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Unlocking Gut-Driven Metabolic Repair: The Role of Glucomannan Porang (*Amorphophallus muelleri* Blume) in Insulin Resistance and Short-Chain Fatty Acid Modulation in a Type 2 Diabetes Mellitus Rat Model

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin sensitivity and alterations in gut microbial metabolites, particularly short-chain fatty acids (SCFAs). The gut microbiota contributes to energy homeostasis through metabolites involved in insulin signalling. Glucomannan porang (GMP), a prebiotic fibre native to Indonesia, may serve as a therapeutic agent by modulating gut microbiota and improving glucose regulation. This study evaluated the effects of GMP on insulin resistance and SCFAs modulation in a streptozotocin-nicotinamide (STZ-NA)-induced T2DM rat model. Thirty male Wistar rats were acclimatized for seven days, then randomly assigned to five groups: control, diabetic, Acarbose (1.8 mg/200 g BW), GMP50 (50 mg/200 g BW), and GMP100 (100 mg/200 g BW). T2DM was induced in all but the control group using STZ-NA, and induction success was validated three days later through fasting blood glucose (FBG) levels exceeding 250 mg/dL. Following validation, treatments were administered orally for 28 consecutive days. At the end of the study, blood samples were collected to measure FBG, insulin, HbA1c, HOMA-IR, GLP-1, GLUT-4, IGF-1, and SCFA profiles. GMP100 significantly reduced FBG and HbA1c ($p<0.001$), improved insulin sensitivity and increased GLP-1, GLUT-4, and propionic acid levels. GMP100 also significantly lowered HOMA-IR ($p<0.001$) and elevated IGF-1, acetate and butyrate levels, showing effects comparable to acarbose. GMP50 produced moderate, but less pronounced, improvements compared to GMP100. In conclusion, GMP at 100 mg/200 g BW effectively ameliorated insulin resistance and favourably modulated SCFA profiles in T2DM rats, suggesting its potential as an adjuvant therapy for metabolic improvement in T2DM.

Keywords: Glucomannan, Porang, Diabetes Mellitus, Insulin Resistance, SCFAs

Introduction

DM (Diabetes mellitus) is a condition of chronic hyperglycemia that result in complications in various organs. Glucose regulation is primarily mediated by insulin, a hormone secreted by pancreatic beta cells. Several organs, often referred to as "The Egregious Eleven" influence glucose regulation through mechanisms including the gastrointestinal tract, immune dysregulation, and gut microbiome, representing only a subset of all eleven organs involved.[1] Furthermore, the renin-angiotensin-insulin system and vitamin D pathways have been identified as modulators of insulin secretion.[2] World Health Organization (WHO) defines type 2 diabetes mellitus (T2DM) based on markers of insulin resistance, including fasting blood glucose (FBG) ≥126 mg/dL (7 mmol/L), glycated hemoglobin (HbA1c) ≥6.5% (48 mmol/mol), 2-hour postprandial blood glucose (2hPPG) ≥200 mg/dL (11.1 mmol/L), or random blood glucose (RBG) ≥200 mg/dL accompanied by classic symptoms like polyuria, polyphagia, polydipsia, and weight loss.[3]

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International Diabetes Federation (IDF) reported that the global prevalence of diabetes among adults aged 20-79 years was approximately 11.1% in 2024 and is projected to increase to around 853 million people by 2050.[4] Additionally, the occurrence among the age group of 20 to 79 years old is a global problem due to high risk of morbidity and mortality, as well as contribution to the burden on countries. American Diabetes Association (ADA) mentioned that the rising prevalence increased the global burden to USD 1.015 trillion by 2024, a 338% change over the past 17 years.[3] In Indonesia, the prevalence of diabetes among adults aged 20 - 79 years is estimated at 11.3%, affecting approximately 20.4 million people. This represents a significant public health challenge due to the associated risk of complications, morbidity, and healthcare burden.[4] Over time, high glucose consumption has become the key contributing factor, specifically in young adults who are of productive age.[5] It causes impaired glucose tolerance; hence, insulin sensitivity decreases, followed by a reduction in insulin production.[6,7] A simple high-glucose diet has been reported can enhance intestinal permeability and trigger the release of pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α) through changes in the intestinal microbiota and toll-like receptor 4 (TLR-4) signaling.[8,9] This also affects the intestinal microbiota diversity, which helps control the homeostasis of the immune system in the body.[10] The complex pathophysiology of T2DM causes a poor prognosis, as uncontrolled glycemia increases the risk of damage to various organs.[11] Gut microbiota is essential in energy metabolism through metabolites production including SCFA (short-chain fatty acid), which plays a role in insulin signaling.[12] It has an effect on the regulation of the immune system and anti-microbial protection by balancing normal flora diversity.[13] Insulin resistance in T2DM triggers dysbiosis and damage

to the structure of the intestinal flora, followed by chronic low-grade inflammation.[14] A high-glucose diet causes an imbalance in the normal intestinal flora, thereby disrupting the relationship with epithelial cells and increasing mucosal permeability.[15] Increased intestinal permeability allows lipopolysaccharide (LPS), an active component of the cell wall of gram-negative bacteria, to enter systemic circulation and stimulate the release of pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP). These cytokines directly inhibit insulin receptor signaling, causing insulin resistance.[16,17] Gut dysbiosis conditions caused by chronic inflammation and insulin resistance are characterized by reduced diversity of normal flora and metabolites such as SCFA that maintain the balance of microbiota.[18] Based on observation, butyrate is an important SCFA composition in insulin signaling. It improves phosphorylation of AMP-activated protein kinase (AMPK), thereby increasing insulin sensitivity.[19] Previous analysis have reported that endotoxemia from gut microbiota can trigger inflammatory activity, worsening insulin resistance.[20] This condition inhibits glucagon like peptide-1 (GLP-1), a hormone responsible for stimulating insulin release from pancreatic beta cells in response to blood glucose levels[21]. Insulin resistance also causes changes in glucose transporter type 4 (GLUT-4) expression, which controls the amount of glucose entering cells, including myocytes and adipocytes.[22] However, butyrate, discovered in SCFA, can increase GLP-1 and GLUT-4, supporting glucose homeostasis in the blood and tissues. *Bifidobacterium adolescentis* supplementation restores gut microbiota homeostasis and raises microbial production of SCFA, improving chronic inflammation and lowering blood glucose levels.[23] Currently developed treatment efforts entail modulating gut microbiota and its metabolites.[24] The combination of antidiabetic drugs with a healthier diet can improve gut microbiome remodeling and potentially enhance the therapeutic effects.[25] A high-fiber diet, such as consuming glucomannan porang is essential in reducing intestinal permeability and inflammatory status by increasing the butyrate component in SCFA products.[13] Several herbal treatments are known to improve the structure of microbiota by increasing the normal flora and the concentration of butyrate, thereby inhibiting opportunistic pathogens. [26,27]

Amorphophallus muelleri Blume, locally known as "porang" is a plant native to Indonesia and belonging to the *Araceae* family. The plant has a single fleshly stem, large divided leaves, and an underground corm that serves as the main storage organ and the source of glucomannan used in this study. *Amorphophallus muelleri* Blume is widely cultivated in East Java, Indonesia, and contains water-soluble fiber that affects glucose homeostasis due to the formation of a gel. It also contains several active component, including soluble polysaccharides, phenolic compounds, and dietary fiber, which may improve insulin resistance and secretion.[28] This causes slower gastric emptying and glucose diffusion into the intestinal lumen, thereby increasing insulin sensitivity.[29,30] Among *Amorphophallus* species, *A. muelleri* has the highest content of soluble fiber, making it potentially effective in maintaining blood glucose control.[31] Previous studies using *Amorphophallus konjac*, a species from the same genus as porang, have shown that its glucomannan inhibits the *Eschericia coli* growth in the intestine and increases SCFA production.[32] Another antidiabetic mechanism of glucomannan porang has been shown through the inhibition of alpha-amylase activity, leading to decreased blood glucose levels due to the inhibition of simple carbohydrate breakdown.[33] This mechanism was later developed as an antidiabetic drug through acarbose. The drug is a competitive inhibitor of pancreatic alpha-amylase and intestinal alpha-glucoside hydrolase, inhibiting the breakdown of complex carbohydrates into oligosaccharides.[34] Glucomannan porang, with its inulin content, affects triglycerides and improves HDL levels, thereby reducing HOMA-IR (Homeostasis Model Assessment for Insulin Resistance), an insulin resistance marker, and halting the inflammatory process in rat models of T2DM. [35,36] Several previous studies have confirmed that long-term administration of glucomannan has no side effects and is effective in controlling blood glucose levels.[37] The effects of the various active compounds in the plant provide developmental benefits, but the utilization remains largely unstudied. There has been no preliminary study comprehensively examining glucomannan porang effects on insulin resistance and SCFA profiles in T2DM animal models. The antidiabetic properties of the plant could be used as an adjuvant therapy for T2DM.

Long-term insulin resistance risks increasing morbidity in patients with T2DM.[38] This condition is modulated by increased oxidative stress, causing prolonged damage to pancreatic beta cells and other target organs.[39,40] Glucomannan porang, with an antidiabetic effect, effectively improves insulin sensitivity and glycemic control. This is evidenced by a decrease in parameters used to diagnose DM, such as fasting blood glucose (FBG)[37], insulin level[41], and HbA1c.[42] Insulin resistance conditions assessed by reducing HOMA-IR levels were discovered to improve after administration of glucomannan porang.[43] Currently, IGF-1 has been examined to have a direct role in glucose homeostasis because it can reduce gluconeogenesis, thereby decreasing insulin uptake.[44] An analysis has indicated that the integration of glucomannan porang with a high-protein diet improves IGF-1 parameters and triggers the aging process through direct activity on insulin.[45] Glucomannan porang with prebiotic activity also helps reduce insulin resistance by enhancing GLP-1 secretion and increasing short-chain fatty acids (SCFAs) production.[46] It delays gastric emptying, inhibits food intake, and induces beta cell proliferation through GLP-1 activity.[30] The effects act synergistically with the maximum SCFA activity produced by porang, thereby reducing the accumulation of free fatty acids in insulin target tissues that cause lipotoxicity and peripheral insulin resistance.[47,48] This study assesses glucomannan porang influence on insulin resistance and modulation of SCFAs in streptozotocine-nicotinamide (STZ-NA)-induced T2DM model rats. Field evidence shows that only limited studies have comprehensively evaluated insulin resistance markers and SCFA profiles following glucomannan porang supplementation. The findings of this study may provide a basis for the use of glucomannan porang as an adjuvant therapy in T2DM to support improved blood glucose control.

Materials and Methods

Ethics statement

The ethical approval for the study was obtained from the Research Bioethics Commission, Medicine Faculty, Sultan Agung Islamic University, Semarang, Central Java, Indonesia (No. 343/X/2020/Komisi Bioetik).

Animals and criteria

The study used an experimental design with a post-test only control group, using male Wistar rats as subjects. The rats were approximately 12 weeks old (3 months) and weighed 175-200 g. This experiment was conducted at the Food and Nutrition Laboratory, Gadjah Mada University, Yogyakarta, Indonesia.

The sample size for each group was determined using the WHO formula, with a minimum of five rats per group plus one additional rat to account for potential loss to follow-up, resulting in six rats per group and a total of 30 rats for the study. Randomization was performed using a completely randomized design with a draw. All animals were acclimatized for 7 days to standardize conditions and minimize stress prior to the experiment. Each rat was housed in an individual cage in an air-conditioned room maintained at 18–25ºC, 50–70% humidity, and a 12-hour light-dark cycle. Water and standard feed were provided ad libitum during acclimatization. No animals were lost during this period, as all remained healthy and suitable for the experiment.

Induction of diabetes mellitus and experimental design

A total of 30 experimental animals were randomly and equally allocated into five groups. These include (1) Control group, receiving standard AIN-93M feed; (2) DM group, induced with T2DM using STZ-NA and maintained on standard AIN-93M feed; (3) Acarbose group, induced with T2DM and treated with 1.8 mg/200 g BW Acarbose; (4) GMP50 group, induced with T2DM and treated with 50 mg/200 g BW glucomannan porang; and (5) GMP100 group, induced with T2DM and treated with 100 mg/200 g BW glucomannan porang. All animals received standard AIN-93M feed and water ad libitum for 7 days. After a 7-day adaptation period, rats in the DM, Akarbose, GMP50, and GMP100 groups were intraperitoneally indeuced wist a combination of Streptozotocin (STZ: 65 mg/kg BW) and Nicotinamide (NA:230 mg/kg

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BW) to establish the T2DM model. Nicotinamide was administrated 15 minutes before STZ injection. During the induction phase, rats had free access to drinking water. Three days after induction, fasting blood glucose (FBG) levels were measured using the Glucose Oxidase–Peroxidase (GOD-PAP) method. Rats with FBG levels above 250 mg/dL were considered successfully induced as T2DM models. After validation, each group received its respective treatment orally for once daily for 28 consecutive days. At the end of the study, approximately 1 - 3 mL of blood was obtained from the ophthalmic vein and collected into plain and EDTA tubes. Blood samples were used to measure insulin resistance using the ELISA method and SCFAs profile using Gas Chromatography-Mass Spectrometry (GC-MS) method. Parameters measured included FBG, insulin, HOMA-IR, HbA1c, GLUT-4, IGF-1, GLP-1, and SCFAs components (butyric acid, acetic acid, and propionic acid). The experimental workflow is shown in Figure 1.

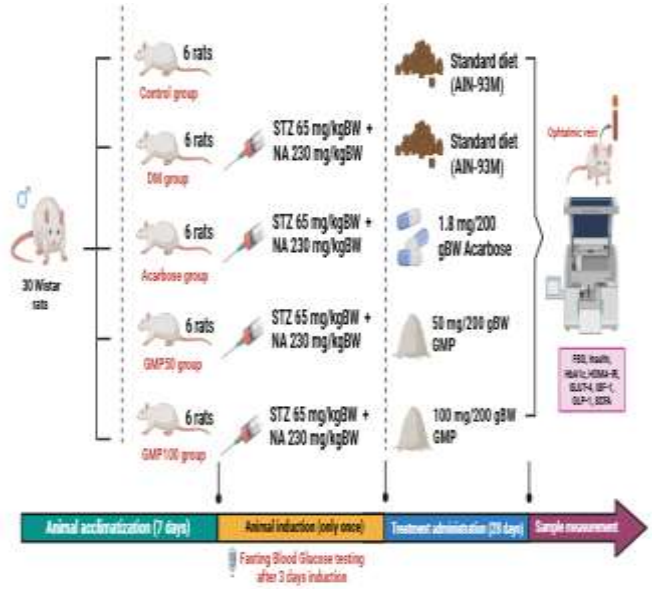

Figure 1: Experimental research design. A total of 30 experimental animals were randomly allocated into five groups (Control, DM, Acarbose, GMP50, and GMP100) and acclimatized for seven days. Type 2 diabetes mellitus (T2DM) was induced in the DM, Acarbose, GMP50, and GMP100 groups using a combination of streptozotocin (65mg/kg BW) and nicotinamide (230 mg/kg BB). After confirmation of hyperglycemia (FBG ≥250 mg/dL), treatment was administered for four weeks using acarbose (1.8 mg/kgBW), GMP 50 mg/200 gBW, and GMP 100 mg/200 gBW. Blood samples were collected at the end of the treatment period for biochemical analyses.

Plant Collection and Identification

Amorphophallus muelleri Blueme (porang) was collected in February 2020 from Madiun, East Java, Indonesia (7°37'35.0"S, 111°31'20.0"E) and authenticated by Integrated Biomedical Laboratory Universitas Islam Sultan Agung, Semarang, Central Java, Indonesia (2FW6+9P3), with specimen number FKSA-PE1-V077.

Glucomannan porang preparation

Glucomannan porang used in this study was obtained in powder form from CV. Nura Jaya Surabaya, Indonesia. The powder was derived from *Amorphophallus muelleri* Blueme tubers cultivated in East Java, Indonesia. The glucomannan content was analyzed at the Testing Laboratory of the Agricultural Postharvest Research and Development Center, Bogor Indonesia. Experimental animals received doses of 50 and 100 mg/200 g BW. Previous studies reported that supplementation starting at 50 mg/200 g BW was effective in improving insulin resistance, inflammatory status, kidney function, SCFA profile, pancreatic beta cell image, and exerting antioxidant effects.[45,49]

Endpoint of experimental study

The primary endpoints of this study were insulin resistance parameters (FBG, insulin, HbA1c, HOMA-IR, GLP-1, GLUT-4, and IGF-1) and SCFAs profiles (butyric, propionic, and acetic acid). Blood serum samples were collected from the ophthalmic vein, and SCFA samples were taken from the cecum. Insulin resistance markers were analyzed using ELISA kits according to the manufacturer's instructions, while SCFAs profiles were measured by gas chromatography–mass spectrometry (GC-MS).

Statistical analysis

Insulin resistance and SCFA profile data were entered, processed, and visualized using Graphpad Prism9 software, Boston, MA, USA. Data were analyzed using One-Way ANOVA (Analysis of Variance) followed by post-hoc tests. Differences were considered statistically significant at $p \leq 0.05$.

Results and Discussion

STZ-NA induction successfully conditioned the experimental animal model of T2DM by increasing FBG levels

DM is marked by chronic hyperglycemia caused by insulin resistance. STZ, a glucose analog with a similar structure, is transported into pancreatic beta cells through glucose transporter 2 (GLUT-2).[50] Based on this mechanism, STZ is widely adopted to induce DM in experimental animals.[51] White rats in DM, Acarbose, GMP50, and GMP100 groups were induced to condition the experimental animals for T2DM before being given their respective treatment. As shown in Figure 2, induction elevated FBG levels in all four groups to >250 mg/dL.

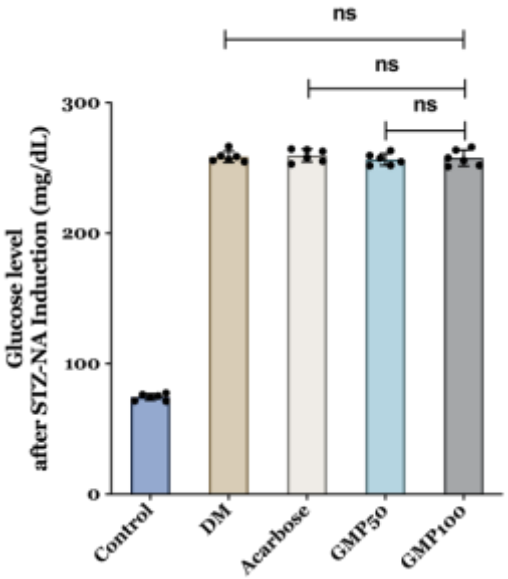

Figure 2: Fasting blood glucose (FBG) levels in four groups after STZ-NA induction. Statistical analysis was performed by one-way ANOVA followed by Post Hoc; ns = not significant.

No significant differences were analyzed among the induced groups, confirming the comparability and suitability for subsequent treatment. The induction of T2DM with STZ-NA damages pancreatic β-cells, thereby reducing insulin secretion and elevating plasma glucose levels. Previous reports have showed that STZ administration increased pro-inflammatory cytokines, particularly IL-1, contributing to insulin resistance.[52] The use of STZ at a dose 50 mg/kg BW in a preclinical study caused selective damage to pancreatic beta cells, while intraperitoneal nicotinamide at a dose of 100 mg/kg reduced this damage and prevented complete insulin insufficiency.[50] Mechanistically, STZ entered β-cells through GLUT-2 transporters and induced DNA damage, activating DNA repair enzyme poly (ADP-ribose) polymerase (PARP-1).[51] This supports the use of nicotinamide

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to partially prevent excessive β-cell destruction, thereby producing a T2DM model rather than total β-cell failure. The results obtained are in line with previous investigations that used STZ 50 mg/kg combined with NA 230 mg/kg, which increased FBG to more than 250 mg/dL and caused nephropathy effects through increased urea and creatinine.[53]

GMP 100 mg/g BW is superior in improving insulin resistance in T2DM

According to the Indonesian Endocrinology Association, the diagnosis of T2DM is based on fasting blood glucose (FBG) ≥126 mg/dl, 2-hour postprandial glucose (2hPPG) ≥200 mg/dL, HbA1c ≥6.5%, random blood glucose (RBG) ≥200 mg/dL, accompanied by classic symptoms such as polydipsia, polyuria, polyphagia, and weight loss.[54] Administration of glucomannan porang either at 50 or 100 mg/200 g showed a positive influence through a decrease in FBG and HbA1c levels as markers of glucose in the blood. It synergized with increased insulin sensitivity and improved insulin resistance through a decrease in HOMA-IR levels, as presented in Figure 3. The decrease in FBG levels was observed to be less than 150 mg/dL in the GMP100 group compared to GMP50, although a significant difference ($p<0.001$) with the Acarbose group existed as a positive control. HbA1c levels after administration of glucomannan porang improved to less than 6% of the normal limit than the control and DM groups, as detailed in Figure 3B. Between the GMP50 and GMP100 groups, the levels were nearly identical, but both showed significantly lower ($p<0.001$) than DM group and higher ($p<0.001$) than the Acarbose group (Figure 3B). This findings indicate that GMP effectively improved glycemic control, although its effect did not reach the potency of Acarbose. Increased insulin sensitivity and production were proven to be more effective through the administration of GMP100 compared to GMP50, with results similar to Acarbose. Based on observation, insulin resistance markers through HOMA-IR decreased after administration of 100 mg/200 g glucomannan porang in the GMP100 group, which was reinforced by the absence of significant differences with the Acarbose group, as detailed in Figure 3D.

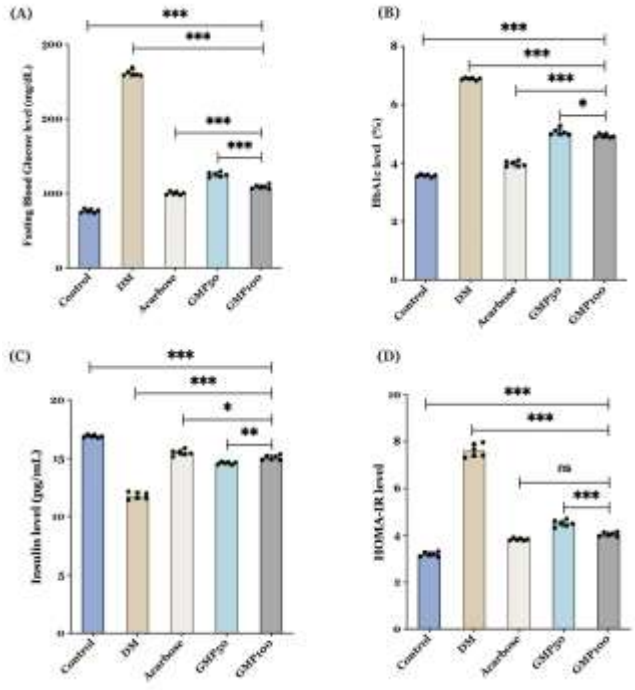

Figure 3: Effects of glucomannan porang on insulin resistance markers (A) fasting blood glucose (B) HbA1c (C) insulin (D) HOMA-IR levels in 5 treatment groups: control, DM, Acarbose, GMP50, and GMP100. Statistical analysis was performed by one-way ANOVA followed by Post Hoc; significant at *p<0.05, **p<0.01,***p<0.001, and ns = not significant.

FBG testing had high sensitivity as a predictor of DM because insulin remained stable during fasting, while glycogenolysis occurred in the liver.[55] This antidiabetic effect was reinforced by a decrease in other markers of glycemic control, particularly insulin, HbA1c, and insulin resistance markers such as HOMA-IR. The fiber contained in glucomannan porang triggered a feeling of fullness more effectively than other polysaccharides through its intrinsic fiber effect, which improved fasting and postprandial blood glucose levels as well as insulin response.[56] Furthermore, the food plant inhibited gluconeogenesis by decreasing the enzymes glucose-6-bisphosphate and fructose-1, preventing uncontrolled increases in blood glucose levels.[57] Differing results were discovered in Andre (2023), where administration of porang extract at 200, 400, and 800 mg/kg did not produce significant differences than the positive control group, Acarbose, or the control group.[58] This may be due to the type of porang used, *Amorphophallus onchopyllus*, which had a lower hypoglycemic effect than *Amorphophallus muelleri* Blume.[59]

Another marker of DM that is specific for elevated blood glucose is HbA1c. This parameter represents hemoglobin bound to glucose in a concentration proportional to blood glucose levels, making it a key predictor in establishing a diagnosis.[60] Since HbA1c measures the average blood glucose level over the past 3 months, testing is recommended at 3-month intervals.[42] As presented in Figure 3B, HbA1c levels improved to within the normal range (<6.5%) after GMP administration, showing significant improvement compared to the DM group. However, the control and Acarbose groups had significantly lower HbA1c levels ($p < 0.001$) than the DM group. The GMP50 and GMP100 groups also showed reduced HbA1c levels compared to the DM group, but the reduction was less pronounced than in the control and Acarbose group. The beneficial effect of glucomannan porang, a water-soluble dietary fiber with high viscosity, is attributed to rapid expansion in the stomach. This reduced carbohydrate absorption and limited glucose uptake in the intestine, thereby lowering blood glucose levels, including glucose bound to hemoglobin. [61] The results follows previous study, where HbA1c, as an indicator of T2DM, improved after administration of glucomannan porang.[62]

The additional antidiabetic effect of glucomannan porang was shown by higher insulin levels compared to the DM group. Administration of a 100 mg/200g dose effectively improved insulin sensitivity, showing results comparable to the Acarbose group ($p < 0.05$), as detailed in Figure 3C. The shared mechanism of action between GMP and Acarbose produced positive outcomes in reducing stress on pancreatic beta cells and increasing insulin sensitivity.[63] A previous study reported that GMP improved insulin sensitivity and glycemic control.[64] Furthermore, controlled glucose homeostasis after administration led to improvements in FBG, insulin, and HOMA-IR levels.[37] Previous investigation had also shown that consuming GMP slowed the absorption of branched-chain amino acids, causing decreased mTOR and S6 Kinase activity, which contributed to increased insulin sensitivity.[65] This was supported by several mechanisms where the porang triggered the expression of active proteins related to the repair and regeneration of pancreatic beta cells through the tyrosine kinase pathway.[66] HOMA-IR is known to detect insulin resistance in T2DM.[67] HOMA-IR measures insulin sensitivity by comparing FBG levels with insulin levels. Therefore, the higher the HOMA-IR value, the greater the insulin resistance in inhibiting gluconeogenesis, which causes hyperglycemia.[43] Results showed that HOMA-IR levels in the group receiving 100 mg/200 g GMP were significantly lower ($p< 0.001$) than those in the DM group and were not significantly different from the Acarbose group. A previous study also evaluated the administration of porang in jelly form, at 1,500 kcal/day and combined with inulin, leading to lower HbA1c and HOMA-IR levels, although almost similar with the control.[36]

The reduction in HOMA-IR levels after administration of GMP is known to decrease triglyceride levels and increase HDL, reducing the risk of dyslipidemia, a major complication of T2DM.[68] These results are further supported by a previous study where the intrinsic compounds contained in GMP induced hunger more effectively than other polysaccharides. Insulin response was triggered, and glucose diffusion was reduced through the impermeable membrane, leading to a decrease in HOMA-IR.[61,69]

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Glucomannan porang 100 mg/200 g is able to induce glycogenolysis and restore glucose homeostasis through the hormones: GLP-1, IGF-1, and GLUT-4

This study confirmed that the GMP100 group successfully triggered higher GLP-1 levels compared to the DM and GMP50 groups ($p<0.001$), reaching values comparable to those in the Acarbose group, as detailed in Figure 4A. The results are in line with higher IGF-1 levels after administration of GMP at a dose of 100 mg/200 g BW in experimental animals, compared to the DM and GMP50 groups, as shown in Figure 4B. Administration of GMP at a higher dose resulted in IGF-1 levels that were almost similar with the Acarbose group, which served the role of a positive control, as shown in Figure 4B. Another marker of insulin sensitivity was further assessed through the GLUT-4 receptor, with the highest results observed in the control group, followed by the Acarbose and GMP100 groups, as shown in Figure 4C. The GMP 100 group had higher GLUT-4 values, which were significantly different ($p<0.001$) from DM and GMP50 groups, and similar to Acarbose, as detailed in Figure 4C.

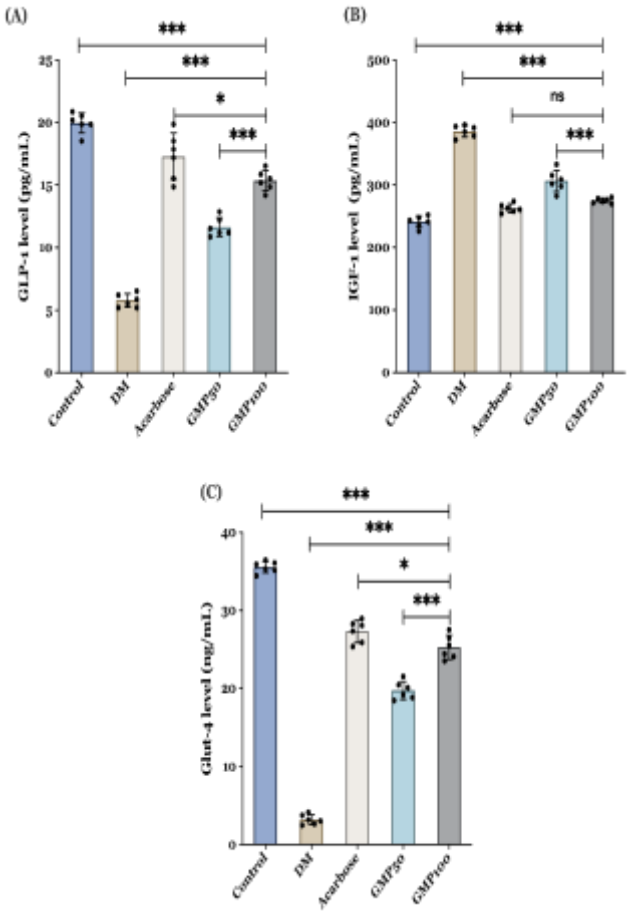

Figure 4: Effects of glucomannan porang on (A) GLP-1 (B) IGF-1 (C) GLUT-4 levels in 5 treatment groups: control, DM, Acarbose, GMP50, and GMP100. Statistical analysis was performed by one-way ANOVA followed by Post Hoc; significant at *$p<0.05$, **$p<0.01$,***$p<0.001$, and ns = not significant.

Porang induced intestinal gluconeogenesis and sympathetic activity by increasing glucose and energy homeostasis. The fiber contained in GMP was easily fermented by normal flora and bound to G proteins that produce peptide YY (PYY) and GLP-1 hormones.[70] This affected satiety by slowing gastric emptying time and glucose homeostasis. GLP-1 stimulated insulin release from pancreatic beta cells, causing an increase in the levels after GMP100 administration, as well as elevated insulin secretion, as detailed in Figure 4A. Despite being able to regulate insulin release during hyperglycemia, the GLP-1 hormone does not cause the condition. GLP-1 increases insulin production and prevents beta cell apoptosis, specifically in T2DM and PCOS.[71] The results of this study align with previous research, which found that administration of GMP to rats with a DM model improved GLP-1 levels, lowered low density lipoproteins (LDL) and triglyceride levels, and reduced the risk of complications in DM.[72] Previous investigation reported that glucomannan at a 300 mg/kg BW dose had a more effective antidiabetic effect than 100 mg/kg BW in improving glucose homeostasis markers such as GLP-1.[30]

DM with insulin resistance affects the regulation of IGF-binding proteins (IGFBPs), leading to increased IGF-1 levels. A previous study has shown that IGF-1 decrease after administration of GMP at the dose of 100 mg/200 g BW.[45] The parameter is directly regulated by growth hormone (GH) and is closely related to insulin regulation in lowering blood glucose levels.[73] Its regulation by GH into an active form can induce hypoglycemia, reduce gluconeogenesis, and prevent lipotoxicity, which causes glucose levels to decrease.[74] GMP triggers the secretion of GH, a lipolytic agent with anti-lipogenic activity, which has a positive effect on the management of DM.[75] These findings align with a previous study, which reported that GMP-100 can reduce free IGF-1 levels produced during hyperglycemia, as detailed in Figure 4B. Another study also stated that GMP caused an imbalance in the GH/insulin ratio with higher insulin levels. This causes adipose cells to store nutrients and not initiate lipolysis, thereby maintaining insulin sensitivity.[76] The findings are appropriate to those proven through previous investigation, where administration of GMP combined with a high-protein diet was effective in enhancing IGF-1, an essential parameter in the pathophysiology of aging and DM.[45]

Administration of GMP had a positive effect on increasing GLUT-4 levels in T2DM, as detailed in Figure 4C. The 100 mg/200 g dose exhibited better results than the 50 mg/200 g dose and was comparable to acarbose in enhancing GLUT-4 activity as a glucose transporter in skeletal muscle and adipose tissue. In insulin resistance, the GLUT-4 release to the cell membrane is reduced, leading to its accumulation in the intracellular compartment and impaired glucose metabolism in muscle.[77] Furthermore, reduced insulin signaling activity makes GLUT-4 ineffective in exocytosis to the cell membrane surface, resulting in excess glucose that is not perfectly controlled.[22,78] Various natural compounds derived from plants show potential as T2DM therapy by increasing GLUT4 expression and translocation to the plasma membrane, primarily driven by the activation of the PI3K or AMPK signalling pathways.[79] Based on a previous study, administration of GMP has been shown to increase the expression of GLUT-4 as an insulin transporter in tissues and muscles through PI3K/Akt signaling activity.[80,81]

The SCFAs profile in GMP100 group was comparable to that of the Acarbose group, indicating similar effects on gut microbial metabolism

Dysbiosis in DM is closely related to decreased levels of SCFAs, particularly butyrate, which is essential in glucose regulation in the intestine. Several studies have shown that in DM, there is a decrease in bacterial diversity and a reduction in bacteria that produce butyrate.[82] SCFA is an organic fatty acid produced by the large intestine when anaerobic bacteria ferment GMP. Each of its components is reported to have a distinct role in insulin sensitivity, improving insulin resistance, and inflammatory status. According to the results, SCFA acetic acid levels in the GMP100 group was superior to the DM and GMP50 groups. This is reinforced by the finding that acetic acid levels, as the largest component, did not differ significantly from those in the Acarbose group, as shown in Figure 5A. Propionic acid, a short-chain fatty acid involved in glucose metabolism and known to enhance insulin sensitivity, was significantly higher ($p<0.001$) after administration of GMP at 100 mg/200 g BW compared to the DM group, as presented in Figure 5B. Although the levels were slightly lower than those in the Acarbose group, GMP supplementation clearly improved propionate production. Positive results were also evidenced by significantly higher ($p< 0.001$) butyric acid levels in the GMP100 group compared to the DM and GMP50 group, and levels were similar to the Acarbose group, as shown in Figure 5C.

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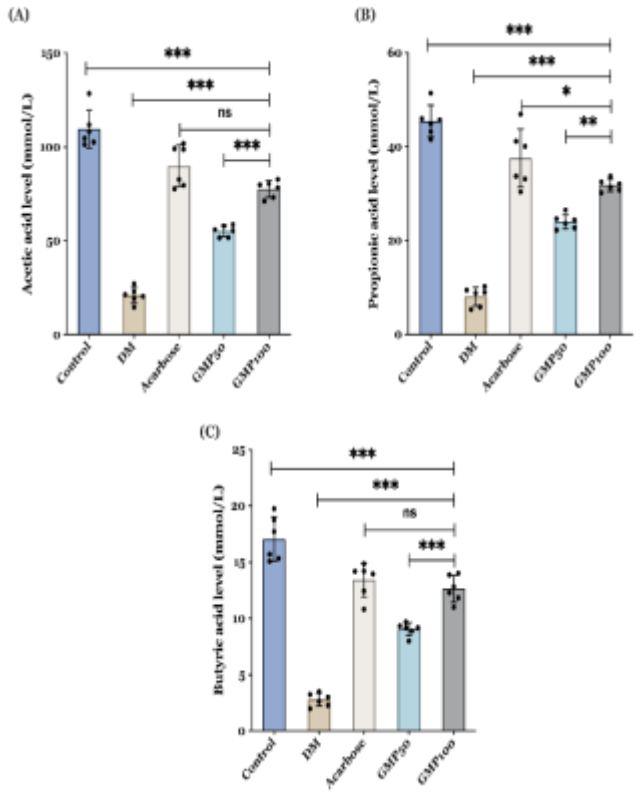

Figure 5: Effects of glucomannan porang on short-chain fatty acids profile (A) acetic acid (B) propionic acid (C) butyric acid levels in 5 treatment groups: control, DM, Acarbose, GMP50, and GMP100. Statistical analysis was performed by one-way ANOVA followed by Post Hoc; significant at *p<0.05, **p<0.01,***p<0.001, and ns = not significant.

SCFAs reduces insulin resistance by alleviating lipotoxicity, which impairs glucose uptake and glycogen synthesis and leads to peripheral insulin resistance.[48] GMP, acting as a prebiotic, promotes SCFAs formation by resisting digestion in the upper gastrointestinal tract and undergoing fermentation by *Bifidobacterium* or *Lactobacillus* into SCFAs.[82,83] The main metabolites, acetic, butyric, and propionic acids, are absorbed in the large intestine and contribute to lowering intestinal pH during transit from the terminal ileum to the proximal colon.[84] Acetate is the most abundant component, readily absorbed into systemic circulation, where it participates in lipogenesis.[85] Butyrate and propionate, on the other hand, exert butyrogenic effects by selectively stimulating the growth of *Bifidobacteria* and supporting microbial balance.[86,87] Previous study reported that GMP supplementation increases butyrate production, which has been associated with enhanced anti-inflammatory activity and improved intestinal homeostasis.[88,89] Butyrate produced by intestinal microbiota can enhance insulin sensitivity and reduce neuroinflammatory responses.[90]

DM is an example of a dysbiosis condition characterized by an increase in the *Firmicutes/Bacteroides* (F/B) ratio compared to healthy individuals.[91,92] The normal intestinal flora of *Bacteroides* can trigger glucose tolerance and insulin sensitivity.[93] Furthermore, dysbiosis in DM provides a condition for an increase in anaerobic bacteria that can produce acetate, reduce sulphate, as well as degrade urea and arginine.[94] High microbiota diversity in the intestine is closely related to the digestion of various types of complex carbohydrates and the production of several SCFAs, thereby affecting blood glucose homeostasis.[95] The findings showed an effective metabolic role in GMP 100 mg/g BW through measuring the levels of acetic acid, butyric acid, and propionic acid contained in the SCFAs profile. Previous studies support these results, showing that GMP promotes SCFAs production and reduces insulin resistance in body cells (HOMA-IR) and adipose tissue (Adipo-IR) by mitigating fat accumulation.[96,97] The butyrate content in SCFAs is effective in improving FBG levels and insulin resistance and protecting against the DM risk in experimental induced diabetic animals.[98] Furthermore, the anti-inflammatory effect of GMP is mediated by SCFAs, which reduces the production of pro-inflammatory cytokines and chemokines, stimulates regulatory T cell activity, and inhibits interferon gamma-induce protein-10 (IP-10) release in colonic myofibroblasts. These actions underpin the role of SCFAs in modulating the immune system and controlling inflammatory responses.[99]

The presence of short-chain fatty acids (SCFAs) in the gut–brain microbiota axis influences inflammation by altering intestinal permeability, allowing the translocation of bacterial products that elevate cytokine levels and compromise the blood–brain barrier.[100] Recent studies have shown that gut microbiota plays an important role in modulating insulin resistance and cognitive function through multiple of mechanisms.[101] Among these pathways is the hypothalamic-pituitary-adrenal (HPA) axis, an endocrine communication link between the gut and the brain. Certain gut microbes affected by SCFAs also trigger the release of hormones release hormones, including GLP-1[102], IGF-1[103], ghrelin, and leptin which regulate energy and glucose homeostasis.[104] Previous study have shown that in skeletal muscle and adipose tissue, SCFAs produced from GMP fermentation can enhance glucose uptake through increased GLUT-4 expression mediated by AMPK activation.[105] The positive correlation between GMP as a prebiotic and increased SCFA content suggests a beneficial role in the management of T2DM.

Conclusion

In conclusion, glucomannan porang at a dose of 100 mg/200 g BW was effective in reducing insulin resistance. This effect was accompanied by favorable modulation of the short-chain fatty acid (SCFA) profile, indicating a potential prebiotic role in supporting metabolic regulation through the gastrointestinal tract. These findings highlight the beneficial metabolic effects of glucomannan porang in a type 2 diabetes mellitus model. Further studies are needed to confirm its mechanism and clinical relevance.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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