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REVIEW

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Dietary regulations for microbiota dysbiosis among post-menopausal women with type 2 diabetes

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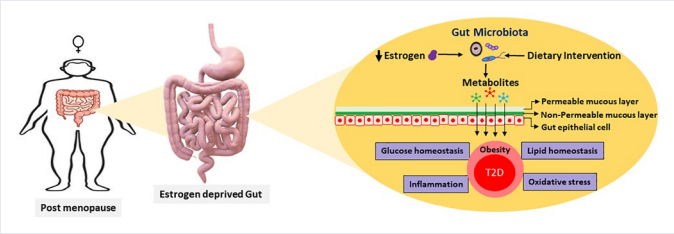
ABSTRACT

Type 2 diabetes (T2D) and T2D-associated comorbidities, such as obesity, are serious universally prevalent health issues among post-menopausal women. Menopause is an unavoidable condition characterized by the depletion of estrogen, a gonadotropic hormone responsible for secondary sexual characteristics in women. In addition to sexual dimorphism, estrogen also participates in glucose–lipid homeostasis, and estrogen depletion is associated with insulin resistance in the female body. Estrogen level in the gut also regulates the microbiota composition, and even conjugated estrogen is actively metabolized by the estrobolome to maintain insulin levels. Moreover, post-menopausal gut microbiota is different from the pre-menopausal gut microbiota, as it is less diverse and lacks the mucolytic *Akkermansia* and short-chain fatty acid (SCFA) producers such as *Faecalibacterium* and *Roseburia*. Through various metabolites (SCFAs, secondary bile acid, and serotonin), the gut microbiota plays a significant role in regulating glucose homeostasis, oxidative stress, and T2D-associated pro-inflammatory cytokines (IL-1, IL-6). While gut dysbiosis is common among post-menopausal women, dietary interventions such as probiotics, prebiotics, and synbiotics can ease post-menopausal gut dysbiosis. The objective of this review is to understand the relationship between post-menopausal gut dysbiosis and T2D-associated factors. Additionally, the study also provided dietary recommendations to avoid T2D progression among post-menopausal women.

GRAPHICAL ABTSRACT



KEYWORDS

Dietary regulation; dysbiosis; estrogen deficiency; gut microbiota; post-menopause; type 2 diabetes

Introduction

Almost 38 trillion microbes harbor the human intestinal tract and are collectively known as the gut microbiota. The gut microbiota functions as a virtual organ and affects host health and metabolism by producing several metabolites such as short-chain fatty acids (SCFAs; mainly acetate, propionate, and butyrate) and secondary bile acids (Valdes et al. 2018). Gut microbiota is a dynamic community that is easily affected by several factors such as diet, disease, metabolic variation, and age.

Natural menopause is a serious metabolic variation in mid-age women, elevating dyslipidemia, obesity, and irregular carbohydrate metabolism, which affect the gut microbial community (Santos-Marcos et al. 2018). Usually, menopause occurs in mid-aged women (47–52 years) when their ovaries stop maturing ovum and simultaneously ceases estrogen and progesterone secretion. According to the National Institute for Health and Care Excellence (NICE, UK) guidelines, the time after 12 successive months of the last period or menstrual cycle is regarded as post-menopause (Hope 2016). This permanent shift from the reproductive to post-reproductive phase causes multiple metabolic and psychotic changes in a female body, mainly due to the depleted female steroid hormones. Hormonal depletion among post-menopausal women potentially enhances their vulnerability to disorders in the hormone-responsive tissues such as brain, kidney, bones, and cardiovascular system (Lobo et al. 2014). Additionally, metabolic disorders including abdominal obesity, dyslipidemia, insulin resistance, impaired glucose tolerance, and type 2 diabetes (T2D), may also occur because of menopause, affecting the quality of life during the post-menopausal phase (Joon Cho et al. 2008; Stachowiak, Pertyński, and Pertyńska-Marczewska 2015).

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In general, women are less susceptible to metabolic diseases than men. However, this situation reverses after menopause, particularly in cases of diabetes and cardiovascular disease (CVD) (Heianza et al. 2013; Joon Cho et al. 2008; Lisabeth and Bushnell 2012). The depleted levels of the gonadotropic hormone estrogen causes this susceptibility in women, leading to detrimental effects (Rosano et al. 2007). This is further fueled by dyslipidemia, characterized by higher low-density lipoprotein (LDL) and lower high-density lipoprotein (HDL) levels, leading to CVD (Stachowiak, Pertyński, and Pertyńska-Marczewska 2015). Previous studies have also addressed several associated metabolic risk factors termed as metabolic syndrome (MS), characterized by obesity, T2D, insulin resistance, lower HDL level, high blood pressure, and elevated triglyceride level, negatively affecting the quality of life and life expectancy among post-menopausal women (Liang et al. 2013; Pu et al. 2017).

Post-menopausal period is a very sensitive phase for diabetes and can even be regarded as a period of active diabetic vigilance. The association between menopausal status and T2D is also supported by multiple longitudinal cohort studies conducted in South Africa, China, and other countries (Mauvais-Jarvis et al. 2017; Mtintsilana et al. 2019). Estrogen depletion after menopause is a major cause of obesity and T2D among elderly women (Marchand et al. 2018; Ren et al. 2019). Estrogen is actively metabolized by the gut microbiota, and its depletion shifts gut microbiota, enhances intestinal permeability, and induces obesity (Vieira et al. 2017). This review systematically examines the discrete information regarding the roles of gut microbiota associated with post-menopausal T2D, thereby providing a detailed account of the relevance of dietary interventions in its regulation.

T2D and its relation to post-menopausal repercussions

T2D is a complex metabolic disorder where the body cannot utilize glucose in the blood. This condition arises due to a lack of insulin or imperfect response to insulin. According to the World Health Organization (WHO), the mortality of diabetes was 1.5 million in 2019 (https://www.who.int/news-room/fact-sheets/detail/diabetes), with T2D being more common (90%) than type 1 diabetes (Franzosa et al. 2019). T2D etiology is a complex process characterized by persistent hyperglycemia and depends on multiple factors, ranging from genetic to lifestyle choices (Carlsson 2019; Kommoju and Reddy 2011).

Insulin receptors are present in almost all tissues, when insulin binds to these receptors, glucose transport proteins are activated, enhancing glycogenesis and lipid biosynthesis, and reducing gluconeogenesis (De Paoli, Zakharia, and Werstuck 2021). When insulin receptors do not respond, insulin resistance absurdly increases hepatic glucose production, thus secreting insulin (De Paoli, Zakharia, and Werstuck 2021). Insulin resistance in skeletal muscles is the earliest detectable sign of T2D (Taylor 2013). T2D is one of the most common metabolic ailments among post-menopausal women, which further lead to other severe metabolic conditions such as CVD and chronic kidney diseases (Ahmed 2017; Koye et al. 2018). A major reason for this susceptibility is the depletion of a primary sex hormone, estrogen, after menopause. Table 1 summarizes the ailments in several organs caused by estrogen depletion in post-menopausal women.

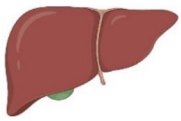
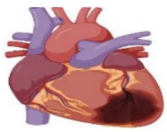
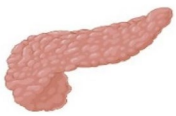
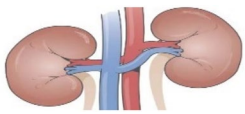
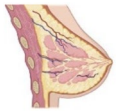
Estrogen actively participates in glucose metabolism; thus, a low estrogen level (~10 pg/mL) escalates T2D etiology by increasing inflammation and inducing obesity (De Paoli, Zakharia, and Werstuck 2021; Ko and Kim 2020). The effects of estrogen on various T2D-related metabolic activities are summarized in Figure 1. Estrogen binds to its receptors, then undergoes conformational changes, and are translocated to the nucleus where they act as mitogenic stimulants and regulate immunological cell expression (Moulton 2018; Straub 2007). Moreover, estrogen receptors are expressed in the visceral, hepatic, and subcutaneous adipocytes, so that a lower level of estrogens enhances fat accumulation in the body (Ko and Kim 2020; Marchand et al. 2018). This surplus fat adversely affects lipid metabolism by producing excessive triglycerides and free fatty acids. These triglycerides and free fatty acids accumulate in non-fatty tissues and impair insulin signaling and β-cell regulation, causing insulin resistance (Ko and Kim 2020). Estrogen also acts effectively against T2D by promoting degradation of ill-folded pro-insulin, thus reviving the endoplasmic reticulum from stress and β-cell dysfunction (Xu et al. 2018).

Association of gut microbiota with post-menopausal T2D

Post-menopausal gut dysbiosis, metabolic changes, and their relation with T2D

Estrogen deprivation causes gut dysbiosis, which induces and worsens the symptoms of T2D. The characteristics of post-menopausal gut dysbiosis include lower Firmicute/Bacteroidetes ratio, lower abundance of the family Lachnospiraceae, and a higher abundance of the genera *Prevotella*, *Parabacteroides*, *Bacteroides*, and *Bilophila* (Mayneris-Perxachs et al. 2020; Ozaki et al. 2021; Santos-Marcos et al. 2018). Other studies have reported that post-menopausal gut microbiota have few SCFA producers such as *Faecalibacterium*, *Bifidobacterium*, *Alistipes*, *Ruminococcus*, and *Roseburia* (Mayneris-Perxachs et al. 2020; Santos-Marcos et al. 2018; Schreurs et al. 2021; Zhao et al. 2019). Interestingly, the abundance of *Faecalibacterium* and *Roseburia* in post-menopausal women with T2D or obesity is often more decreased than that in non-T2D post-menopausal women (Alemán et al. 2018). Conversely, "metformin," a commonly used antidiabetic, increases the abundance of SCFA-producing bacteria, while improving glucose regulation (Wang, Yu et al. 2021). In addition to the low abundance of SCFA producers, post-menopausal women also have a low abundance of other beneficial bacteria such as *A. muciniphila*, *Eubacterium eligens*, *E. rectale*, and *L. vaginalis* (Brahe et al. 2015b; Schreurs et al. 2021; Zhu et al. 2018). Obesity during post-menopause worsens

Table 1. A summary of post-menopausal ailments.

Illustration	Organ	Effect	Reference
	Liver	Higher Risk of nonalcoholic fatty liver disease	(Chen and Madak-Erdogan 2018; Wang, Gorelick, and Bhargava 2021)
	Skeletal muscles	Reduced insulin sensitivity, and glucose uptake	(Hevener et al. 2020)
	Adipose tissue	Reduced insulin sensitivity, and higher oxidative stress	(De Paoli, Zakharia, and Werstuck 2021)
	Cardiac tissue	Cardiac stroke, and endothelial dysregulation	(Lisabeth and Bushnell 2012)
	Pancreas	Higher risk of pancreatic carcinoma, and compromised function of β cells.	(De Paoli, Zakharia, and Werstuck 2021; Wang, Gorelick, and Bhargava 2021)
	Kidney	Higher chances of chronic kidney diseases	(Ahmed 2017)
	Bones	Osteoporosis, and higher risk of bone fracture	(Eastell et al. 2016)
	Breast Tissue	Increased risk of breast cancer	(Dashti et al. 2020; Qureshi et al. 2020)

post-menopausal gut dysbiosis due to reduced microbial richness and low abundance of *A. muciniphila* (Brahe et al. 2015b; Schreurs et al. 2021). As *A. muciniphila* is responsible for maintaining the thickness of the gut epithelial mucus layer, its reduced abundance can lead to leaky gut, enhancing the translocation of inflammatory toxins through the gut epithelial layer (Brahe et al. 2015b).

Estrogen and estrogen-like compounds modulate the gut microbial ecosystem and promote the proliferation of certain microbial communities over others (Chen and Madak-Erdogan 2016; Kaliannan et al. 2018). Gut microbiota with genes encoding estrogen-metabolizing enzymes, referred to as the "estrobolome," flourishes in the presence of estrogen (Chen and Madak-Erdogan 2016). Studies also reported that low microbial diversity during the post-menopausal period adversely affects microbial beta-glucuronidase activity (Baker, Al-Nakkash, and Herbst-Kralovetz 2017). Beta-glucuronidase enzyme influences estrogen metabolism by deconjugating estrogen and phytoestrogen, making them available in the bloodstream upon absorption in the gut. These freed estrogens act on estrogen receptors to regulate blood glucose levels (Baker, Al-Nakkash, and Herbst-Kralovetz 2017; Kwa et al. 2016). Studies on ovariectomized murine models have also demonstrated that lack of estrogen reduces the abundance of the genera *Bacteroidetes* and *Akkermansia*, while inducing a significantly high level of serum cholesterol, hepatic adipogenesis, and expression of lipogenesis genes, suggesting that estrogen plays important roles in obesity, glucose, and lipid homeostasis through modulating gut microbiota (Acharya et al. 2021; Lei et al. 2021). In addition, the gut microbiome during the post-menopausal period is reported to be filled with higher trimethylamine N-Oxide (TMAO) and hydrogen sulfide (H_2S), which increase gluconeogenesis and so the glucose level (Grassi et al. 2016; Jang and Lee 2021; Liu et al. 2020). TMAO is synthesized from trimethylamine by gut microbiota, and H_2S is generated by colonic sulfur-reducing microbes (Blachier et al. 2021; Janeiro et al. 2018).

Studies on intestinal metabolic differences between pre and post-menopausal gut microbiota showed that metabolic activities involved in the pentose phosphate pathway were enriched in pre-menopausal microbiota, while those involved in homocysteine synthesis was enriched in post-menopausal microbiota (Zhao et al. 2019). The

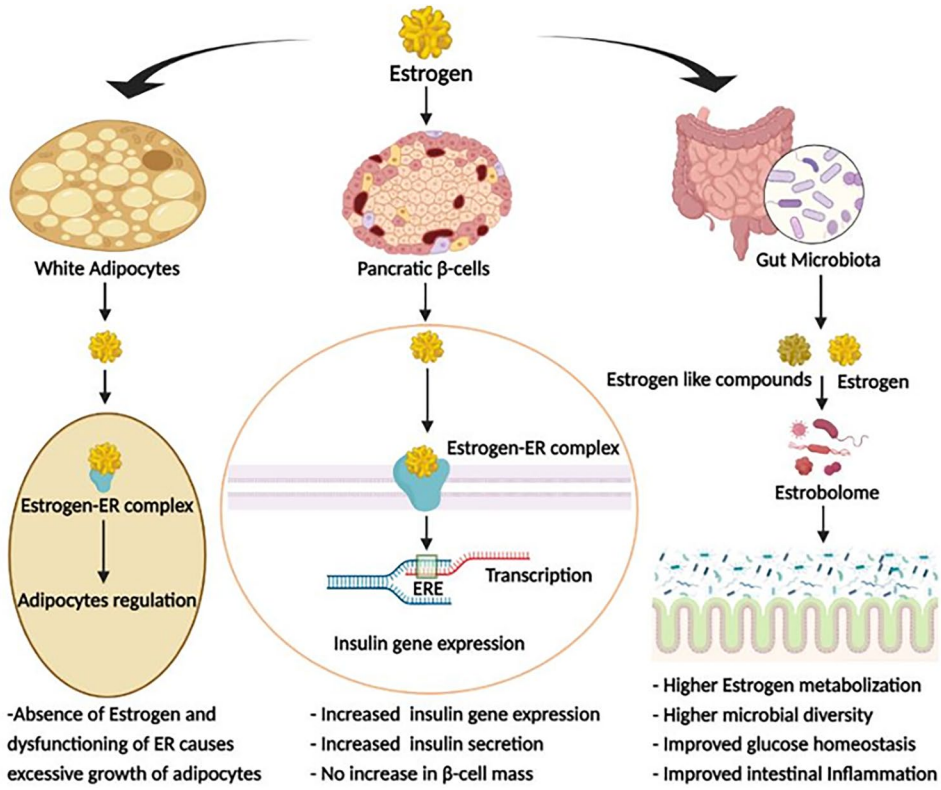


Figure 1. Effect of estrogen; Estrogen affects various metabolic activities related to T2D, such as glucose metabolism, adiposity, systemic inflammation, etc., via its direct action and by involving gut-microbiota (ER = Estrogen receptor, ERE = Estrogen responsive element).

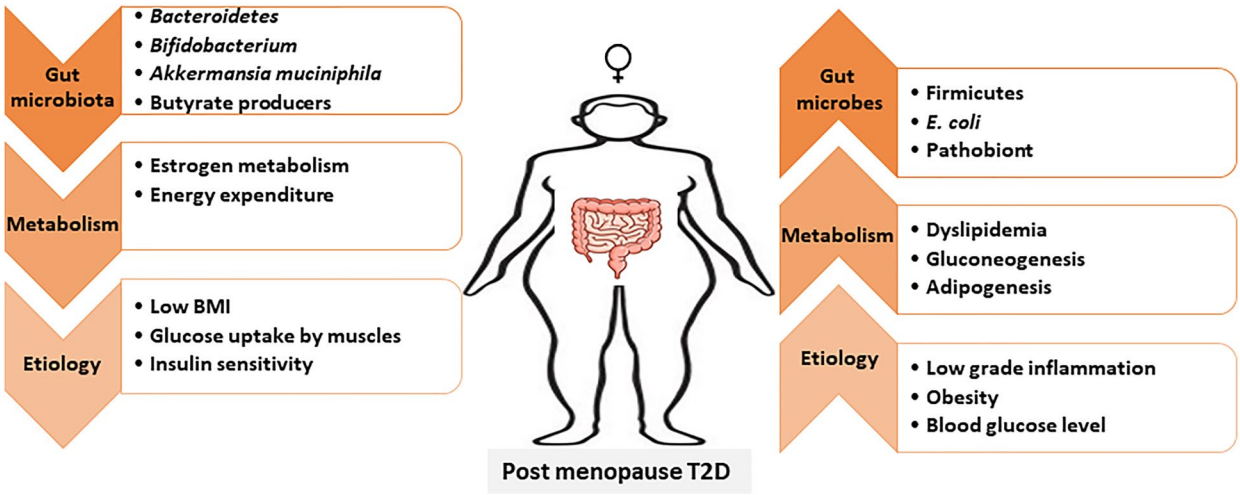


Figure 2. Impact of Post-menopausal Type 2 Diabetes; Post-menopausal type 2 diabetes affects the multiple regulators including gut microbiota to metabolism, and their impact can be seen on various T2D specific markers i.e., BMI, blood glucose level.

pentose phosphate pathway generates acetyl-CoA, which forms butyrate-CoA, a substrate that directly participates in butyrate production (Ge et al. 2020; Louis and Flint 2017), suggesting a low amount of SCFAs in the gut of post-menopausal women. Together, menopause induces gut dysbiosis, and direct hormonal functions are prone to induce obesity and diabetes (Figure 2). Other than that, post-menopausal osteoporosis is another common ailment induced due to estrogen deficiency resulting in lower bone density due to higher bone resorption and lower bone rate of bone formation, which leads to the higher occurrence of bone fracture (Eastell et al. 2016). Common gut-associated adversities among post-menopausal women are summarized in Table 2.

Regulatory microbial metabolites in T2D

Decreased SCFAs adversely influences the signal transduction linked to T2D factors, such as glucose utilization and dyslipidemia (Alexander et al. 2019). SCFAs enhance glucose uptake in skeletal muscles via glucose transporter protein (GLUT4) (Frampton et al. 2020). GPCR41- and

Table 2. Common gut associated adversities in post-menopausal women.

Post-menopausal adversities	Model	Study	Reference
Lower SCFA level	Mice	SCFA regulate systemic bone mass	(Lucas et al. 2018)
	Human	Depletion of butyrate producers in postmenopausal gut microbiota	(Zhao et al. 2019)
Gut dysbiosis	Human	Gut microbiota features and metabolic markers in postmenopausal women	(Brahe et al. 2015b)
	Human	Gut dysbiosis in post-menopausal women	(Ozaki et al. 2021)
Osteoporosis	Human	Intestinal microbiota as a target for the treatment of post-menopausal osteoporosis	(Xu et al. 2017)
	Human	Gut microbiota alteration in post-menopausal women and its association with osteoporosis	(Rettedal et al. 2021)
Inflammation	Human	Intervention induced variation in inflammatory markers in post-menopausal women	(Masala et al. 2020)
	Mice	Estrogen-mediated gut microbiome alterations influence sexual dimorphism in metabolic syndrome in mice	(Kaliannan et al. 2018)
	Human	Gut microbiota features and metabolic markers in postmenopausal women	(Brahe et al. 2015b)
	Human	Gut permeability, and inflammation across menopause transition	(Shieh et al. 2020)

GPCR43-bound SCFAs increase plasma GLP-1 levels, maintain glucose homeostasis, and control appetite (Delzenne et al. 2015). Propionate also controls blood glucose levels by suppressing gluconeogenesis in the liver by increasing the phosphorylation of AMP-activated protein kinase (AMPK) (Jang and Lee 2021). Activated AMPK inhibits gluconeogenesis by inhibiting various transcription factors that control the expression of gluconeogenesis enzymes, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (Jeon 2016). Additionally, propionate also enhances GLP-1, which reduces hepatic visceral fat by limiting triglyceride synthesis. Propionate regulates cellular lipid metabolism by modulating Fiaf, GPCR43, and histone deacetylases (HDAC) (Lukovac et al. 2014). Members of the phylum Bacteroidetes are the largest propionate producers in the gut (Chambers et al. 2015; Rios-Covian et al. 2017), thus a decreased Bacteroidetes abundance can result in increased blood glucose level (Cunningham, Stephens, and Harris 2021).

Reduced SCFAs are linked to decreased production of mucin 2, a major component of mucin protein present in the gut mucus layer, thus compromising the gut epithelial barrier (Fang et al. 2021). The reduction of the mucus layer decreases the abundance of the genus *Akkermansia*, which exerts antidiabetic effects through the Amuc_1100 outer membrane protein. Amuc_1100 plays an immunoregulatory role in the gut and promotes the secretion of serotonin, a glucose-homeostatic neurotransmitter (Wang, Xu et al. 2021). *A. muciniphila* also produces propionate in the gut that regulates the blood glucose as discussed above. Moreover, *A. muciniphila* and *Bacteroides* species are negatively associated with T2D markers, such as insulin resistance, low-grade inflammation, and lipid dysregulation (Brahe et al. 2015b). Hence, *A. muciniphila* regulates T2D and obesity via glucose homeostasis. Even oral administration of *A. muciniphila* is also effective in countering insulin resistance (Depommier et al. 2020; Greer et al. 2016). Interestingly, metformin, the first line of defense medicine against T2D, also enhances *A. muciniphila* abundance in T2D patients, which further supports the antidiabetic role of *Akkermansia* (Lee, Ko, and Griffiths 2014).

Gut microbiota also participates in glucose homeostasis regulation by controlling serotonin secretion from enterochromaffin cells (EC cells) in the gut lining (Martin et al. 2019). Serotonin is a neurotransmitter associated with glucose homeostasis as it regulates insulin secretion from pancreatic β-cells, while improving insulin sensitivity and hyperglycemia (Al-Zoairy et al. 2017; Watanabe, Rose, and Aso 2011). Approximately 90% serotonin is secreted into the body from EC cells, and the gut microbiota controls its secretion by signaling EC cells through metabolites, such as SCFAs and secondary bile acids (Martin et al. 2019). In addition, Amuc_1100, an outer surface protein of the mucolytic *A. muciniphila*, also participates in serotonin biosynthesis (Wang, Xu et al. 2021).

Secondary bile acids are also a major type of metabolites that play an important role in T2D development. Bile acids are synthesized in the liver, help in lipid digestion, and also function as endocrine molecules that enhance glucagon-like peptide-1 (GLP-1) secretion in the gut (Taylor et al. 2014; Zaborska and Cummings 2018). Most of the bile acids are actively absorbed back into the ileum through bile acid transporters, and only a small fraction of them reaches the colon (Legry et al. 2017). Gut microbiota metabolizes bile acids into secondary bile acids, such as deoxycholic acid (DCA) and lithocholic acid (LCA). Secondary bile acids are bactericidal and play a critical role in balancing the microbial community by suppressing pathobionts. However, excessive amounts of secondary bile acids may inhibit the growth of Bacteroidetes and Actinobacteria phyla, increasing the overall abundance of phylum Firmicutes (Ridlon et al. 2014). Secondary bile acids also interrupt glucose homeostasis by inhibiting TGR5, which participates in glucose homeostasis at high energy expenditure in muscles and brown adipose tissues while releasing GLP-1 (Molinaro, Wahlström, and Marschall 2018). Although some gut microbes are also known to reduce the secondary bile acid toxicity by transforming DCA and LCA into iso-DCA and iso-LCA, respectively (Legry et al. 2017).

Gut microbiota in regulation of oxidative stress and systemic inflammation

Oxidative stress indicates inner mitochondrial and cellular damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS are extremely

reactive and unstable free radicals that can activate various pathways with an adverse impact on the body (Ceriello, Testa, and Genovese 2016). Oxidative stress overloads glucose, and increased oxidative stress can lead to insulin resistance (Molehin, Adefegha, and Adeyanju 2020; Wright, Scism-Bacon, and Glass 2006). Several studies have also reported associations between increased oxidative stress and T2D among post-menopausal women due to low free thiol (R–SH) level, a key extracellular antioxidant (Bourgonje et al. 2021; Song et al. 2009).

Imbalanced gut microbial communities allow the propagation of opportunistic pathogens in the gut. Invasion by these bacteria secreting toxic metabolites (such as lipopolysaccharides (LPS) and enterotoxins) causes leaky gut syndrome and systemic inflammation. Systemic inflammation is associated with insulin resistance and T2D in post-menopausal women. Pro-inflammatory cytokine levels, such as IL-1, IL-6, and TNF-α, are high among T2D patients (Spranger et al. 2003). These pro-inflammatory cytokines induce insulin resistance (Kanmani et al. 2019) and regulate C-reactive protein, a major inflammatory marker of T2D. Chronic inflammation with elevated C-reactive protein levels is associated with T2D (Kanmani et al. 2019; Masala et al. 2020). On the other hand, IL-1 hinders insulin secretion and induces apoptosis in pancreatic β-cells, thus contributing to T2D occurrence (Banerjee and Saxena 2012). Moreover, an inflammatory load is negatively associated with circulatory estrogen levels and obesity among post-menopausal women (Masala et al. 2020).

Dietary interventions and their efficacy in controlling T2D severity

Diet directly affects most T2D components, such as glucose metabolism, caloric intake, lipid metabolism, and gut microbiota. Since gut microbiota largely impacts the metabolic regulation among T2D patients, various dietary interventions have been studied to understand their possible beneficial roles in post-menopausal T2D. The effect of these dietary interventions are mostly mediated by gut microbiota, and they benefit the host in multiple ways by simultaneously affecting the inflammatory markers and glucose-regulatory metabolism (Figure 3).

Biologically active compounds in diet

Isoflavones are polyphenolic compounds classified as phytoestrogens, as their functions are similar to those of human estrogen. Isoflavone-rich dietary sources such as soybean, fermented soy products, and chickpea sprouts are advised for post-menopausal T2D women to maintain a healthy gut microbiome (Fukuda, Kobayashi, and Honda 2017; Ma et al. 2013). Studies also reported that isoflavone administration effectively enhances the abundance of butyrogenic *E. rectale* (Zhao et al. 2019). Daidzin, an isoflavonoid abundant in a soy-based diet, can be metabolized by gut microbes into compounds similar to estrogen (Chen and Madak-Erdogan 2016). Another isoflavone, Genistein is metabolized by the gut microbiota into 4-ethylphenyl sulfate, 3-phenylpropionate, and methyl-4-hydroxybenzoate, which improves the oxidative

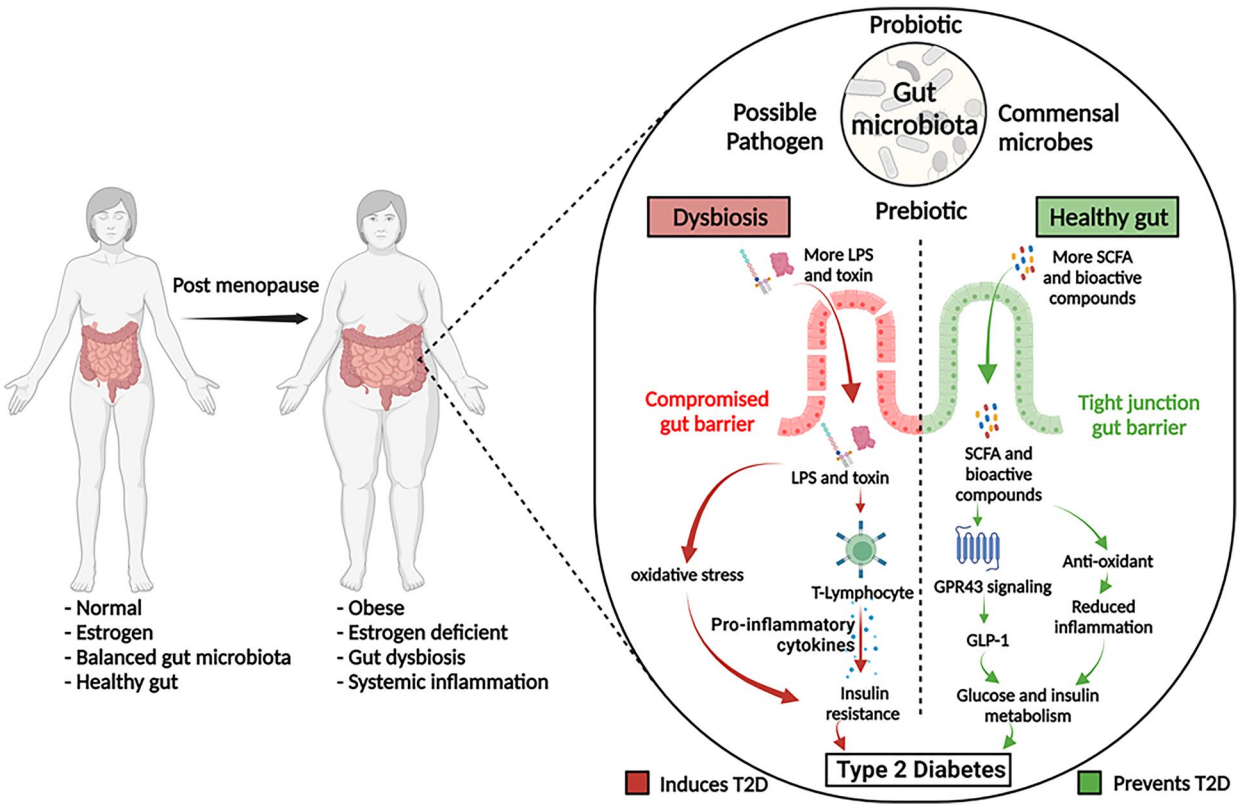


Figure 3. Role of gut microbiota in the progression of type 2 diabetes among post-menopausal women.

capacity of muscles and ameliorates T2D symptoms in post-menopausal women (Braxas et al. 2019; Guevara-Cruz et al. 2020). Genistein also decreases endotoxemia and controls body glucose levels by supporting *Akkermansia* growth (Braxas et al. 2019). Soy isoflavone administration in post-menopausal women has increased the count of *Bifidobacterium*, while decreasing the abundance of family Clostridiaceae, which participates in systemic inflammation among post-menopausal obese women (Vieira et al. 2017).

Dietary polyphenols also enrich *A. muciniphila* and reduce glucose-6-phosphate mRNA expression in a T2D mouse model, which eventually reduces gluconeogenesis and improves fasting hyperglycemia (Everard et al. 2013). Most polyphenols are indigestible, thus reaching the large intestine where more than 90% polyphenols are metabolized by gut microbiota to low molecular weight active polyphenolic compounds, such as phenolic acids and hydroxyphenyl moieties (Cardona et al. 2013; Wan, Co, and El-Nezami 2021). Green tea is a rich source of polyphenol "catechins," which account for 30–40% brewed tea solids, and is metabolized by *Eubacterium*, *Enterobacter*, *B. longum*, *L. plantarum*, and *Bacillus subtilis* (Chen and Sang 2014; Guo et al. 2019). Catechins also limit the abundance of possible harmful intestinal microbes such as *Helicobacter pylori*, *Escherichia coli*, and *Staphylococcus aureus*, while maintaining a high abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* (Guo et al. 2019). Tea catechin also decreases Firmicutes/Bacteroidetes ratio, generally referred to as an obesity indicator, while effectively controlling the postprandial glucose level and oxidative stress among post-menopausal T2D patients (Guo et al. 2019; Takahashi et al. 2014).

Bioactive compounds obtained from turmeric herb also have proven effective in T2D treatment. Turmerin is a secondary metabolite of turmeric with an antidiabetic property (Kalaycıoğlu, Gazioğlu, and Erim 2017; Lekshmi et al. 2012). Turmeric oil inhibits the activity of glucosidase, which is commonly used to control postprandial hyperglycemic conditions (Lekshmi et al. 2012). On the other hand, curcumin, a polyphenolic compound present in turmeric, boosts the abundance of probiotics (*Bifidobacterium* and *Lactobacillus*) while reducing pathogenic strains such as *Enterobacteria* and *Enterococci* (Di Meo et al. 2019). Curcumin also manages oxidative stress and inhibits several pro-inflammatory cytokines in adipose tissue to control systemic inflammation in T2D patients (Pivari et al. 2019). A murine study also reported that curcumin shifts the gut microbiota and reduces weight gain in estrogen-deficient ovariectomized rats (Zhang et al. 2017). Spent turmeric has significant antioxidant activity and contains almost 45% fiber that can be metabolized by the gut microbiota to produce SCFAs (Sowbhagya 2019).

Dietary glucosinolates are abundant in broccoli and metabolized by gut microbiota to isothiocyanate sulforaphane, which reduces blood glucose levels in T2D patients (Angelino et al. 2015; Liou et al. 2020). Additionally, broccoli is rich in phytoestrogens and helps to curb post-menopausal hormone-dependent dysregulations, including obesity and T2D (Petrine and Bianco-Borges 2021; Shoff et al. 1998). Gut microbiota metabolizes phytoestrogens to produce bioactive substances that interact with estrogen receptors and induce estrogenic effects (Stojanov and Kreft 2020).

Plant seed mucilage shifts gut microbiota, improves serum lipid profiles, and increases insulin sensitivity among post-menopausal women (Soukoulis, Gaiani, and Hoffmann 2018). Flaxseed mucilage, for example, improves postprandial glucose, insulin sensitivity, and lipid profile (Kay et al. 2017; Soltanian and Janghorbani 2018), while modulating gut microbiota in post-menopausal obese women (Brahe et al. 2015a). Flaxseed mucilage treatment in mice also enhances the abundance of genera *Lactobacillus* and *Clostridium*, which are often depleted in post-menopausal women. Some *Clostridium* species chiefly metabolize flaxseed mucilage to produce acetate and propionate (Luo et al. 2018). Another study has showed the anti-obesity effects of flaxseed by significantly increasing the abundance of genera *Akkermansia* and *Bifidobacterium* and decreasing that of obesity-associated bacteria (i.e., *Oscillospiraceae*) in mice gut microbiota (Xu, Chen et al. 2020). Flaxseed polysaccharides also limit oxidative stress and reduce pro-inflammatory markers, such as IL-6 and IL-1, while enhancing the anti-inflammatory cytokine IL-10 (Xu, Chen et al. 2020). Yellow mustard mucilage also has antioxidant properties and improves postprandial glycemic conditions (Lett, Thondre, and Rosenthal 2013; Wu et al. 2016). Fenugreeks have antidiabetic effects because they improve postprandial glycemic conditions and glucose homeostasis in T2D patients (Hannan et al. 2007; Kay et al. 2017). Moreover, fenugreek seed mucilage and spent turmeric are rich dietary fiber sources that effectively limit the higher disaccharidase (maltase, sucrase, and lactase) activity in diabetics (Kumar, Shetty, and Salimath 2005). Additionally, in vitro colonic fermentation of fenugreek enhances the abundance of *Bifidobacterium* and *Lactobacillus*, which are depleted in post-menopausal T2D patients (Kumar, Shetty, and Salimath 2005; Navarro del Hierro et al. 2020). Murine studies have also reported the therapeutic relevance of fenugreek fiber in T2D by improving glucose tolerance, dyslipidemia, and weight gain. In addition, fenugreek fiber also enhances the abundance of phylum Bacteroidetes and family Lachnospiraceae, members of which are often depleted among obese people and post-menopausal T2D patients (Bruce-Keller et al. 2020; Ozaki et al. 2021; Shtriker et al. 2018). Lastly, clinical studies have proven that fenugreek seed is effective against hyperlipidemia, inflammation, and oxidative stress in T2D patients. Thus, regular fenugreek seed administration may help T2D control in post-menopausal women (Chaturvedi et al. 2013; Roberts 2011; Tavakoly et al. 2018). Besides fenugreek seed, chia seed mucilage is also a potential remedy for post-menopausal T2D patients because it has antidiabetic properties and increases the abundance of *Lactobacillus* and the amount of SCFAs in vitro, although further studies are required to investigate how it modulates the gut microbiome in T2D patients (Tamargo et al. 2018).

A healthy diet normally comprises omega 3 fatty acids (n-3) and omega 6 fatty acids (n-6), where n-3 is effective in significantly controlling insulin resistance, triglycerides,

Table 3. Prebiotics and their role in T2D management in post-menopausal women.

Prebiotic	Monosaccharide	Microbiota variation	Antidiabetic role	References
Resistant Dextrin	D-Glucopyranose	↑*Peptostreptococcus* ↑*Fusobacterium* ↑*Bifidobacterium*	Enhances SCFA production; specially butyrate production, Improves insulin resistance	(Aliasgharzadeh et al. 2015; Wang et al. 2020)
Oligofructose	Fructose and glucose	↑*Bifidobacterium* ↑*Lactobacilli* ↓*Enterobacteriaceae*	Improve glycemic condition, lipid profile, and antioxidant level	(Dehghan, Pourghassem Gargari, and Asghari Jafar-abadi 2014; Nie et al. 2019; Niness 1999)
Inulin	Fructose and glucose	↑*Cyanobacteria* ↑*Bacteroides* ↓*Deferribacteres* ↓*Tenericutes*	Improves fasting glucose level, body weight and blood lipid	(Wang et al. 2020; Yan et al. 2019)
Oligofructose enriched inulin	Fructose and glucose	↑*Bifidobacterium*	Improves fasting glucose level, limits IL-6 and TNF-α, while increases IL-10	(Dehghan, Pourghassem Gargari, and Asghari Jafar-abadi 2014)
Stachyose	2, α-D-galactose, α-D-glucose and fructose (Tetra-saccharide nature)	↑*Phascolarctobacteria* ↑*Bilophila* ↑*Oscillospira* ↑*Turicibacter*	Decreases serum LPS and expression of inflammatory cytokines i.e., Il-6 and TNF-α	(Liu et al. 2018; Yan et al. 2016)
Fructooligosaccharide	Fructose and glucose	↑*Bifidobacterium* ↑*Lactobacilli*	Improves body weight, antioxidant capacity and reducing hyperglycemia	(Gobinath et al. 2010; Nie et al. 2019)
Xylo-oligosaccharides	Xylose	↑*Bifidobacterium* ↑*Lactobacilli*	Improves body weight, antioxidant capacity and reducing hyperglycemia	(Gobinath et al. 2010; Wang et al. 2020)

and pro-inflammatory IL-6 among post-menopausal women with metabolic syndromes (Tardivo et al. 2015). Clinical evidences suggest that n-3 reverses dysbiosis by restoring Firmicutes/Bacteroidetes proportion and enhancing the Lachnospiraceae members producing anti-inflammatory metabolites such as butyrate (Costantini et al. 2017). Moreover, studies have also shown that n-3 controls endotoxemia by increasing the abundance of probiotics (i.e., *Bifidobacterium*) and decreasing that of gram-negative bacteria whose LPS causes systemic inflammation (Cani et al. 2007; Costantini et al. 2017). Interestingly, further studies have suggested that a rationalized mixture of n-3 and n-6 is more effective in controlling the elevated triglycerides in post-menopausal T2D women than individual treatments (Griffin et al. 2006).

Effect of prebiotics and probiotics against T2D progression

Prebiotics are non-digestible polysaccharides and oligosaccharides that confer beneficial effects to the host by supporting beneficial bacterial growth. Table 3 summarizes some prebiotics reported to reduce insulin resistance and T2D progression. However, clinical trials have shown that the administration of oligosaccharides such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) has a limited impact on insulin resistance and glycemic control (Luo et al. 2000; Nie et al. 2019).

Probiotics are live beneficial microbes and their administration usually positively modulates the microbial community and improves the intestinal barrier function and immunity, which supports host health. Evidence from numerous studies have reported that *Bifidobacterium*, *Lactobacillus*, *Bacillus*, *Streptococcus*, *Akkermansia*, and *Roseburia* administration showed beneficial health effects in T2D patients (Gurung et al. 2020). *Lactobacillus* is a lactic acid bacteria (LAB) that commonly alters the microbial flora by reducing the gut pH, which inhibits the growth of opportunistic pathogens. Lactic acid produced by LAB is further cross-fed by SCFA-producing bacteria (Li et al. 2017). *Bifidobacterium*, another LAB, is also a well-known beneficial bacterium that inhibits opportunistic pathogens, produces antioxidants, reduces inflammation, and cross-feeds SCFA producers (Rivière et al. 2016). *Bifidobacterium* also improves glucose levels, endotoxemia, fat accumulation, and insulin resistance (Cani et al. 2007; Cano et al. 2013; Kikuchi, Ben Othman, and Sakamoto 2018). Clinical studies in T2D patients have also found that probiotics are effective in improving the glycemic condition and dyslipidemia (Kocsis et al. 2020; Tao et al. 2020). The murine T2D model showed that probiotics increases SCFA production, improves gut barrier function, and enhances insulin secretion via GLP-1 secretion (Xu, Wang et al. 2020). The co-administration of different *Bifidobacterium* and *Lactobacillus* strains significantly improves obesity, insulin resistance, glycemic condition, dyslipidemia, hyperuricemia, pro-inflammatory markers, and LPS levels in post-menopausal obese women (Skrypnik et al. 2019; Szulińska et al. 2018). Table 4 summarizes the strain-specific antidiabetic effects of these probiotic strains.

Fermented dairy products such as yogurt and kefir also proven their roles against obesity and T2D. Milk fermentation involves various probiotic *Lactobacillus* and *Streptococcus* strains, whose ingestion contributes to maintaining a healthy microbial ecosystem by producing SCFAs, reverting dysbiosis, and limiting harmful microbes by decreasing the gut pH (Fernandez and Marette 2018; Marco et al. 2017). Moreover, milk fermentation by LAB also increases the conjugated linoleic acid content, which significantly decreases obesity and adipogenesis among post-menopausal T2D patients (Norris et al. 2009). The antidiabetic role of fermented milk products is also supported by their ability to reduce colonic pro-inflammatory cytokines and ROS in intestinal enterocytes, and the presence of a high amount

Table 4. Probiotic strains used in previous studies and their roles against T2D (*L.* = *Lactobacillus*, *B.* =*Bifidobacterium*).

Probiotic strain	Model	Antidiabetic role	Reference
L. salivarius AP-32	Mice	Improves glycemic condition	(Hsieh et al. 2020)
L. gasseri BNR17, SBT2055	Mice/human	Improves blood glucose level, glucose sensitivity and obesity	(Sáez-Lara et al. 2016; Yun, Park, and Kang 2009)
L. plantarum MG4229, MG4296, MG5025 and CCFM0236	Human/Mice	α-glucosidase and α-amylase inhibitory, anti-oxidant activity	(Sáez-Lara et al. 2016; Won et al. 2021)
L. acidophilus KLDS1.1003, KLDS1.0901 and NCFM	Mice/Human	Improves gut-barrier function, glucose-lipid metabolism, and inflammation	(Andreasen et al. 2010; Yan et al. 2019)
L. rhamnosus GG	Human	Improves the glycemic condition	(Sanborn, Azcarate-Peril, and Gunstad 2020)
L. casei CCFM419, CCFM0412	Mice	Improves glucose level, insulin-resistance and inflammatory markers, higher SCFA	(Chen et al. 2014; Wang et al. 2017)
L. paracasei MG5012, NL41	Human/Mice	Improves blood glucose regulation and insulin resistance	(Won et al. 2021; Zeng et al. 2019)
L. reuteri ADR1, ADR3 and GL-104	Mice	Reduces insulin sensitivity and improves anti-oxidant activity	(Hsieh et al. 2018; Hsieh et al. 2020)
B. lactis HY8101	Mice	Improves insulin sensitivity, glucose and lipid metabolism	(Kim et al. 2014)
B. animalis 01	Mice	Improves hepatic insulin sensitivity	(Zhang et al. 2020)
B. longum DD98	Mice	Improves glucose level, regulates insulin and lipid metabolism	(Zhao et al. 2020)
B. pseudocatenulatum CECT 7765	Mice	Improves glucose tolerance and insulin resistance	(Cano et al. 2013)
Saccharomyces boulardii Biocodex	Mice	Improves body mass and inflammation	(Everard et al. 2014)
Clostridium butyricum CGMCC0313.1	Mice	Improves fasting blood glucose, glucose tolerance ad insulin resistance	(Jia et al. 2017)

Table 5. Synbiotic administration used in different T2D studies (*L.*=*Lactobacillus*, *B.*=*Bifidobacterium*, *S.* = *Streptococcus*).

Synbiotic	Model	Antidiabetic role	References
L. sporogenes and Inulin	Human	Decreases Triacylglycerol and VLDL	(Shakeri et al. 2014)
L. acidophilus and powdered Cinnamon	Human	Improves glycemic control and antioxidant status	(Mirmiranpour et al. 2020)
L. acidophilus ATCC 4357 with fructo-oligosaccharide and iso maltooligosaccharide	Rabbit	Reduction in blood glucose, urea and creatinine levels, Limits the abundance of E. *coli*	(Shafi et al. 2019)
L. fermentum and β-glucans from cauliflower mushroom	Mice	Improves dysbiosis	(Jeong et al. 2017)
L. acidophilus, B. *bifidum,* and fructooligosaccharide	Human	Improves glycemic condition	(Moroti et al. 2012)
L. sporogenes, inulin, and beta-carotene	Human	Improves triglyceride, insulin and antioxidant stress level	(Asemi et al. 2016)
L. casei, *L.* acidophilus, *L.* rhamnosus, *L.* bulgaricus, *B.* breve, *B. longum, S. thermophilus*, and fructooligosaccharide	Human	Improves serum insulin, insulin resistance and glycemic profile	(Raji Lahiji et al. 2021)
L. sporogenes, inulin, isomalt, Sorbitol,	Human	Improves serum insulin, and glucose homeostasis	(Asemi et al. 2014)
Bacillus coagulans, *L. rhamnosus, L. acidophilus* and fructo-oligosaccharide	Human	Improves fasting blood glucose level, and insulin resistance	(Velayati et al. 2021)

of bioactive peptides (Marco et al. 2017). Bioactive peptides are derived from the enzymatic digestion of milk proteins by LAB, which is hypothesized to be antidiabetic through regulating the genes participating in glucose uptake, inflammatory responses, and insulin production (Fernandez and Marette 2018). Studies on ovariectomized mice have shown that kefir peptide consumption increased gut microbial richness and SCFA-producing bacteria such as *Anaerostipes*, *Ruminococcus*, and *Streptococcus* (Tu et al. 2020).

Effects of synbiotic treatment against T2D progression

Synbiotic treatments involve the co-administration of probiotics and prebiotics. Synbiotic treatments often have a better impact than individual treatments. For example, *L. acidophilus* DSM20079 produced 14.5 times more butyrate in the presence of inulin or pectin than that in their absence (Kim, Keogh, and Clifton 2018). Several studies have found that synbiotic administration effectively reduces insulin resistance and plasma lipid profiles in T2D patients (Kim, Keogh, and Clifton 2018; Sáez-Lara et al. 2016). A previous study on an estrogen-deficient murine model has reported that synbiotic treatments alters the gut microbiota and alleviates dyslipidemia and insulin resistance (Jeong et al. 2017). Synbiotic administration also significantly reduced blood glucose levels and insulin resistance in post-menopausal T2D patients (Lee et al. 2020; Raji Lahiji et al. 2021). Synbiotic treatment of fermented milk containing *L. paracasei* and inulin enhances the bioavailability of soy-derived isoflavones in post-menopausal women, thus enhancing the conversion of isoflavones into estrogen-like compounds (Timan et al. 2014). Table 5 summarizes the antidiabetic effects of synbiotic treatments.

Effects of postbiotic treatment against T2D progression

The postbiotic treatment is a comparatively new strategy in which non-viable microbial products such as SCFAs, functional proteins, extracellular polysaccharides, and cell lysate

can be administered without evoking the host-immune response (Chaudhari and Dwivedi 2022). Recently, various postbiotic approaches have been successfully used to treat obesity and diabetes, which includes the anti-obesity impact of lipoteichoic acid from *Bifidobacterium animalis* subsp. lactis BPL1 (Balaguer et al. 2022), and insulin-sensitizing role of bacterial cell wall-derived muramyl dipeptide (Cavallari et al. 2017). Postbiotic were also found to be effective in controlling the post-menopausal osteoporosis in the murine model (Jang et al. 2021; Montazeri-Najafabady et al. 2021), but their efficacy against post-menopausal T2D has yet to be tested, as till date there is no information is available regarding it.

Conclusion

Permanent estrogen depletion poses a significant pressure on metabolic regulation and intestinal dysbiosis. As the gut microbiota is a pivotal component that regulates the glucose homeostasis, oxidative stress, and systemic inflammation, it is important to maintain intestinal health and to avoid the vicious spread of T2D among post-menopausal women. To exploit the possible antidiabetic potential of gut microbiota and its regulatory impact on T2D, different dietary interventions can be administered under close medical guidance to ease post-menopausal diabetic conditions.

Contribution

VS and TU conceptualized the manuscript, VS wrote and drafted the manuscript, YP and GL participated in illustration, TU and JS supervised and finalized the final draft of the manuscript.

Declaration of interest statement

The author declares no conflict of interest.

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