species (Xu et al., 2003) possess numerous active glycoside hydrolases in their genomes and can express α-glucosidases, β-glucosidases, α-galactosidases, α-mannosidases, β-galactosidases, β-glucuronidases, β-fructofuranosidases, endo-1,2-β-xylanases and amylases (Xu et al., 2003). A reduction in the populations of these bacteria would therefore influence complex carbohydrate metabolism in the gut. Meanwhile, though fermented beetroot may modulate the structure and function of the gut microbiota, the specific component(s) in the fermented samples that were involved in the bacteria and enzyme inhibition would need to be investigated to understand the mechanism behind its (their) activities. It is however noteworthy that, although consumption of beetroot can significantly affect specific microbial groups in the gut, the levels of certain bacteria characteristic of a given disease condition may remain unaltered even after intervention (Fragiadakis et al., 2020; Walker et al., 2011) and remission. This therefore makes a complete reversal of the diabetes gut microbial profile to its initial profile before the onset of the disease almost impossible.

4.3. *Direct and indirect mechanisms by which beetroot mitigates diabetes*

4.3.1. *Direct effect on the host*

Beetroot may directly mitigate diabetes by inhibiting carbohydrate hydrolysis and glucose metabolism. Indeed, glucose released from carbohydrate digestion and increased gluconeogenesis in the liver of

diabetic patients are the main causes of hyperglycemia (Jiang et al., 2020). Therefore, inhibiting the activities of carbohydrate-digesting enzymes and controlling hepatic carbohydrate metabolism in the host would drastically reduce postprandial blood glucose levels (Hedrington & Davis, 2019). In a recent study, we demonstrated that fermentation of beetroot with *L. curvatus* PN39MY significantly increased its anti--α-glucosidase ability (Daliri, Balnionytė, et al., 2023; Daliri, Ofosu, et al., 2023). Results from other studies have shown that betanins in beetroot can inhibit both α-amylase and α-glucosidase thereby reducing glucose release from food (Koss-Mikołajczyk et al., 2019; Montiel-Sánchez et al., 2021). Betanin consumption can also promote glycolysis by activating glucokinase and pyruvate kinase while decreasing gluconeogenic enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase in the liver (Dhananjayan et al., 2017). In addition, beetroot nitrates can generate nitric oxide which plays a crucial role in glucose transport in adipocytes and myocytes, increases glucose oxidation and decreases glycogenesis (Jobgen et al., 2006). The ability of beetroot to control glucose metabolism could account for the significant reduction in fasting blood glucose levels in diabetic patients after they consumed beetroot juice (Aliahmadi et al., 2021; Bahadoran Mirmiran et al., 2021).

Beetroot may also alleviate diabetes due to its antioxidant abilities. In fact, hyperglycemia induces rapid fragmentation of mitochondria, which offsets the production of ROS –generating substrate by the Krebs cycle. This results in an upsurge in ROS production (Nishikawa et al., 2000; Rena et al., 1999; Yu et al., 2006) which activates intracellular formation of precursors of advanced glycation end products (AGEs) and the overexpression of AGE receptors as well as their activating ligands (Brownlee, 2005). These AGE precursors modify intracellular proteins that regulate gene transcription (Kim et al., 2012) as well as other extracellular matrix molecules to alter cell signaling resulting in cellular dysfunction (Ahmad et al., 2022). Recent studies have demonstrated the antioxidant and radical scavenging abilities of beetroot flavonoids, phenolics and betalains, suggesting that beetroot has the potential to prevent oxidative damage to lipid molecules and DNA (Esatbeyoglu et al., 2014). Betalains are immonium derivatives of betalamic acid that have an aromatic amino molecule capable of radical stabilization. The ability of betalain to donate electrons is directly related to this stabilization (Slimen et al., 2017). Due to the fact that radicals are electron-deficient molecules, betalains can provide electron density to the half-filled orbital and maintain its stability. For betaxanthins, the amount of hydroxy and imino residues present determines their antioxidant activity (Gliszczyńska-Świgło et al., 2006). Acylation is known to increase the antioxidant activity of betacyanin while glycosylation decreases it. Furthermore, 6-*O*-β-glycosylated betacyanins are more effective in scavenging free radicals than their 5-*O*-β-glycosylated counterparts (Gliszczyńska-Świgło et al., 2006). Betanin triggers cellular antioxidant defense by inducing the transcription factor nuclear factor erythroid 2-related factor 2 which increases levels of heme oxygenase 1 protein and cellular glutathione as well as transactivation of paraoxonase 1 (Esatbeyoglu et al., 2014). This may be the reason why consumption of betanin reduces oxidative stress by increasing the activity of antioxidant enzymes, terminating lipid peroxidation and reversing liver damage in Wistar rats fed with HFD (da Silva et al., 2019). Meanwhile, indicaxanthin is a chain-terminating lipoperoxyl radical-scavenger which inhibits lipid oxidation by inducing a lag phase and decreasing the rate of lipid oxidations reaction (Tesoriere et al., 2007).

Recent studies have shown that some components of beetroot (specifically betanin) may inhibit the formation of AGE by binding to methylglyoxal (the main intermediate in the formation of AGE), making them unavailable for the formation of AGE. Although betanin may not directly bind to serum proteins to inhibit the formation of AGE, thermal degradation products of betanin such as betalamic acid can bind to bovine serum albumin at positions LYS920 and SER930, disabling it from binding with sugars (Xu et al., 2023). These antioxidant and anti-AGE effects of betanin may account, at least in part to the reduced glycated hemoglobin (HbA1c) levels observed in diabetes patients when fed with beetroot juice (Aliahmadi et al., 2021) and in mice after they were fed with betanin-loaded liposomes (Amjadi et al., 2019).

4.3.2. *Indirect effect on the host through gut microbiota modulation*

It is evident that the gut microbiota influences gut permeability and inflammation (Liu et al., 2021), host glucose and lipid metabolism as well as insulin sensitivity (Aw & Fukuda, 2018). In view of this, we discuss the indirect mechanisms by which beetroot and its components modulate the gut microbiota for diabetes remission.

Recent studies have demonstrated that the gut microbiota can influence glucose homeostasis by altering gut hormones in the host (Gérard & Vidal, 2019). For instance, sulphate-reducing bacteria have been shown to produce H_2S which can trigger the p38 mitogen-activated protein kinase (MAPK) pathway to increase glucagon-like peptide-1 (GLP-1) secretion from by colonic GLP-1–secreting L-cells (Pichette et al., 2017). However, *Enterococcus faecalis* (which is overly represented in diabetics but reduced during treatment and in healthy individuals (Su et al., 2015)) can secrete the metalloprotease GelE which disrupts the gut epithelia and cleaves GLP-1 to upset glucose homeostasis (LeValley et al., 2020). Meanwhile, beetroot consumption promotes the levels of *Bifidobacterium* spp and *Lactobacillus* spp in the gut (de Oliveira et al., 2023) which produce metabolites that enhance glucose transporter-4 translocation through IRS-1/PI3K/Akt insulin signaling pathway in L-cells (Kim et al., 2014) and the liver (Li et al., 2017) to mitigate insulin resistance. Indeed, many gut *Lactobacilli* produce metabolites with potent α-glucosidase inhibitory abilities that retard glucose release from complex carbohydrates, thereby reducing postprandial hyperglycemia (Panwar et al., 2014). In addition, gut *Bifidobacterium* and *Lactobacillus* have bile salt hydrolases which convert primary conjugated bile salts to secondary bile acids (Golubeva et al., 2017; Ishimwe et al., 2015). Secondary bile acids such as 6α-hydroxylated bile acid can activate the TGR5-GLP1R axis to increase the release of incretin hormone and signal transduction (Makki et al., 2023). Beetroot consumption also promotes the production of butyrate which acts as a ligand of G-protein coupled receptors (GPCR41 and GPCR43) that stimulate entero-endocrine *l*-cells to release PYY, GLP-1 and GLP-2 (Allin et al., 2015).

Additionally, there is increasing evidence to show that alterations in gut microbiota fatty acid metabolism play a role in diabetes pathogenesis. In fact, diabetic patients have reduced expression of gut microbial genes involved in the biosynthesis of short chain fatty acids, whereas this is not the case in healthy patients (Vatanen et al., 2018). Furthermore, patients with β-cell autoantibodies have low populations of butyrate-producing bacteria in their gut (de Goffau et al., 2013) and this accounts for the low levels of butyrate levels observed in their stools. Meanwhile, beetroot consumption increases the levels of *Lactobacillus* spp which produce butyrate. Butyrate in turn can inhibit histone deacetylation (Steliou et al., 2012) to stimulate mitochondria biogenesis and fatty acid oxidation (Hong et al., 2016) which alters insulin signaling (Chriett et al., 2017) in the host. Butyrate also activates browning and up-regulates fatty acid β-oxidation genes *CPT1α, PPARα* and *ACOX1* in adipocytes (Zhang et al., 2023). In the gut, *A. muciniphila* can increase lipid metabolism by activating Lxr, Cpt1 and HMG-CoA synthase genes which are involved in fatty acid, cholesterol and bile acid metabolism (Derrien et al., 2011; Lukovac et al., 2014). Hence, beetroot modulates members of the microbiota to regulate host fatty acid metabolism and energy expenditure, which is important for the control of T2DM (Denisenko et al., 2020).

Further, diabetes is associated with low-grade inflammation characterized by elevated levels of circulating pro-inflammatory cytokines, chemokines and inflammatory proteins (Pesaro et al., 2021) and gut bacteria have been shown to modulate inflammation. Gut bacteria such as *Fusobacterium*, *Blautia* and *Ruminococcus* are overrepresented during diabetes (Gurung et al., 2020) and these bacteria trigger pro-inflammatory metabolites that activate pro-inflammatory cytokines in the host (Brennan et al., 2021; Juste et al., 2014). In fact, *Fusobacterium nucleatum* metabolites and vesicles can provoke the infiltration of

inflammatory cells, such as macrophages, creating a pro-inflammatory microenvironment (Rubinstein et al., 2013). When macrophages are infected with *F. nucleatum*, *they* induce the release of inflammatory cytokines such as NF-κB, IL-6, IL-8, IL-10 and IL-18 (Engevik et al., 2021; Rubinstein et al., 2013). Similarly, some *B. fragilis* strains can produce *B. fragilis* toxin which can induce the cleavage of E-cadherin and IL-8 secretion via β-catenin, NF-κB, and MAPK pathways in the gut epithelium (Lee et al., 2022). However, beetroot consumption promotes the populations of bacteria such as *A. muciniphila* (Gurung et al., 2020) whose extracellular vesicles and metabolites may stimulate anti-inflammatory cytokines (Raftar et al., 2022) by suppressing TNF-α, IFN-γ and IL-8 expression in the gut (Zhai et al., 2019) resulting in improved glucose metabolism (Abot et al., 2023). *A. muciniphilla* butyrate also suppresses NF-κB/Rel activation and inhibits the expression of IL-8 in the gut (Kinoshita et al., 2002).

Increased gut membrane permeability is common among T2DM patients and results in the leakage of gut microbes and toxins into the bloodstream (Zhao et al., 2020). This compromised gut membrane integrity can be caused by the overexpression of extracellular vesicles by some pathobionts in the gut during diabetes. For instance, *Fusobacterium nucleatum* extracellular vesicles can activate receptor-interacting protein kinase 1 and receptor-interacting protein kinase 3 resulting in gut epithelia necroptosis and membrane dysfunction (Liu et al., 2021). Meanwhile, *A. muciniphila* (whose populations are boosted by beetroot consumption) produce extracellular vesicles which can mitigate gut membrane permeability by stimulating intestinal tight junction protein expression through the activation of adenosine monophosphate-activated protein kinase (AMPK) in the gut epithelium (Chelakkot et al., 2018). Furthermore, the outer membrane protein of *A. muciniphila*, Amuc_1100, can stimulate the expression of occludin and tight junction protein-1 which enhance gut membrane integrity (Riley et al., 2023). In addition, Amuc_1100 can inhibit intestinal cannabinoid receptor type 1 which could reduce gut permeability (Plovier et al., 2017). A recent study has demonstrated that *A. municiphilla* as well as their cell membrane proteins can upregulate and activate intestinal cAMP-responsive element-binding protein H which increases tight junction proteins claudin-5 and claudin-8 expression to improve gut integrity (Wade et al., 2023). Moreover, butyrate produced by *A. municiphilla* may also protect membrane integrity by enhancing the expression of zonula occludens and also through the peroxisome proliferator-activated receptor γ pathway (Kinoshita et al., 2002). Consumption of beetroot could therefore boost the levels of beneficial commensal microbes that enhance gut membrane integrity during diabetes management.

5. Challenges and future perspectives

Despite the tendency of beetroot consumption to improve diabetic conditions, factors such as variations in gut enteroypes, and metabolic phenotypes a play crucial role in the outcome of dietary interventions (Dahal et al., 2022; Mayneris-Perxachs et al., 2020). Even in healthy subjects (control groups), their metabotypes and enterotypes may differ though they display the same phenotypes (Kang et al., 2016). In fact, the type and amount of food-derived compounds that reach the gut microbiota is strongly affected by the digestive and metabolic efficiency of the individual. More so, with the exception of *A. muciniphilla* and butyrate, there is no consensus on which other specific beneficial gut bacteria and metabolites are enriched after beetroot consumption. For this reason, future microbiota studies would need to stratify participants based on their genetic, gut enterotype and metabotype diversity to reveal a more personalized effect of beetroot interventions on health and disease.

In addition, current studies pertaining to the effects of beetroot on diabetes and the gut microbiota have focused on individual potential causal bacteria while neglecting the mycobiome and virome which symbiotically interact with the bacteria. This is particularly important because the quality and function of the gut mycobiome (Mingaila et al., 2023; Salamon et al., 2021; Van Syoc et al., 2023) and virome (Fan et al., 2023; Yang et al., 2021) are altered during diabetes and by dietary interventions. For this reason, grouping microbial consortia based on functional similarities would provide a clearer information of the community-level dynamics of the gut microbiota in health and disease. Meanwhile, knowledge on bacteriophages that may control the levels and functions of gut commensal bacteria in diabetes is crucial for understand the etiology of diabetes caused by gut microbial dysbiosis. This is plausible because phages usually infect bacteria and affect their metabolism, survival and death (Daliri, Ofosu, Chelliah, Lee, & Oh, 2020; Seed et al., 2014). It is therefore possible that these phages could influence certain nonpathogenic bacteria to display pathogenic phenotypes when the gut homeostasis is compromised. In such a case, certain bacteria regarded as beneficial may be overrepresented in the diseased group and yet overlooked though they may be key players in the disease (Daliri, Balnionytė, et al., 2023; Daliri, Ofosu, et al., 2023).

Meanwhile, it is anticipated that essential microbial products such as *A. muciniphila* extracellular vesicles and Amuc_1100 proteins would be purified and their effective doses needed to mitigate the leaky gut associated with diabetes would be determined. In the meantime, it would be interesting to know whether or not beetroot actually triggers the production of these *A. muciniphila* products in the gut and in fermenters (*in vitro*). This would enable the overproduction of these molecules as safe and affordable non-pharmacological therapies for combating diabetes. Moreover, in the near future, a new generation of analytical techniques is expected to emerge that will model cause-and-effect relationships and determine the targets of such non-pharmacological therapeutic treatments.

6. Conclusions

Although beetroot possesses great anti-diabetic potential, the results of beetroot consumption in diabetic patients are inconsistent, probably due to differences in the experimental designs and variations in the enterotype and metabotype of the patients/subjects. Stratification of the experimental groups, taking into account their genetics, enterotypes and metabolic phenotypes, may allow the full potential of beetroot to be realized. However, food processing strategies such as fermentation, enzyme treatment and heating could improve the levels of antidiabetic compounds in the vegetable. Once consumed, these compounds could significantly alter the microbial profile and function of the gut by affecting host glucose clearance, energy metabolism, inflammation and gut barrier function, while suppressing populations of pathobionts in the gut. The mechanism described in this work could at least, in part account for the antidiabetic potential of beetroot.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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