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Research Article

Antioxidant and Antihyperglycemic Effects of Bay Leaf (*Syzygium polyanthum* [Wight.] Walp) Kombucha in Alloxan-Induced Diabetic Mice

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ABSTRACT

Kombucha is a popular functional beverage known for its health benefits, and recent research has focused on using alternative substrates for its production. *Syzygium polyanthum* (bay leaf) is a medicinal plant with various pharmacological properties, yet its potential as a kombucha fermentation substrate remains unexplored. This study aimed to evaluate the polyphenol content, antioxidant capacity, and antihyperglycemic effects of kombucha made from *S. polyanthum* extract. The research followed four main stages: *S. polyanthum* extraction, fermentation, product standardization, and pharmacological testing. Chemical analysis quantified the total phenolic and flavonoid content, while biological evaluations included an *in vitro* antioxidant assessment using the DPPH assay and an *in vivo* antihyperglycemic study in alloxan-induced diabetic mice. Data were analyzed using independent T-tests and ANOVA with a 95% confidence interval. A non-significant increase was observed in the total phenolic content of *S. polyanthum* kombucha (8.01±0.69 mg GAE/g) compared to the non-fermented infusion (7.71±0.37 mg GAE/g, $p = 0.547$), along with a slight increase in flavonoid content (5.04±0.25 mg QE/g vs. 4.74±0.23 mg QE/g, $p = 0.196$). The kombucha also exhibited significantly stronger antioxidant activity than its non-fermented infusion (IC_{50}: 449.31±38.9 µg/mL vs. 578.93 ±20.67 µg/mL; $p < 0.05$), although both were considerably less potent than the standard gallic acid (IC_{50}: 25.68±3.26 µg/mL). Furthermore, after 14 days of treatment, *S. polyanthum* kombucha significantly reduced blood glucose levels in diabetic mice by 61.45±11.63%, surpassing both metformin (50.47±4.28%) and the non-fermented *S. polyanthum* infusion (53.34±5.71%) ($p=0.001$; $p<0.05$). These findings indicate that the kombucha is a promising functional beverage with potential applications in diabetes management.

Keywords: Kombucha, Bay leaf, *Syzygium polyanthum*, SCOBY, antioxidant, antihyperglycemic

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Introduction

Diabetes is a metabolic disorder involving carbohydrate, lipid, and protein metabolism, characterized by elevated blood glucose levels. This condition arises either from insufficient insulin production by pancreatic β cells or from the body's inability to respond effectively to insulin. As a key hormone, insulin enables cells to utilize glucose and convert it into energy [1]. Recently, there has been growing interest in utilizing natural plant-based remedies for diabetes management, largely due to their perceived safety profile and fewer side effects compared to synthetic drugs [2]. One plant that has gained attention for its antihyperglycemic properties is *Syzygium polyanthum* (Wight) Walp [3]. This plant has a long history of traditional use in Southeast Asia, particularly for the treatment of diabetes [4].

S. polyanthum is a tropical plant extensively found across Asian countries, including Indonesia, Malaysia, and Thailand. In Indonesia, it is widely recognized by various names such as salam, Indonesian bay leaf, gowok, and manting [3]. The leaves, fruits, and bark of *S. polyanthum* have traditionally been employed for both medicinal and non-medicinal uses, often prepared as infusions or decoctions, and sometimes combined with other herbs. The leaves, in particular, are commonly used to treat a variety of health conditions, including diabetes mellitus, hypertension, gastritis, ulcers, diarrhea, skin diseases, and infections [3–5].

Research has identified a range of bioactive compounds in *S. polyanthum* with diverse pharmacological properties. Myricetin, Caffeic acid, gallic acid, and 4-allyl-1,2-dihydroxybenzene (hydroxychavicol) have been previously identified in these plant extracts [4, 6]. Palmitic acid, which exhibits anti-inflammatory and antibacterial activities; and nerolidol, which demonstrates anti-inflammatory, antinociceptive, antifungal, and antiulcer properties. Other notable compounds include linalool, which possesses antibacterial, anti-inflammatory, antidiabetic, and hepatoprotective effects; α-pinene, which shows anti-inflammatory, antibacterial, and hypotensive properties; and α-tocopherol and β-tocopherol, both recognized for their antioxidant capabilities. Additionally, squalene, a major compound, has been highlighted for its antioxidant, antitumor, and chemopreventive activities, while phytol exhibits anti-inflammatory, anticancer, antimicrobial, antioxidant, and antinociceptive effects. These findings collectively emphasize the significant therapeutic potential of *S. polyanthum*. [3, 7, 8].

Research on *S. polyanthum* and its antidiabetic properties has yielded promising results. The methanol extract of *S. polyanthum* has been shown to significantly lower blood glucose levels in streptozotocin-induced diabetic rat, with the most effective dose being 500 mg/kg body weight [6]. Additionally, the ethanol extract of *S. polyanthum* has been demonstrated to reduce malondialdehyde (MDA) levels, an organic compound produced through lipid peroxidation by reactive oxygen species (ROS). MDA serves as a key marker in the development and progression of diabetes and its complications, particularly in patients with Type 2 diabetes [9]. Furthermore, combining *S. polyanthum* with other herbal extracts, such as *Elaeocarpus ganitri*, has been found to enhance antidiabetic effects, indicating potential for complementary therapies in Type 2 diabetes management [10]. These findings underscore the fundamental role of *S. polyanthum* in antidiabetic treatments.

Kombucha is a fermented beverage traditionally prepared from green or black tea leaves, 5–10% sucrose, and a Symbiotic Culture of Bacteria and Yeast (SCOBY), undergoing fermentation for a typical period of 7 to 21 days [11]. This beverage is highly regarded for its abundant content of polyphenols, organic acids, vitamins, minerals, and sugars [12]. Recently, there has been growing interest in developing kombucha using alternative substrates such as herbal infusions, fruits, and vegetables [13]. These substrates not only provide unique bioactive compounds but also exhibit distinct pharmacological properties [11]. Moreover, kombucha fermentation can transform the sensory qualities of various infusions, such as tea flower extracts, leading to improved sweetness and fruity notes. The fermentation process increases the production of volatile compounds that contribute to aroma, significantly enhancing the drink's appeal [14]. Hence, utilizing *S. polyanthum* leaves as a kombucha substrate holds promise due to their well-documented antidiabetic properties, potentially enhancing kombucha's therapeutic efficacy and also increasing flavor profiles of kombucha.

Developing fermented functional beverages is not only a growing trend but also highlights the health benefits derived from their natural chemical compounds. Despite extensive evidence on the antidiabetic activity of *S. polyanthum*, its potential as a fermentation substrate for kombucha to enhance bioactivity remains unexplored. To address this gap, the present study evaluates the antihyperglycemic effects of *S. polyanthum* kombucha in an alloxan-induced diabetic mice model.

Materials and Methods

Plant material

Fresh leaves of *S. polyanthum* were collected from Mayang District, Jambi City, Jambi Province, Indonesia. The leaves were oven-dried at 50 °C for 72 hours and then ground into a fine powder using a commercial grinder. The plant material was identified and authenticated by a taxonomist from Universitas Padjadjaran, and a voucher specimen was deposited under registration number 49/HB/06/2023. Dried simplicial was standardized based on guideline in Indonesian Herbal Pharmacopeia [15].

Research instrument

This study utilized various analytical instruments, including a UV-Vis spectrophotometer (Genesys 10S UV-Vis®, Thermo Scientific®, USA), a hot plate stirrer (AREX Digital Pro, Velp Scientifica®, Italy), and an oven (UN55, Memmert®, Germany). Other equipment included a water bath (WNB 10, Memmert®, Germany) and a glucometer with test strips (Auto-check®, PT Enzy Medical, Indonesia) for blood glucose measurement.

Research material and reagent

All chemicals used in this study were of analytical grade. The solvents and reagents included methanol p.a. (Emsure®), sodium carboxymethyl cellulose (NaCMC) (Sigma-Aldrich®), alloxan monohydrate (Sigma-Aldrich®), and Folin-Ciocalteu reagent (Supelco®). Additional compounds used

were sodium hydroxide (NaOH) (Supelco®), aluminum chloride ($AlCl_3$) (Sigma-Aldrich®), sodium acetate (CH_3COONa) (Supelco®), quercetin (Sigma-Aldrich®), gallic acid (Sigma-Aldrich®), and 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Sigma-Aldrich®). Metformin 500 mg was included as a positive control in the study.

Preparation of Syzygium polyanthum leaf infusion and kombucha

The infusion was prepared by steeping 10 g of dried *S. polyanthum* leaves powder in 100 mL distilled water at 90 °C for 15 minutes, following Antolak et al. (2021) [16]. After filtration through flannel cloth, the volume was adjusted to 100 mL with distilled water at room temperature. For kombucha fermentation, 3 g of SCOBY and 10% (w/v) sucrose were added. The mixture was incubated at 25±2 °C for 14 days in a gauze-covered container to prevent direct sunlight exposure. Organoleptic properties (appearance, color, odor, taste) were evaluated following Indonesian Herbal Pharmacopoeia guidelines [15, 16]

Determination of total phenolic content (TPC)

The TPC of *S. polyanthum* infusion and kombucha was determined using the Folin-Ciocalteu colorimetric method in accordance with the Indonesian Herbal Pharmacopoeia [15]. A gallic acid stock solution (400 μg/mL) was prepared by dissolving 10 mg gallic acid in 25 mL ethanol and serially diluted to concentrations of 25, 30, 45, 50, and 60 μg/mL. Each standard (1 mL) was mixed with 5 mL of 7.5% Folin-Ciocalteu reagent, allowed to react for 8 minutes, then combined with 4 mL of 1% NaOH. After 1 hour of incubation at room temperature, absorbance was measured at 730 nm and the same procedure was applied to samples in triplicate. Total phenolic content was calculated from the gallic acid calibration curve and expressed as mg gallic acid equivalents (GAE) per gram of dry simplicia.

Determination of total flavonoid content (TFC)

The TFC of *S. polyanthum* infusion and kombucha was determined following the Indonesian Herbal Pharmacopoeia guidelines [15]. A quercetin stock solution (400 μg/mL) was prepared and serially diluted to 3, 12, 25, 50, and 75 μg/mL. Each standard or 1 mL of infusion and kombucha sample was mixed with 1.5 mL ethanol, 0.1 mL of 10% aluminum chloride, 0.1 mL of 1 M sodium acetate, and 2.8 mL distilled water, then incubated at room temperature for 30 minutes. Absorbance was measured at 415 nm and all measurements were performed in triplicate. Total flavonoid content was quantified from the quercetin calibration curve and expressed as milligrams of quercetin equivalents (mg QE) per gram of dry simplicia.

Determination of antioxidant activity

The antioxidant activity of *S. polyanthum* infusion and kombucha was evaluated using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, as adapted from Christodoulou et al [17]. In brief, 0.2 mL of each sample (1.56–100 μg/mL in methanol) was added to 3.8 mL of 50 μM

DPPH solution and incubated in the dark for 30 minutes. The absorbance was then measured at 517 nm using a blank solution containing DPPH and methanol. All measurements were performed in triplicate. The radical scavenging activity (RSA) was calculated using the equation: % scavenging of DPPH = $[(A_{control} - A_{sample})/A_{control}] \times 100$, The IC_{50} value, defined as the concentration required to scavenge 50% of DPPH radicals, was determined by plotting RSA against concentration and applying linear regression (y = a + bx). The IC_{50} was calculated using the formula: $IC_{50} = (50 - a) / b$, where a and b represent the intercept and slope of the regression line, respectively.

Determination of antihyperglycemic activity

All animal procedures followed institutional protocols and adhered to the ethical guidelines established by The Ethics Committee of Politeknik Kesehatan Kementerian Kesehatan Jambi, with approval granted under the approval number LB.0206/2/092/2025. Twenty male mice (2–3 months old, weighing 20–23 g) were housed under controlled environmental conditions with ad libitum access to food and water. Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (125 mg/kg body weight) following a 12-hour fasting period. To prevent alloxan-induced hypoglycemia, a 10% glucose solution was administered orally for three consecutive days post-induction. After seven days, mice with fasting blood glucose (FBG) levels ≥170 mg/dL were considered diabetic and included in the study. The diabetic mice were randomly divided into four groups (n=5 per group): Group 1: Negative control (alloxan only), Group 2: Positive control (alloxan + metformin 65 mg/kg BW), Group 3: *S. polyanthum* infusion (10%), Group 4: *S. polyanthum* kombucha (10%). All treatments were administered orally once daily for 14 consecutive days. The volume of each administered solution was adjusted to 1% of the individual mouse's body weight. Fasting blood glucose levels were measured on days 0 (prior to treatment), 5, 10, and 14 using a glucometer. The antidiabetic efficacy of the treatments was evaluated by calculating the percentage reduction in blood glucose levels using the following formula: % Reduction = $[(G_0 - G_x)/G_0] \times 100$, where G_0 = fasting blood glucose level on day 0 (before treatment) and G_x = fasting blood glucose level on day X (after treatment on day 5, 10, or 14).

Data analysis

The results are presented as means ± standard deviation. Statistical analyses were performed using an independent t-test to assess TPC and TFC. One-way ANOVA was used to compare the IC_{50} values of antioxidant activity, while two-way ANOVA was applied to evaluate the percentage reduction in fasting blood glucose levels. Duncan's multiple range test was used for post-hoc comparisons. A p-value of < 0.05 was considered statistically significant.

Results and Discussion

Characterization of S. polyanthum in three forms

The quality evaluation of *S. polyanthum* preparations; simplicia powder, infusion, and kombucha, was conducted through organoleptic and physicochemical assessments. Organoleptic analysis

revealed observable differences among the three forms. The infusion displayed a dark brown color with a tea-like odor, whereas the kombucha appeared lighter in color with a distinct sour and fermented aroma, indicative of successful microbial fermentation. Physicochemical analysis of the simplicia showed a loss on drying (LOD) of 1.94%±0.01, well below the 10% threshold outlined in the Indonesian Herbal Pharmacopoeia [15]. This low moisture content indicates proper drying, which minimizes microbial growth and enzymatic degradation of active constituents, thus preserving product stability. The total ash content was 0.29%±0.01, far below the pharmacopoeial limit of 2.5%, suggesting minimal inorganic or heavy metal contamination and affirming the purity of the herbal material [15, 18] (Table 1).

Table 1 Characterization of *S. polyanthum* in three forms.

Characterization	Simplicia	Infusion	Kombucha
Organoleptis evaluation			
Shape	Powder	Liquid	Liquid
Color	Brown	Dark brown	Light brown
Odor	Distinctive	Distinctive, tea-like	Sour, fermented
Taste	Bitter	Bitter	Bitter and slightly sour
Simplicia Characteristic			
Loss on drying (LOD)	1.94±0.01		
Total ash content	0.29±0.01		

Total Phenolic Content and Total Flavonoid Content

The total phenolic content (TPC) was slightly higher in *S. polyanthum* kombucha (8.01±0.69 mg GAE/g) compared to the unfermented infusion (7.71±0.37 mg GAE/g); however, the difference was not statistically significant ($p = 0.547$). Similarly, the total flavonoid content (TFC) was greater in kombucha (5.04±0.25 mg QE/g) than in the infusion (4.74±0.23 mg QE/g), with a non-significant difference ($p = 0.196$) (Figure 1A). These findings suggest a 1.04-fold and 1.06-fold increase in TPC and TFC, respectively, following fermentation. Although the differences were not statistically significant, possibly due to biological variability in microbial fermentation, the trend indicates enhanced phytochemical content in the kombucha.

These results are consistent with previous studies. For instance, Kim et al. demonstrated that fermentation significantly increased the TPC of black tea from 70.87±1.20 to 250.52±3.90 μg GAE/mL, representing a 1.27- to 3.53-fold enhancement over the unfermented tea [19]. The rise in TPC and TFC observed in kombucha is primarily attributed to the biochemical transformations that occur during fermentation. Microbial activity leads to the production of hydrolytic enzymes, which break down complex polyphenolic and flavonoid compounds into simpler, more bioavailable forms. Additionally, fermentation generates various metabolites such as organic acids, alcohols, and esters, which may

improve the release and solubility of bioactive compounds from plant matrices, thereby increasing the measurable concentrations of phenolics and flavonoids [20, 21].

The enzymatic activity of the kombucha microbial consortium also contributes to the liberation of bound phenolic compounds, enriching the beverage's bioactive profile [22]. Furthermore, the organic acids produced during fermentation lower the pH, which not only enhances the solubility and bioavailability of phenolic compounds but also improves the sensory attributes of the beverage. The resulting lower pH contributes to a more palatable flavor profile compared to the unfermented infusion [21].

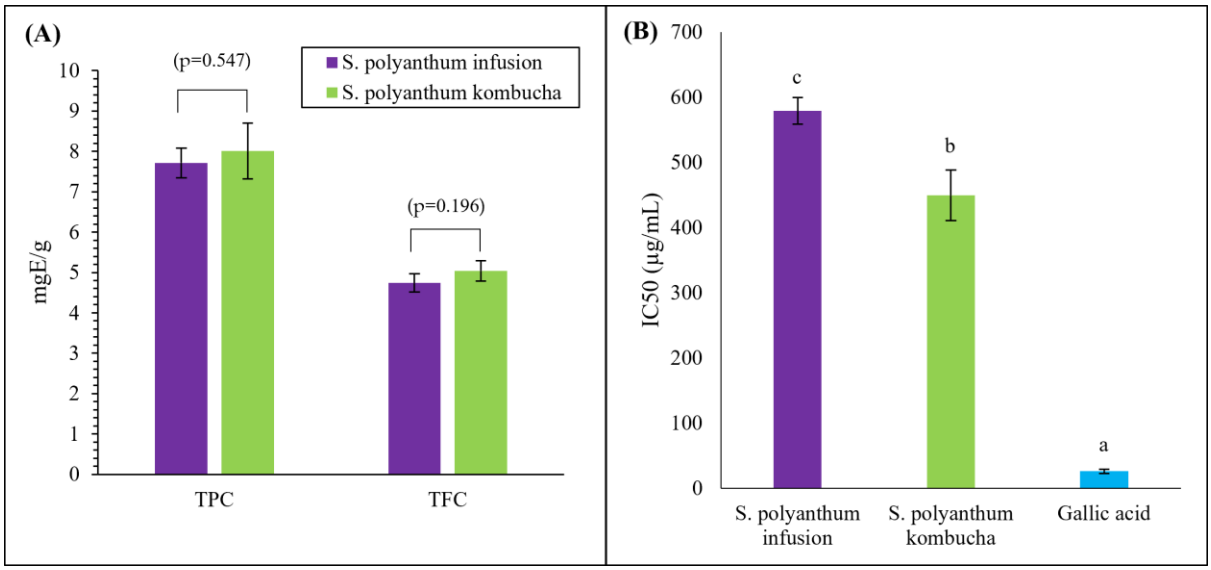

Figure 1 (A) Total Phenolic Content (TPC), Total Flavonoid Content (TFC) and **(B)** Antioxidant of *S. polyanthum* infusion and kombucha (n=3).

Antioxidant activity

The results demonstrated that *S. polyanthum* kombucha exhibited significantly stronger antioxidant activity than its non-fermented infusion (IC_{50}: 449.31±38.9 µg/mL vs. 578.93±20.67 µg/mL; $p < 0.05$), although both were considerably less potent than the standard gallic acid (25.68±3.26 µg/mL) (Figure 1B). These IC_{50} values are higher than those typically reported for organic solvent extracts; 20.90±0.26 µg/mL [23], 12.65 µg/mL [24], and 21.24±1.14 µg/mL [25] for methanolic and ethanolic extracts, which is expected due to the lower extraction efficiency of aqueous-based methods. The observed reduction in IC_{50} following fermentation indicates that kombucha fermentation enhances the antioxidant potential of *S. polyanthum*, likely through the release or transformation of bioactive compounds by microbial enzymatic activity [22]. Comparable findings were also reported for fresh juice of *S. polyanthum* leaves, which exhibited 64.93% DPPH radical scavenging activity, statistically similar to that of quercetin (69.21%; $p > 0.05$) [26]. This further validates the antioxidant potential of water-based preparations of *S. polyanthum* and suggests that even non-organic extractions retain appreciable bioactivity.

Antihyperglycemic Activity

The findings of present study demonstrate the antidiabetic potential of *S. polyanthum* leaves in managing fasting blood glucose levels, as evidenced by the significant reduction in blood glucose percentages across all treatment groups after 14 days of treatment. Notably, the *S. polyanthum* kombucha group exhibited the most pronounced effect, achieving a mean reduction of 61.45% on day 14, compared to 53.34% in the *S. polyanthum* infusion group and 50.47% in the positive control group ($p=0.001$; $p<0.05$) (Table 2). These results suggest that the fermentation process in kombucha enhances the bioavailability or potency of active compounds in *S. polyanthum* leaves, thereby amplifying its hypoglycemic effects.

Table 2 Percentage reduction in blood glucose levels of Infusion and Kombucha of *S. polyanthum* leaves.

Treatment given	Percentage reduction in blood glucose levels (%)			Mean±SD
	Day 5	Day 10	Day 14	
Negative control	3.69±1.57	6.13±1.25	9.44±1.86	6.42±2.89[a]
Positive control	23.18±3.68	37.49±4.57	50.47±4.28	37.05±13.64[b]
S. polyanthum infusion	18.96±11.87	36.93±8.39	53.34±5.71	36.41±17.20[b]
S. polyanthum kombucha	19.70±12.27	49.76±10.82	61.45±11.63	43.64±21.53[c]
Mean±SD	16.39±8.66[p]	32.58±18.60[q]	43.68±23.29[r]	

Values are presented as mean±SD. Different letters in the column (a,b,c) indicate a significant difference between the negative control and treatment groups ($p=0.001$; $p<0.05$). Different letters in the row (p,q,r) indicate a significant difference between day 5 and other day groups ($p=0.001$; $p<0.05$), based on Duncan's Multiple Range Test.

This study aligns with previous research highlighting the antidiabetic properties of *S. polyanthum* leaves. A study on diabetic rats reported significant reductions in blood glucose levels after 28 days of treatment, attributed to the plant's ability to mitigate hyperglycemia-induced cardiac apoptosis [27]. Similarly, a study employing nanoparticle formulations of *S. polyanthum* leaf extracts demonstrated a significant reduction in blood glucose levels in rat models, indicating that formulation strategy and dosage may influence the therapeutic efficacy of the extract [28]. Additionally, the combination of *S. polyanthum* leaves and Andrographis paniculata in alloxan-induced diabetic rats further demonstrated synergistic effects, with a significant reduction in blood glucose levels within just seven days of treatment [29].

The current findings are also supported by evidence identifying specific bioactive compounds in *S. polyanthum*, such as myricitrin and epigallocatechin gallate (EGCG), as potent antidiabetic agent by inhibiting the digestion and absorption of saccharides, enhancing insulin secretion as a potential GLP-1 receptor agonist, and alleviating complications related to type 2 diabetes mellitus (T2DM) by protecting

endothelial cells from hyperglycemia-induced oxidative stress [30]. Furthermore, a metabolomics and in silico analysis suggests the presence of other secondary metabolites in *S. polyanthum* leaves that contribute to its antidiabetic activity, supporting its traditional use in managing diabetes [31].

The enhanced efficacy of *S. polyanthum* leaves kombucha in managing hyperglycemia, compared to its unfermented counterpart, has been similarly observed in studies on other kombucha substrates, such as those by Zubaedah et al [32]. Their research demonstrated that snake fruit kombucha exhibited effects akin to metformin and was more effective in reducing fasting plasma glucose (FPG) levels than its unfermented infusion in a rat model. These findings align with previous studies underscoring the superior antihyperglycemic potential of kombucha. For instance, Xu et al [33] found that kombucha significantly improved hyperglycemic profiles in type 2 diabetes mellitus (T2DM) models compared to unfermented tea. This improvement is attributed to the polyphenols and organic acids produced during fermentation, which regulate glucose metabolism by inhibiting carbohydrate-digesting enzymes, enhancing insulin sensitivity, and mitigating oxidative stress. Furthermore, kombucha's antihyperglycemic effects may involve gut microbiota modulation, promoting the growth of short-chain fatty acid (SCFA)-producing bacteria, reducing pathogenic bacteria, and strengthening intestinal barrier function. Collectively, these mechanisms alleviate inflammation and insulin resistance in T2DM [34].

Although the flavonoid content in *S. polyanthum* kombucha was not significantly different from that of its infusion, the slightly higher total flavonoid content (TFC) observed in the kombucha may contribute to its enhanced antioxidant capacity. Moreover, the improved palatability resulting from fermentation makes it a more acceptable and enjoyable functional beverage for regular consumption [35]. To strengthen the evidence supporting the health benefits of *S. polyanthum* kombucha and its potential role in diabetes management, future research should address current limitations. This includes optimizing fermentation parameters, such as microbial strains, temperature, and duration, to improve product consistency and bioactive compound stability. Long-term studies are also needed to evaluate the sustained antihyperglycemic effects in diabetic models. Additionally, investigating the metabolic pathways involved in polyphenol biotransformation during fermentation could help elucidate the mechanisms responsible for its therapeutic efficacy. By addressing these research gaps, future studies can contribute significantly to the development of *S. polyanthum* kombucha as an effective functional beverage for diabetes prevention and management.

Conclusions

Kombucha derived from *S. polyanthum* leaves demonstrated notable levels of total phenolic and flavonoid content, along with promising antioxidant activity, as evidenced by its DPPH radical scavenging capacity. Furthermore, it effectively reduced blood glucose levels in alloxan-induced diabetic mice, indicating its potential role in diabetes management. These findings support its development as a functional beverage with both antioxidant and antihyperglycemic properties, warranting further investigation to optimize its therapeutic potential.

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