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FLAXSEED, SEA BUCKTHORN AND CORNELIAN CHERRY IN TYPE 2 DIABETES: GUT MICROBIOTA AND METABOLIC BENEFITS—A NARRATIVE REVIEW

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ABSTRACT

Type 2 diabetes mellitus (T2DM) represents over 90% of diabetes cases worldwide and continues to rise in prevalence due to aging populations, sedentary lifestyles, obesity, and nutritional transitions. The disease is characterized by progressive insulin resistance, pancreatic β-cell dysfunction, chronic hyperglycemia, oxidative stress, and low-grade inflammation, leading to multi-organ complications including cardiovascular, renal, neural, and ocular damage. Emerging evidence identifies gut microbiota dysbiosis and metabolic endotoxemia as central contributors to T2DM pathogenesis. Reduced microbial diversity, impaired short-chain fatty acid (SCFA) production, and increased intestinal permeability facilitate lipopolysaccharide (LPS) translocation, triggering inflammatory cascades that may interfere with insulin signaling.

Dietary bioactive compounds capable of modulating gut microbial composition and supporting intestinal barrier integrity have therefore gained attention as adjunctive therapeutic strategies. This review analyzes the mechanistic effects of three phytochemically rich plant sources—flaxseed (*Linum usitatissimum*), sea buckthorn (*Hippophae rhamnoides*), and cornelian cherry (*Cornus mas*) - in the context of T2DM. Flaxseed lignans and fermentable fibre may enhance SCFA production, potentially suppress hepatic gluconeogenesis, and attenuate inflammatory signaling. Sea buckthorn polyphenols may help reshape microbial ecology, activate AMPK-dependent pathways, improve lipid metabolism, and are associated with multi-organ protection. Cornelian cherry iridoids and anthocyanins may modulate antioxidant and inflammatory pathways, contribute to improved insulin sensitivity, and support vascular and endothelial function.

Collectively, these plant-derived bioactives converge on shared metabolic nodes, including restoration of gut barrier integrity, reduction of metabolic endotoxemia, activation of AMPK signaling, suppression of hepatic glucose production, enhancement of peripheral glucose uptake, and improvement of lipid homeostasis. Targeting the gut–liver–pancreas axis through microbiota-mediated mechanisms may represent a rational adjunctive strategy for mitigating insulin resistance and limiting the progression of T2DM and its complications.

Keywords: type 2 *diabetes mellitus,* gut microbiota**,** sea buckthorn, cornelian cherry, flaxseed, metabolic endotoxemia, short-chain fatty acids

INTRODUCTION

T2DM is a multifaceted systemic disorder driven by insulin resistance, progressive pancreatic β-cell dysfunction, chronic hyperglycemia, oxidative stress, and low-grade inflammation. These disturbances may promote advanced glycation end products (AGEs), mitochondrial impairment, and endothelial damage, culminating in microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (atherosclerosis, cardiovascular disease) complications (**Capcarova *et al.*, 2019**).

While traditional models emphasize defects in pancreatic and peripheral insulin signaling, the gut microbiota has emerged as a pivotal regulator of metabolic homeostasis. In health, microbial fermentation of dietary fibres yields short-chain fatty acids (SCFAs) that may bolster epithelial integrity, stimulate glucagon-like peptide-1 (GLP-1) secretion, inhibit hepatic gluconeogenesis, and temper immune responses. T2DM-associated dysbiosis—marked by reduced diversity, depleted SCFA producers, and heightened intestinal permeability—facilitates lipopolysaccharide (LPS) translocation, or metabolic endotoxemia. This is associated with the activation of Toll-like receptor 4 (TLR4)/NF-κB signaling, cytokine release (TNF-α - tumor necrosis factor, IL-6 - interleukin), and serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby exacerbating insulin resistance across liver, muscle, and adipose tissue (**Mashal *et al.*, 2025**).

Addressing this gut–microbiota–host axis through dietary modulation offers mechanistic promise. Phytochemically rich plants such as flaxseed (*Linum usitatissimum*), sea buckthorn (*Hippophae rhamnoides*), and cornelian cherry (*Cornus mas*) warrant attention for their capacity to reshape microbial ecology, enhance SCFA production, and restore barrier function. Flaxseed's lignans (e.g., secoisolariciresinol diglucoside) and fermentable fibres promote enterolignan generation and butyrate enrichment via taxa like *Ruminococcus* and *Faecalibacterium*. Sea buckthorn polyphenols (flavonols, carotenoids) foster *Akkermansia muciniphila* proliferation and phenolic acid metabolites, yielding anti-lipogenic effects. Cornelian cherry iridoids (loganic acid, cornuside) and anthocyanins uniquely inhibit α-glucosidases while activating Nrf2/eNOS pathways, supporting endothelial integrity alongside microbial shifts (**Livingston *et al.*, 2023, Yuan *et al.*, 2025, Oledzka *et al.*, 2022**).

Despite phytochemical diversity, these plants converge on the gut–liver–pancreas axis: reducing endotoxemia, activating AMPK/PPAR signaling, suppressing gluconeogenesis, enhancing GLUT4-mediated uptake, and modulating lipids/inflammation (Fig 1). Mechanistic insights from preclinical models suggest they may mitigate upstream drivers of T2DM progression, complementing pharmacotherapy (**Sharma *et al.*, 2026, Paliwal *et al.*, 2023, Liang *et al.*, 2025**).

This narrative review elucidates these interconnected mechanisms, evaluating how flaxseed, sea buckthorn, and cornelian cherry influence microbiota composition, metabolic signaling, and organ-level outcomes. By integrating gut-directed nutritional strategies, such approaches hold potential as adjunctive components of T2DM management.

To improve interpretative clarity, mechanistic findings discussed in this review are contextualized according to the level of evidence. Observations derived from in vitro experiments, animal models, and human clinical studies are distinguished where possible, acknowledging that translational applicability may vary. This stratification is particularly relevant for pathways such as AMPK activation, GLUT4 translocation, and multi-organ protective effects, which are often predominantly supported by preclinical data.

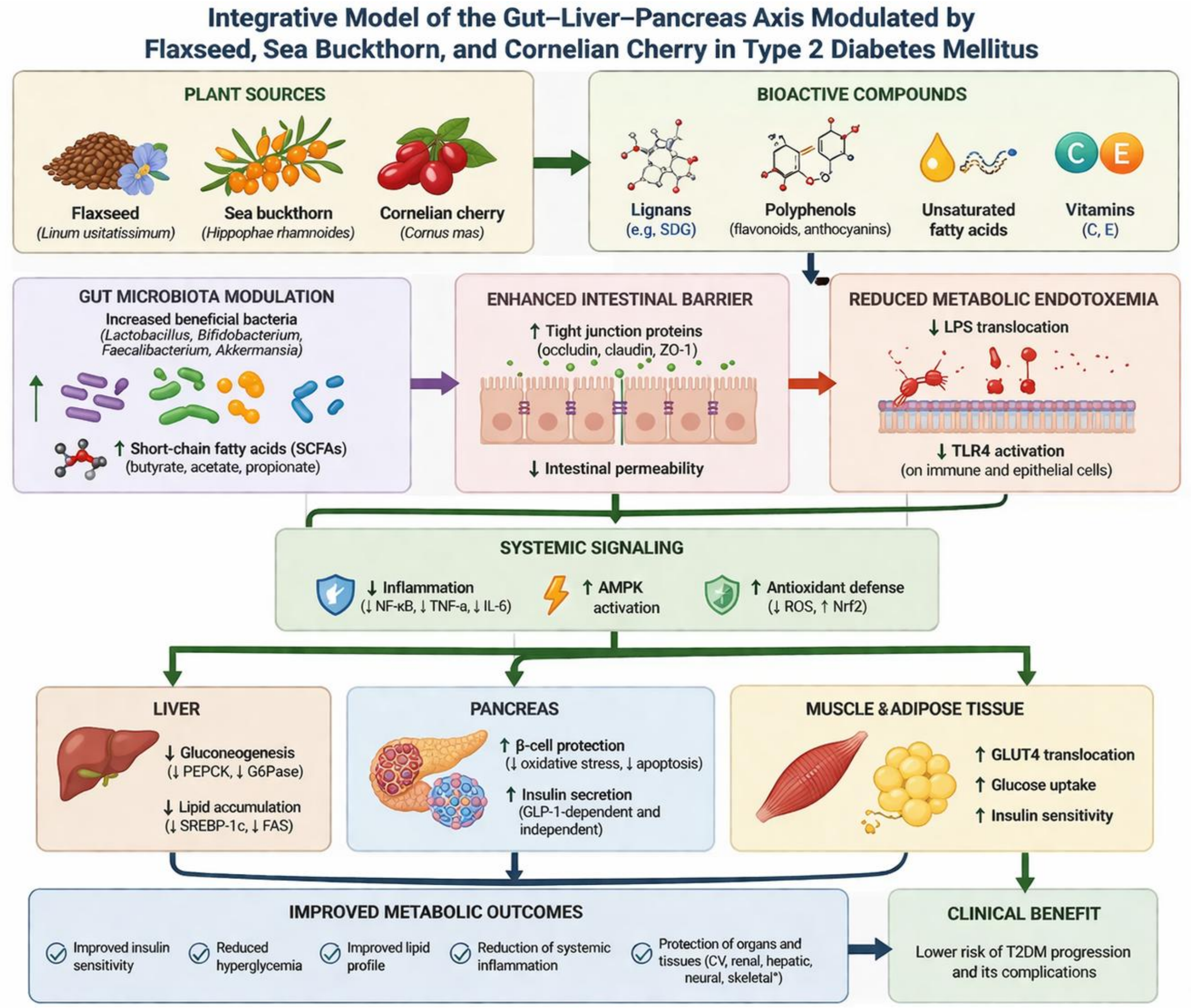

Figure 1 Representative scheme of the gut–liver–pancreas axis modulated by flaxseed, sea buckthorn, and cornelian cherry in T2DM (the schematic representation was created using an AI-assisted tool based on the authors' synthesis of the cited literature)

Legend: SDG- secoisolariciresinol diglucoside, LPS- lipopolysaccharides, TLR 4- Toll-like receptor 4, NF-κB - nuclear factor kappa B, TNF-α - tumor necrosis factor-α , IL-6- interleukin 6, AMPK- AMP-activated protein kinase, ROS-reactive oxygen species, Nrf2- nuclear factor erythroid 2-related factor, PEPCK-phosphoenolpyruvate carboxykinase, G6pase- glucose-6-phosphatase, SREBP-1c- sterol regulatory element-binding protein 1c, FAS- fatty acid synthase, GLUT4-glucose transporter 4, GLP1- glucagon-like peptide-1, CV-cardiovascular

MATERIAL AND METHODS

This narrative review was conducted using a structured literature search strategy to improve transparency and reproducibility. Relevant studies were identified primarily through the PubMed database, supplemented by Elsevier ScienceDirect and Google Scholar.

Search terms included combinations of the following keywords: *type 2 diabetes mellitus*, *gut microbiota*, *metabolic endotoxemia*, *short-chain fatty acids*, *flaxseed*, *sea buckthorn*, and *cornelian cherry*. The search focused on articles published in English between 2000 and 2026.

Studies were screened based on relevance to the interaction between dietary bioactive compounds, gut microbiota modulation, and metabolic regulation inT2DM. Both experimental (in vitro and animal studies) and clinical studies were considered. However, priority was given to studies with clearly described methodologies and mechanistic insights.

A total of approximately 140 studies were initially identified, of which 80 were included after title/abstract screening and full-text evaluation. Due to the narrative nature of this review, formal risk-of-bias assessment and meta-analysis were not performed. Instead, evidence was critically synthesized with consideration of study design, model system (in vitro, animal, or human), and consistency of findings across studies.

TYPE 2 DIABETES MELLITUS AND THE GUT MICROBIOME

T2DM is among the most prevalent chronic diseases worldwide. T2DM alone accounts for over 90% of all diabetes cases and is steadily increasing in prevalence. The rising incidence correlates with population aging, sedentary lifestyle, unhealthy dietary patterns, and obesity. Countries with low and middle socioeconomic status exhibit disproportionately higher rates of T2DM, underscoring the influence of lifestyle transitions and health disparities (**Capcarova *et al.*, 2019**).

T2DM is defined by impaired insulin secretion and insulin resistance. Dysfunction of pancreatic β-cells—characterized by a reduced number and decreased insulin production—coexists with impaired cellular responsiveness to insulin in skeletal muscle, adipose tissue, and the liver. Initially, compensatory hyperinsulinemia develops as the pancreas increases insulin secretion to maintain normoglycemia (**Liu *et al.*, 2025**). Over time, β-cell exhaustion occurs, leading to overt hyperglycaemia. Chronic hyperglycaemia is associated with non-enzymatic glycation of proteins and lipids, yielding advanced glycation end products (AGEs), which activate inflammatory pathways and promote oxidative stress. These mechanisms contribute to the progression of microvascular complications such as neuropathy, nephropathy, and retinopathy, as well as macrovascular disorders including atherosclerosis and cardiovascular disease (**Simkova *et al.*, 2025**). Moreover, T2DM can be associated with chronic pain due to progressive systemic complications (**Martuliak *et al.*, 2024**). Hyperglycaemia alters immune cell programming, leading to chronic low-grade inflammation and oxidative stress (**Hrnkova *et al.*, 2022**). Insulin-induced stress in β-cells accelerates their dysfunction, while toxic lipid accumulation impairs organ systems. Mitochondrial dysfunction promotes reactive oxygen species (ROS) formation, propagating endothelial dysfunction - a hallmark of early diabetes - characterized by impaired vasodilation, increased permeability, and inflammatory activation (**Guan *et al.*, 2024**). Endothelial dysfunction precedes observable structural vascular changes and plays a key role in diabetic angiopathy. Adipose tissue, central to metabolic regulation, becomes dysfunctional in most individuals with T2DM, particularly those with obesity. Dysfunctional adipose tissue secretes pro-inflammatory cytokines and exacerbates insulin resistance, thereby accelerating vascular damage (**Ma *et al.*, 2025**).

Beyond classical endocrine and metabolic disturbances, growing evidence identifies the gut microbiota as a central regulator in T2DM pathophysiology. The gut microbiota is a key regulator of host immunity and an important source of bioactive metabolites, particularly SCFAs. These compounds arise primarily from the microbial fermentation of dietary carbohydrates and, to a lesser extent, amino acids. SCFAs exert multiple physiological effects: they support intestinal gluconeogenesis, strengthen epithelial barrier function, promote glucagon-like peptide-1 (GLP-1) secretion, and influence pancreatic β-cell performance and insulin release (**Sadagopan *et al.*, 2023**). Maintenance of intestinal homeostasis depends on tightly coordinated mechanisms. The epithelial barrier is stabilized by tight junction proteins, endocannabinoid system activity, and the detoxifying action of intestinal alkaline phosphatase against lipopolysaccharides (LPS), which helps regulate lipid handling, inflammatory signalling, energy balance, and preservation of gut barrier integrity. In healthy individuals, the gut microbiome demonstrates stable diversity and functional resilience, with dominant and less abundant taxa coexisting in balance. Commonly represented phyla and genera include *Bacteroidetes, Firmicutes, Ruminococcus, Lactobacillus, Clostridium, Fusobacteria, Actinobacteria*, and *Verrucomicrobia*. In contrast, T2DM is characterized by compositional shifts in the microbiota, including a reduced Firmicutes-to-Bacteroidetes ratio. Both prediabetic and T2DM populations consistently show diminished microbial richness and diversity compared with individuals exhibiting normal glucose tolerance. Dysbiosis frequently involves a decline in SCFA-producing bacteria and disruption of metabolic cross-feeding networks essential for barrier maintenance (**Cunningham *et al.*, 2021**).

A central mechanism linking dysbiosis to insulin resistance is metabolic endotoxemia. Metabolic endotoxemia refers to a chronic, low-grade elevation of circulating LPS derived from Gram-negative bacteria. Under physiological conditions, LPS remains confined to the intestinal lumen and is neutralized by epithelial and immune mechanisms. However, in T2DM and obesity, impaired tight junction integrity increases intestinal permeability, allowing LPS to translocate into the bloodstream. Even modest elevations in plasma LPS are sufficient to activate Toll-like receptor 4 (TLR4) on immune and metabolic cells. Activation of TLR4 triggers NF-κB–mediated inflammatory cascades, resulting in increased production of pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines interfere with insulin receptor signalling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby impairing downstream PI3K/Akt signalling and reducing GLUT4-mediated glucose uptake (**Sasidharan *et al.*, 2024, Mohammed and Thiemermann., 2021**). Sustained LPS exposure contributes to chronic low-grade inflammation, oxidative stress, hepatic steatosis, and progressive insulin resistance. Importantly, experimental models - including Zucker diabetic fatty (ZDF) rats - demonstrate that elevated circulating LPS parallels worsening metabolic parameters, reinforcing the concept that microbial components are active drivers rather than passive markers of disease progression. Moreover, LPS-induced inflammation accelerates pancreatic β-cell apoptosis and worsens endothelial dysfunction, further integrating gut-derived signals into systemic metabolic deterioration (**Fang *et al.*, 2025, Mazaheri-Tehrani *et al.*, 2025**).

SCFAs, bile acids, and components of the endocannabinoidome operate in an interconnected manner to maintain gut barrier competence and metabolic balance. Through these interactions, they contribute to lower food intake, improved lipid and glucose profiles, enhanced insulin sensitivity, and reduced inflammatory activity. When dysbiosis develops, SCFA synthesis is disrupted, bile acid composition is altered, and endocannabinoid signalling becomes dysregulated. These disturbances weaken barrier function and initiate a cascade of metabolic consequences, including reduced insulin responsiveness, persistent low-grade inflammation, increased oxidative stress, hepatic steatosis, and adipose tissue expansion. Experimental and clinical evidence indicates that elevating SCFA levels can improve insulin sensitivity in individuals with obesity and T2DM (**Sadagopan *et al.*, 2023**).

Within this pathophysiological framework, dietary bioactive compounds capable of modulating microbiota composition, enhancing SCFA production, and restoring barrier integrity gain relevance. Functional plant sources such as flaxseed, sea buckthorn, and cornelian cherry exert metabolic effects that extend beyond direct antioxidant or hypoglycaemic activity. Their bioactive constituents - lignans and fermentable fibre in flaxseed, polyphenols in sea buckthorn, and iridoids and anthocyanins in cornelian cherry - interact with the gut microbiota and promote beneficial shifts in microbial ecology. These shifts favour SCFA-producing taxa, enhance epithelial tight junction expression, and reduce intestinal permeability (**Jin *et al.*, 2023, Chen *et al.*, 2022, Kleigrewe *et al.*, 2022**) By strengthening barrier integrity, these phytochemicals decrease systemic LPS exposure and attenuate TLR4-driven inflammatory signalling. The consequent reduction in metabolic endotoxemia alleviates inhibition of insulin receptor pathways, contributing to improved insulin sensitivity in liver, muscle, and adipose tissue. Simultaneously, SCFA-mediated activation of GPR41 and GPR43 enhances GLP-1 secretion, supports β-cell function, and suppresses hepatic gluconeogenesis. Through these interconnected mechanisms, plant-derived bioactives influence the gut–liver–pancreas axis and address upstream drivers of insulin resistance rather than solely lowering blood glucose levels.

Thus, modulation of metabolic endotoxemia represents a mechanistic bridge linking gut microbiota imbalance to systemic metabolic dysfunction in T2DM. Targeting this axis through diet-based strategies may therefore represent a rational adjunctive approach for mitigating chronic inflammation, restoring insulin responsiveness, and limiting multi-organ complications associated with diabetes (**Nikolaidis *et al.*, 2025**).

PLANT BIOACTIVES MODULATING THE GUT–METABOLIC AXIS IN TYPE 2 DIABETES MELLITUS

Flaxseed

Flaxseed (*Linum usitatissimum*) is a complex functional food rich in biologically active constituents, of which secoisolariciresinol diglucoside (SDG) represents the predominant lignan. SDG is primarily localized in the outer hull and is covalently linked within a macromolecular complex containing fibre and phenolic acids. In addition to lignans, flaxseed contains substantial amounts of soluble and insoluble dietary fibre, including mucilage polysaccharides. This unique matrix is metabolically relevant because the lignan–fibre association influences their bioaccessibility, microbial fermentation, and systemic biological effects (**Mueed et al, 2022**).

Following ingestion, SDG is resistant to digestion in the upper gastrointestinal tract due to its glycosidic bonds and complexation within the seed matrix. In the colon, specific bacterial taxa expressing β-glucosidase activity hydrolyse SDG into its aglycone secoisolariciresinol (SECO). Subsequent demethylation, dehydroxylation, and reduction reactions - mediated by anaerobic bacteria such as species within the genera *Bacteroides*, *Clostridium*, *Eubacterium*, *Ruminococcus*, and *Eggerthella* - convert SECO into the mammalian enterolignans, enterodiol (END) and enterolactone (ENL). These metabolites are absorbed into circulation, undergo enterohepatic recirculation, and may exert systemic endocrine and metabolic effects (**Baldi *et al.*, 2023**). The efficiency of SDG conversion is highly dependent on gut microbial composition. Diets enriched with flaxseed increase the relative abundance of SCFA-producing genera such as *Ruminococcus*, *Faecalibacterium*, and certain members of the *Lachnospiraceae* family, while also promoting *Bifidobacterium* and *Lactobacillus* populations. These compositional shifts enhance fermentation capacity and increase SCFA production - particularly butyrate and propionate - while supporting epithelial barrier integrity. Increased SCFA availability is metabolically significant in the context of insulin resistance and T2DM (**Kleigrewe *et al.*, 2022**). Flaxseed fibre plays a synergistic role in this process. Soluble polysaccharides are fermented by colonic bacteria, leading to elevated SCFA production. Butyrate serves as a primary energy substrate for colonocytes and may upregulate tight junction proteins such as claudin-1 and occludin, thereby strengthening gut barrier function and potentially reducing metabolic endotoxemia. Propionate and acetate enter the portal circulation and influence hepatic metabolism; propionate suppresses hepatic gluconeogenesis by modulating the expression of phosphoenolpyruvate carboxykinase (PEPCK), a rate-limiting enzyme in glucose production. Downregulation of PEPCK may contribute directly to reduced hepatic glucose output and improved glycaemic control (**Portincasa *et al.*, 2021, Yoshida *et al.*, 2019**).

Enterolignans further modulate glucose metabolism through multiple interconnected pathways. ENL has been shown to activate AMP-activated protein kinase (AMPK), enhancing glucose uptake in skeletal muscle and adipose tissue via GLUT4 translocation while suppressing hepatic gluconeogenic genes, including PEPCK and glucose-6-phosphatase. Additionally, enterolignans potentially attenuate nuclear factor kappa B (NF-κB) signalling, reducing pro-inflammatory cytokine production (e.g., TNF-α and IL-6), which are key mediators of insulin resistance. Modulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) further improves lipid handling and insulin sensitivity, enhancing insulin receptor substrate (IRS-1) phosphorylation and downstream PI3K/Akt signaling (**Zhou *et al.*, 2017, Corsini *et al.*, 2010**). The interplay between lignans, fibre fermentation, and microbiome composition is particularly relevant in T2DM, where dysbiosis is characterized by reduced microbial diversity and diminished SCFA-producing taxa. By enriching beneficial anaerobes and increasing butyrate production, flaxseed consumption may counteract lipopolysaccharide (LPS) translocation and Toll-like receptor 4 (TLR4) activation, thereby limiting inflammatory cascades that interfere with insulin signalling. Improvements in gut barrier integrity and reductions in systemic inflammation collectively contribute to enhanced insulin sensitivity and restoration of metabolic homeostasis (**Yu *et al.*, 2025**).

Beyond these microbiota-mediated mechanisms, flaxseed also exerts complementary metabolic effects at the level of nutrient digestion and absorption. The physicochemical properties of its soluble fibre - particularly high viscosity and swelling capacity - slow gastric emptying and delay macronutrient absorption. This "trapping" mechanism reduces the diffusion of glucose, digestive enzymes, and lipids within the intestinal lumen, leading to slower starch hydrolysis, attenuated postprandial glycemia, and moderated insulin secretion. In parallel, inhibition of intestinal glycosidases further delays carbohydrate digestion, contributing to improved short-term glycaemic control (**Moreira *et al.*, 2022**). Flaxseed fibre also interferes with micelle formation and reduces bile acid reabsorption in the intestine. Decreased enterohepatic return of bile acids stimulates hepatic conversion of cholesterol into new bile acids, thereby increasing cholesterol utilization and contributing to reductions in circulating LDL concentrations alongside improvements in HDL levels. These lipid-modulating effects complement the anti-inflammatory and insulin-sensitizing actions of enterolignans and SCFAs, collectively reducing cardiovascular risk associated with T2DM (**Gupta *et al.*, 2025**). Additionally, the high water-binding capacity of flaxseed fibre promotes gastric distension and satiety, supporting body weight regulation - an important determinant of insulin sensitivity. By integrating microbiota-driven lignan biotransformation, SCFA-mediated signalling, modulation of hepatic glucose production, delayed nutrient absorption, and improved lipid handling, flaxseed exerts coordinated, multi-level metabolic effects. These interconnected processes reinforce the concept of a gut–liver–pancreas axis through which flaxseed contributes to improved glycaemic control, lipid metabolism, and overall metabolic stability in T2DM (Tab 1) (**Bongartz *et al.*, 2022**).

Table 1 Bioactive compound from flaxseed, mechanism of action and metabolic effect in T2DM (author)

Bioactive Compound	Main Mechanism	Resulting Effect in T2DM	References	Level of evidence
(SDG), Enterolactone (ENL), Enterodiol (END)	Microbial conversion to enterolignans; activation of AMPK; suppression of hepatic gluconeogenic enzymes (PEPCK, G6Pase); inhibition of NF-κB; modulation of PPAR-γ	↓ Hepatic glucose production; ↑ peripheral glucose uptake; ↓ inflammation; ↑ insulin sensitivity	(**Laveriano-santos *et al.*, 2024, Pilar *et al.*, 2017, Noirot., 2005**)	Animal model
Soluble fibre	Increased intestinal viscosity; delayed gastric emptying; "trapping" of glucose and digestive enzymes; inhibition of intestinal glycosidases	↓ Postprandial glycemia; ↓ insulin secretion peaks	(**Hajnla *et al.*, 2026, , Abdelkarem *et al.*, 2017**)	Animal model
Fermentable fibre fraction, SCFAs (butyrate, propionate)	Increased SCFA production; improved gut barrier integrity; suppression of metabolic endotoxemia; propionate-mediated suppression of PEPCK	↓ Systemic inflammation; ↓ hepatic gluconeogenesis; ↑ insulin responsiveness	(**Hajnla *et al.*, 2026, Yang *et al.*, 2020**)	Animal model
Omega-3 fatty acids	Modulation of inflammatory signaling pathways; activation of fatty acid–sensitive receptors	↓ TNF-α and TNF-α; improved insulin sensitivity	(**Villarreal-Renteria *et al.*, 2022, Abdelkarem *et al.*, 2017**)	Animal model
Fibre–bile acid interaction	Reduced bile acid reabsorption; increased hepatic cholesterol conversion to bile acids	↓ LDL cholesterol; improved lipid profile	(**Ghavani *et al.*, 2023, Mohamed *et al.*, 2012**)	Animal model

Legend: AMPK- AMP-activated protein kinase, SCFA- short-chain fatty acid, PEPCK- phospheenolpyruvate carboxykinase, TNF-α- tumor necrosis factor-α, LDL- low density lipoprotein , IL-6- interleukin 6, G6Pase- glucose-6-phosphatase, PPAR-γ- peroxisome proliferator-activated receptor gamma, NF-κB - nuclear factor kappa B

Sea buckthorn (Hippophae rhamnoides)

Sea buckthorn (*Hippophae rhamnoides*) is a phytochemically dense medicinal plant widely distributed across Europe and Asia. Its yellow -orange berries contain a complex mixture of bioactive compounds, including polyphenols (flavonols such as quercetin, isorhamnetin, and kaempferol derivatives; phenolic acids; proanthocyanidins; and anthocyanins), carotenoids (β-carotene, lycopene), vitamins (notably vitamin C and vitamin E), phytosterols, and unsaturated fatty acids. Although several of these constituents contribute to its biological activity, the polyphenolic fraction is considered the principal driver of its metabolic effects relevant to T2DM (**Jaśniewska *et al.*, 2021**).

A key feature of sea buckthorn polyphenols is that many are present in glycosylated or polymerized forms, limiting their absorption in the upper gastrointestinal tract. Consequently, a significant proportion reaches the colon intact, where they undergo extensive microbial transformation. Colonic bacteria expressing glycosidases, esterases, decarboxylases, and ring-cleaving enzymes metabolize these compounds into smaller phenolic acids, including phenylpropionic, phenylacetic, and benzoic acid derivatives. Genera such as *Bacteroides*, *Clostridium*, *Eubacterium*, *Eggerthella*, and beneficial saccharolytic taxa including *Lactobacillus* and *Bifidobacterium* participate in this biotransformation process. Importantly, these microbial metabolites often exhibit greater bioavailability and, in some cases, may enhance biological potency compared with their parent compounds, emphasizing the central role of the gut microbiota in mediating systemic effects. (**Yuan *et al.*, 2025**)

Beyond being substrates for microbial metabolism, sea buckthorn polyphenols may actively reshape microbial ecology. Experimental studies demonstrate enrichment of SCFA–producing taxa such as *Faecalibacterium prausnitzii*, *Roseburia*, members of the *Lachnospiraceae* family, and notably *Akkermansia muciniphila*, a mucin-degrading bacterium strongly associated with improved metabolic health and reduced adiposity. Concurrent decreases in endotoxin-producing Gram-negative bacteria have also been observed.

As discussed in the flaxseed section, this shift toward a butyrogenic and metabolically favorable microbial community may increases SCFA production, particularly butyrate and propionate, which play central roles in maintaining epithelial barrier integrity, modulating inflammation, and regulating hepatic glucose production (**Ilari *et al.*, 2024**). Through enhanced SCFA availability, sea buckthorn indirectly reinforces gut barrier function by promoting tight junction protein expression and reducing intestinal permeability. Lower translocation of LPS diminishes Toll-like receptor 4 activation and downstream inflammatory cascades, thereby alleviating chronic low-grade inflammation that impairs insulin signalling. Rather than repeating the intracellular pathways described previously (e.g., NF-κB suppression, IRS-1 restoration, PI3K/Akt improvement), it is important to emphasize that sea buckthorn converges on these same signalling nodes via microbiota-derived metabolites (**Rudrapal *et al.*, 2026, Krishna *et al.*, 2025**).

At the hepatic level, sea buckthorn influences both gluconeogenic and lipogenic pathways. Experimental evidence indicates suppression of key gluconeogenic enzymes and enhancement of insulin receptor expression, resulting in decreased endogenous glucose production. Activation of energy-sensing pathways, including AMPK, contributes to reduced hepatic glucose output and inhibition of *de novo* lipogenesis. Simultaneously, downregulation of lipogenic transcription factors and stimulation of fatty acid oxidation reduce hepatic steatosis, a major contributor to insulin resistance. By limiting lipid accumulation in hepatocytes, sea buckthorn indirectly improves insulin receptor responsiveness and systemic glycaemic control (**Yuan *et al.*, 2024, Chen *et al.*, 2023**). Sea buckthorn also exerts effects on peripheral glucose handling. Studies demonstrate increased translocation of GLUT4 to the plasma membrane in skeletal muscle and adipose tissue, enhancing glucose uptake and promoting glycogen synthesis. These insulin-mimetic or insulin-sensitizing actions result in measurable reductions in fasting and postprandial blood glucose concentrations in experimental diabetic models. Improved glucose utilization is accompanied by reductions in circulating insulin levels, suggesting enhanced insulin sensitivity rather than compensatory hyperinsulinemia (**Ollinger *et al.*, 2022**).

In addition to glycaemic effects, sea buckthorn influences lipid metabolism. It suppresses enzymes involved in lipogenesis while promoting energy expenditure, thereby reducing adipocyte hypertrophy and overall fat accumulation. Plasma lipid profiles improve, with reductions in triglycerides and LDL cholesterol. Elevated adiponectin concentrations observed after supplementation further support improved insulin sensitivity and anti-inflammatory status, while reductions in leptin may reflect improved leptin signalling and decreased inflammatory drive.

Organ-protective effects extend the metabolic relevance of sea buckthorn beyond glucose and lipid parameters. In diabetic models, supplementation is associated with improved renal morphology, reduced oxidative stress markers, and preservation of glomerular and tubular structure. Antioxidant components mitigate reactive oxygen species–mediated damage, which may contribute to preventing diabetic nephropathy. Similar associations are noted for cardiac tissue, with attenuation of myocardial oxidative injury, fibrosis, apoptosis, and functional impairment. Histological improvements in diabetic hearts demonstrate reduced necrosis and inflammatory infiltration. Hepatic tissue likewise exhibits reduced vacuolization, diminished lipid droplet infiltration, and improved cellular organization, indicating amelioration of steatosis and lipotoxicity (**Wang *et al.*, 2022, Wang *et al.*, 2025**). Emerging data also suggest endocrine and reproductive benefits. By lowering systemic oxidative stress and inflammation, sea buckthorn appears to preserve reproductive tissue integrity and improve sperm parameters in diabetic models. While these findings extend beyond classical glucose metabolism, they underscore the systemic consequences of improved metabolic homeostasis (**Pekince-Ozoner *et al.*, 2025**). Emerging evidence suggests that bioactive compounds present in these plant sources may also exert beneficial effects on skeletal health. Polyphenols and lignans have been associated with modulation of bone remodeling processes through antioxidant and anti-inflammatory mechanisms, potentially reducing osteoclast activity and supporting osteoblast function. Although these findings are primarily derived from preclinical studies, they indicate a possible role in mitigating diabetes-associated bone fragility (**Martiniaková, *et al.*, 2026**)

Taken together, sea buckthorn exerts coordinated microbiota-dependent and microbiota-independent actions that converge on improved insulin sensitivity, reduced hepatic glucose production, enhanced peripheral glucose uptake, improved lipid handling, and support for multi-organ function (Tab 2). Its mechanisms align with those described for flaxseed yet derive from a distinct phytochemical profile dominated by polyphenols and carotenoids rather than lignans and fibre (**Mihal *et al.*, 2025, Yuan *et al.*, 2025**).

Table 2 Bioactive compound fromsea buckthorn, mechanism of action and metabolic effect in T2DM (author)

Bioactive Compound	**Main Mechanism**	**Resulting Effect in T2DM**	**References**	**Level of evidence**
Polyphenols (flavonols, phenolic acids, proanthocyanidins)	Microbial biotransformation to bioactive phenolic metabolites; enrichment of SCFA-producing bacteria; suppression of inflammatory signaling; activation of AMPK	↓ Hepatic glucose production; ↓ inflammation; ↑ insulin sensitivity	(**Yuan *et al.*, 2025, Shen *et al.*, 2022, Yuan *et al.*, 2024**)	Animal model
Anthocyanins	Stimulation of GLP-1 secretion; activation of AMPK; antioxidant protection of β-cells	↑ Insulin secretion; ↓ fasting glucose; improved glycaemic control	(**Chen *et al.*, 2023, Aboonabi *et al.*, 202**)	Human clinical study Animal model
SCFAs (microbiota-derived)	Strengthening of gut barrier; reduction of LPS translocation	↓ Metabolic endotoxemia; improved insulin signaling	(**Guo *et al.*, 2020, Shen *et al.*, 2022**))	Animal model
Unsaturated fatty acids	Improvement of insulin receptor expression; enhanced GLUT4 translocation	↑ Peripheral glucose uptake; ↓ plasma glucose	(**Ollinger *et al.*, 2022, Huang *et al.*, 2025**)	Animal model
Antioxidant components (carotenoids, vitamins C, E)	Reduction of oxidative stress in liver, kidney, heart, and pancreas	Protection against diabetic organ damage	(**Wang *et al.*, 2022, Sun *et al.*, 2023**)	Animal model

Legend: SCFA- short-chain fatty acid, AMPK- AMP-activated protein kinase, GLP- glucagon-like peptide-1, LPS- lipopolysaccharides, GLUT4- glucose transporter 4

Cornelian cherry (*Cornus mas*)

Cornelian cherry (*Cornus mas*) is a deciduous shrub native to Europe and Asia, valued for its red, astringent fruits rich in bioactive iridoids, anthocyanins, and other polyphenols. Key constituents include iridoids such as loganic acid, cornuside, and sweroside; anthocyanins; hydroxycinnamic acids (e.g., chlorogenic acid); and ascorbic acid. These compounds, particularly iridoids and anthocyanins, underpin its metabolic effects in the context of T2DM, distinguishing it from the lignan-fibre matrix of flaxseed and the flavonol-rich profile of sea buckthorn (**Capcarova *et al.*, 2019, Dupak., 2022**).

Like other plant polyphenols, cornelian cherry bioactives may exhibit limited bioavailability in the upper gut due to their glycosylated structures. A substantial fraction arrives in the colon, where microbial enzymes - including β-glucosidases, α-rhamnosidases, and tannase-like activities—hydrolyse glycosides and cleave anthocyanin aglycones. Metabolites such as protocatechuic acid, syringic acid, and ferulic acid are produced by taxa including *Bifidobacterium spp.*, *Lactobacillus plantarum*, and butyrate-producers like *Roseburia*. Iridoids undergo unique deglycosylation by *Eggerthella* and *Clostridium* species, yielding secoiridoid derivatives with enhanced absorption. These transformations highlight microbiota dependency, with microbial metabolites often retaining or amplifying parent compound bioactivity (**Oledzka *et al.*, 2022**). Cornelian cherry extracts also modulate microbial composition, promoting SCFA producers (*Faecalibacterium*, Lachnospiraceae) and mucin-associated *Akkermansia muciniphila*, while reducing opportunistic pathogens. This eubiotic shift may enhance fermentation efficiency, indirectly supporting barrier function and reducing LPS leakage - as outlined for the prior plants. The resultant decrease in metabolic endotoxemia converges on common anti-inflammatory nodes without necessitating redundant pathway description here (**Bouyahya *et al.*, 2022, Dao *et al.*, 2016, Oledzka *et al.*, 2022**).

Unique to cornelian cherry, iridoids may exhibit potent inhibition of α-glucosidase and α-amylase, delaying carbohydrate digestion and attenuating postprandial glucose excursions. This complements microbiota effects by providing rapid glycaemic modulation. Anthocyanins may further activate Nrf2-mediated antioxidant responses, upregulating enzymes like superoxide dismutase and glutathione peroxidase, which may mitigate oxidative stress - a key amplifier of β-cell dysfunction and endothelial impairment in T2DM (**Paun *et al.*, 2024**). Hepatically, cornelian cherry influences gluconeogenesis via iridoid-induced PPAR-α/γ modulation and AMPK phosphorylation, potentially suppressing genes such as PEPCK and G6Pase. Experimental diabetic models show reduced hepatic glucose output and triglyceride accumulation, with iridoids promoting fatty acid β-oxidation. These actions align with sea buckthorn's lipogenic inhibition but emphasize iridoid-specific SIRT1 activation for improved insulin signalling (**Danielewsky *et al.*, 2023**). Peripherally, anthocyanins may enhance GLUT4 translocation in adipocytes and myocytes through PI3K-independent pathways, potentially via GLP-1 receptor agonism stimulated by gut-derived signals. Studies in streptozotocin-induced diabetic rats report lowered fasting glucose and HbA1c, alongside normalized insulin levels, suggesting contributions to insulin sensitivity (**Maldobra-Mazur *et al.*, 2022, Dzydzan *et al.*, 2019**). Lipid homeostasis benefits from ellagitannin-derived urolithins, which activate PPAR-γ to improve HDL/LDL ratios and reduce VLDL secretion. Hyperlipidaemic models demonstrate decreased aortic plaque formation, linking to anthocyanin stabilization of endothelial nitric oxide synthase (eNOS) (**Danielewsky *et al.*, 2023, Djedjibegovic *et al.*, 2020**). Vascular and endothelial support represents a distinctive emphasis for cornelian cherry. Anthocyanins improve flow-mediated dilation, reduce adhesion molecule expression, and inhibit platelet aggregation, countering T2DM-associated vasculopathy. In retinal and renal models, iridoids preserve microvasculature integrity by lowering AGE-induced inflammation and oxidative damage (**Frumuzachi *et al.*, 2024**). These associations extend to pancreatic protection, where Nrf2 activation may safeguard β-cells from glucotoxicity. Emerging evidence points to incretin-like effects, with iridoids potentially enhancing GLP-1 secretion via distal gut sensing, further integrating gut–pancreas crosstalk (**Sozansky *et al.*, 2019, Szot *et al.*, 2024**). Preclinical studies indicate that extracts of cornelian cherry can improve markers of bone formation and decrease indicators of bone resorption, potentially through the regulation of inflammatory cytokines and enhancement of collagen synthesis. The high vitamin C content may further support osteoblast function and extracellular matrix formation, which are essential for maintaining bone integrity (**Batool, *et al.*, 2024**).

Collectively, cornelian cherry bioactives may promote microbiota-mediated eubiosis, enzymatic glucose modulation, antioxidant defence, and vascular homeostasis, converging with flaxseed and sea buckthorn on insulin sensitization, hepatic glucose suppression, and lipid improvement—yet uniquely via iridoids and anthocyanins (Tab 3). This phytochemical synergy positions it as a complementary modulator of the gut–metabolic axis in T2DM (**Omrani *et al.*, 2025**).

Table 3 Bioactive compound from cornelian cherry, mechanism of action and metabolic effect in T2DM (author)

Bioactive Compound	Main Mechanism (as described in text)	Resulting Effect in T2DM	References	Level of evidence
Iridoids (loganic acid, cornuside, morroniside)	Activation of antioxidant pathways (Nrf2); anti-inflammatory activity; modulation of PPAR pathways	Protection of β-cells; ↓ oxidative stress; improved lipid metabolism	(**Danielewsky *et al.*, 2021, Brodyak *et al.*, 2025**)	Animal model
Anthocyanins	Microbial metabolism to phenolic acids; activation of AMPK; stimulation of GLP-1; enhancement of GLUT4 expression	↓ Hepatic glucose output; ↑ peripheral glucose uptake; improved glycaemic control	(**Szot *et al.*, 2024, Danielewsky at al., 2021**)	Animal model
SCFAs (microbiota-derived)	Strengthening of gut barrier; reduction of endotoxemia-driven inflammation	↑ Insulin sensitivity; improved metabolic homeostasis	(**Blaak *et al.*, 2020**)	Review
Polyphenols	Inhibition of intestinal glucosidases Delayed carbohydrate digestion and glucose absorption	↓ Postprandial glucose levels	(**Dzydzan *et al.*, 2019 , Punovic *et al.*, 2024**)	Animal model

Legend: SCFA- short-chain fatty acid, AMPK- AMP-activated protein kinase, GLP- glucagon-like peptide-1, GLUT4- glucose transporter 4, Nrf2- nuclear factor erythroid 2-related factor, PPAR- peroxisome proliferator-activated receptor

DISCUSSION

This review highlights the complex interplay between dietary bioactive compounds, gut microbiota, and metabolic regulation in type 2 diabetes mellitus. Flaxseed, sea buckthorn, and cornelian cherry share several mechanistic features, primarily related to their capacity to modulate gut microbial composition, enhance short-chain fatty acid production, and improve intestinal barrier integrity.

A recurring mechanistic sequence observed across studies involves increased production of short-chain fatty acids, particularly butyrate, leading to improved epithelial barrier function and reduced translocation of lipopolysaccharides into systemic circulation (**Kleigrewe *et al.*, 2022**). This reduction in metabolic endotoxemia is associated with decreased activation of pro-inflammatory pathways, including NF-κB signaling, and subsequent improvements in insulin sensitivity. However, it is important to note that this sequence is predominantly supported by preclinical studies, and its consistency in human populations remains to be fully established (**He *et al.*, 2020**).

Although all three plant sources demonstrate similar overarching effects, differences exist in their dominant bioactive compounds and specific mechanisms of action. Flaxseed is particularly notable for its lignan content and phytoestrogenic activity, while sea buckthorn provides a broad spectrum of fatty acids and fat-soluble vitamins (**Jaśniewska *et al.*, 2021, Mueed et al, 2022**). Cornelian cherry, in contrast, is characterized by a high concentration of polyphenols and vitamin C, which may exert stronger antioxidant effects (**Capcarova *et al.*, 2019**). These distinctions suggest that their metabolic benefits may be complementary rather than redundant.

Despite promising findings, several limitations must be acknowledged. The majority of mechanistic insights are derived from in vitro systems and animal models, with relatively few well-controlled human clinical trials available. Additionally, considerable variability exists in microbiota composition between individuals, which may influence responsiveness to dietary interventions. This heterogeneity complicates the interpretation of results and limits the generalizability of findings (**Vandeputte eta l., 2021**).

Consideration should also be given to potential interactions between plant bioactives and antidiabetic pharmacotherapy. While generally regarded as safe, compounds influencing glucose metabolism, insulin sensitivity, or hepatic pathways may potentiate or interfere with drug effects. Additionally, optimal dosing strategies and long-term safety profiles remain insufficiently defined, particularly in clinical populations.

Furthermore, some studies report inconsistent effects on specific microbial taxa and metabolic markers, highlighting the need for standardized methodologies and longer intervention periods. The influence of dosage, bioavailability, and interactions with other dietary components also remains insufficiently understood (**Gupta *et al.*, 2017**).

Importantly, while these bioactive compounds may contribute to improvements in glycaemic control and inflammatory status, their effects should not be interpreted as standalone therapeutic strategies. Instead, they should be considered as part of a broader dietary and lifestyle approach to metabolic disease management (**Castro-Barquero *et al.*, 2020**).

Future research should prioritize well-designed clinical trials, detailed characterization of microbiota responses, and identification of population-specific effects. A deeper understanding of these factors will be essential for translating current mechanistic insights into clinically relevant applications.

CONCLUSION

T2DM is a complex metabolic disorder driven by interconnected mechanisms including insulin resistance, β-cell dysfunction, oxidative stress, chronic inflammation, and dysregulated lipid metabolism. Increasing evidence highlights gut microbiota dysbiosis and metabolic endotoxemia as important contributors to disease progression.

Dietary bioactive compounds derived from flaxseed, sea buckthorn, and cornelian cherry demonstrate the capacity to modulate gut microbiota composition, enhance short-chain fatty acid production, and improve intestinal barrier integrity. Through these mechanisms, they may contribute to reduced systemic inflammation and improved metabolic regulation.

While mechanistic studies consistently indicate beneficial effects on pathways such as AMPK activation, hepatic glucose production, and peripheral glucose uptake, it is important to note that a substantial proportion of this evidence is derived from in vitro and animal models. Human clinical data, although promising, remain limited and heterogeneous.

Beyond glycaemic control, these plant-derived compounds have been associated with improvements in cardiovascular, hepatic, renal, and potentially skeletal parameters. However, these broader protective effects require further confirmation in long-term clinical studies.

Future research should focus on standardized intervention designs, dose optimization, and the identification of responder profiles based on microbiota composition. A more precise understanding of these factors will be essential for translating microbiota-targeted nutritional strategies into clinical practice.

Overall, modulation of the gut–liver–pancreas axis through dietary bioactives represents a promising adjunctive approach in T2DM management, although its full clinical relevance remains to be established.

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