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Formulation and Antihyperglycemic Activity of Chayote–Milkfish Bone Cookies in Alloxan-Induced Mice

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ABSTRACT

Introdiction*: Functional cookies prepared from local food resources may provide an alternative approach to support blood glucose control. Chayote (Sechium edule) contains dietary fiber and flavonoids, while milkfish bone (Chanos chanos) is a calcium-rich by-product that can improve the nutritional value of food products.* ***Aims****: This study aimed to formulate cookies containing chayote flour and milkfish bone flour and evaluate their antihyperglycemic activity in alloxan-induced mice.* ***Result:*** *his experimental study used 25 male white mice (Mus musculus) divided into five groups: positive control, Formula 1 (30 g chayote flour:20 g milkfish bone flour), Formula 2 (25 g:25 g), Formula 3 (20 g:30 g) and Formula 4 (negative control). The cookies were administered orally once daily for 14 days. Blood glucose levels were measured before induction, after alloxan induction, and on days 7 and 14 of treatment. Hedonic evaluation was also performed to assess taste, colour, texture, and odour. Data were analyzed using a General Linear Model with repeated measures, followed by the Least Significant Difference test. All cookie formulations reduced blood glucose levels in alloxan-induced mice. Significant differences were observed across measurement times and treatment groups ($p<0.05$). Formula 2 produced the lowest mean blood glucose level on day 14, whereas Formula 1 showed better sensory acceptance for taste, colour, and texture.* ***Conclusion:*** *Chayote and milkfish bone can be formulated into functional cookies with antihyperglycemic activity in alloxan-induced mice.*

KEYWORDS*: Alloxan, blood glucose, chayote, functional cookies, milkfish bone.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels resulting from impaired insulin secretion, impaired insulin action, or both. Persistent hyperglycemia can lead to serious complications affecting the blood vessels, nerves, kidneys, eyes, and cardiovascular system. The global burden of diabetes continues to increase; the World Health Organization reported that 14% of adults aged 18 years and older were living with diabetes in 2022, while diabetes and diabetes-related kidney disease caused more than two million deaths in 2021(World Health Organization, 2024).

This condition highlights the need for preventive and supportive strategies, including dietary approaches that are affordable, acceptable, and based on locally available resources.

Dietary management is an important component in controlling blood glucose levels, particularly through the intake of foods with high fiber content, low glycemic impact, and bioactive compounds that may support glucose metabolism. Functional foods have gained attention as complementary products because they can provide nutritional value while contributing to physiological benefits. Cookies are among the food products that are widely consumed, practical, and acceptable across different age groups. Recent evidence also suggests that bakery products can be reformulated using functional ingredients to improve glycaemic response and support chronic disease management (Naveed et al., 2024). Therefore, developing functional cookies from local ingredients may offer a promising approach to support dietary management in hyperglycemic conditions.

Chayote (*Sechium edule*) is a local plant from the Cucurbitaceae family that has been traditionally consumed as food and has potential as a functional ingredient. It contains dietary fiber and bioactive compounds, including flavonoids and polyphenols, which have been associated with glucose-lowering effects. Recent evidence from clinical and preclinical studies indicates that *S. edule* intake may reduce serum glucose and glycated hemoglobin levels, although it is more appropriate as a complementary dietary approach rather than a substitute for pharmacological therapy (Arista-Ugalde et al., 2025). The fiber content of chayote may delay gastric emptying and glucose absorption, while its phenolic and flavonoid compounds may contribute to improved insulin sensitivity and inhibition of carbohydrate-digesting enzymes.

In addition to plant-based ingredients, fishery by-products may also be utilized to improve the nutritional value of functional foods. Milkfish (*Chanos chanos*) is an important seafood commodity in Indonesia and Southeast Asia, but its bones are often discarded as processing waste. Milkfish bone is rich in minerals, especially calcium and phosphorus, and can be processed into flour for food fortification (Wahid et al., 2024). Previous studies showed that milkfish bone flour can be incorporated into cookies and contributes to calcium, phosphorus, ash, and protein content (Simamora & Hidayat, 2024). The utilization of milkfish bone flour is also relevant from a sustainability perspective because it increases the added value of fishery by-products and reduces environmental waste.

Several studies have explored the hypoglycemic potential of chayote and the nutritional application of fish bone flour separately. However, limited studies have combined chayote flour and milkfish bone flour in a cookie formulation and evaluated its effect on blood glucose levels in an experimental diabetic model. The combination of chayote as a source of fiber and bioactive compounds with milkfish bone as a calcium-rich by-product may provide a functional cookie with both nutritional and antihyperglycemic potential. Based on this rationale, this study aimed to formulate cookies containing chayote flour and milkfish bone flour and to evaluate their antihyperglycemic activity in alloxan-induced white mice (*Mus musculus*).

MATERIAL AND METHODS

Materials

The materials used in this study were Alloxan, aquadest, baking powder, butter, chayote fruit (*Sechium edule*), commercial diet biscuits (WRP®), egg yolk, margarine, milkfish bone (*Chanos chanos*), powdered milk, sodium hydroxide (NaOH), standard mouse feed, and vanilla. Chayote fruit was obtained from Antang Market, Makassar, South Sulawesi, while milkfish bone was obtained from a boneless milkfish processing business in Tamangapa, Antang, South Sulawesi.

Methods

Preparation of Chayote Flour

Fresh chayote fruits were peeled, cut into small pieces, washed with water, and drained. The sliced chayote was dried in an oven at 150°C for 18 hours until completely dry. The dried sample was then ground using a blender and sieved through an 80-mesh sieve to obtain fine chayote flour (Tandi et al., 2021).

Preparation of Milkfish Bone Flour

Milkfish bones were washed with clean water and boiled for 10 minutes to facilitate the removal of attached flesh. The bones were drained and washed again under water. The cleaned bones were heated at 100°C under 1 atm pressure for 1 hour, then soaked in 0.5 N NaOH for 2 hours to remove remaining fat and impurities. The samples were washed, dried, ground using a blender, and sieved through an 80-mesh sieve to obtain milkfish bone flour (Simamora & Hidayat, 2024; Wahid et al., 2024).

Formulation of Cookies

The cookies were prepared using a modified cookie formulation and baking method reported in previous studies (T. Hidayat et al., 2024; Tandi et al., 2021). Cookies were prepared using three formulation contaiing formulations

Table 1. Formulation of chayote and milkfish bone cookies

Ingredients	Function	F1 (g)	F2 (g)	F3 (g)	F4 (g)
Chayote flour	Active ingredient	30	25	20	-
Milkfish bone flour	Active ingredient	20	25	30	-
Margarine	Tenderizing agent	20	20	20	20
Egg yolk	Emulsifier	10	10	10	10
Baking powder	Leavening agent	5	5	5	5
Powdered milk	Flavour enhancer	10	10	10	10
Butter	Crisping agent	2.5	2.5	2.5	2.5
Vanilla	Favouring agent	2.5	2.5	2.5	2.5

containing different ratios of chayote flour and milkfish bone flour. The composition of each formula is presented in Table 1.

The cookie preparation consisted of mixing, moulding, and baking. The dry ingredients, including chayote flour, milkfish bone flour, baking powder, and powdered milk, were mixed in one container. In another container, margarine and egg yolk were mixed using a mixer at high speed for approximately 3 minutes until a cream-like mixture was formed. The dry mixture was gradually added to the cream mixture and kneaded until a homogeneous dough was obtained. The dough was moulded using a cookie mould and baked at 150°C for 15 minutes. The baked cookies were cooled at room temperature before further evaluation and administration to experimental animals (Hidayat, et al., 2024).

Hedonic Evaluation

A hedonic test was conducted to evaluate the sensory acceptance of the cookie formulations. Twenty panelists assessed four sensory attributes, namely taste, colour, texture, and odour. The assessment used a five-point hedonic scale: 1 = strongly dislike, 2 = dislike, 3 = neutral, 4 = like, and 5 = strongly like. The mean score of each attribute was calculated for each formulation (Kusuma & Herawati, 2023).

Experimental Animals

Ethical approval was obtained from the Research Ethics Committee of Universitas Muslim Indonesia, Makassar, Indonesia, under approval number **308/A.1/KEP-UMI/V/2025**. A total of 25 male white mice (*Mus musculus*) aged 2–3 months, weighing 20–30 g, and in healthy physical condition were used in this study. The mice were acclimatized for seven days before treatment. During acclimatization, the animals were housed under laboratory conditions and provided with standard feed and drinking water ad libitum. The mice were randomly divided into five groups, with five mice in each group. Group I served as the negative control (Formula 4) and received the cookie base. Group II served as

the positive control and received commercial diet biscuits. Group III received Formula 1 containing 30 g chayote flour and 20 g milkfish bone flour. Group IV received Formula 2 containing 25 g chayote flour and 25 g milkfish bone flour. Group V received Formula 3 containing 20 g chayote flour and 30 g milkfish bone flour (Percie du Sert et al., 2020).

Alloxan Induction and Treatment

Before alloxan induction, mice were fasted for 8–12 hours with free access to drinking water. Baseline blood glucose levels were measured before induction. Hyperglycemia was induced by intraperitoneal administration of alloxan at a dose of 150 mg/kg body weight (Ighodaro et al., 2017; Lenzen, 2008). Blood glucose levels were measured 72 hours after alloxan induction. Mice with blood glucose levels above 126 mg/dL were considered hyperglycemic and included in the treatment phase (Aminah & Qomariyah, 2023).

The cookie suspension was administered orally once daily for 14 days. The daily cookie dose was calculated based on body weight conversion from the human daily intake dose and converted to the mouse dose using body surface area normalization (Nair & Jacob, 2016). Each mouse received approximately 11.5 g/kg body weight of cookie suspension, equivalent to about 0.23 g for a 20 g mouse, dispersed in aquadest before oral administration.

Blood Glucose Measurement

Blood glucose levels were measured using a digital glucometer and glucose test strips (Autocheck®). Blood samples were collected from the tail vein. Before sampling, the tail was cleaned with an alcohol swab and the tip of the tail was carefully cut using surgical scissors. The first drop of blood was discarded, and the subsequent blood drop was applied to the glucose test strip. Blood glucose levels were measured before alloxan induction, after alloxan induction, and on days 7 and 14 after treatment (Togashi et al., 2016).

Statistical Analysis

The data were analyzed using SPSS software. The normality of the data was evaluated using the Shapiro–Wilk test (Shapiro & Wilk, 1965). Normally distributed data were analyzed using the General Linear Model with a repeated measures design to determine differences across measurement times, treatment groups, and their interaction (Fauziyah, 2020). The analysis was continued with the Least Significant Difference post hoc test to identify specific differences between groups. A p-value of less than 0.05 was considered statistically significant.

Table 2. Hedonic evaluation of chayote and milkfish bone cookies

Formula	Taste	Colour	Texture	Odour
Formula 1 (30:20 g)	4.00 ± 0.65	3.90 ± 0.64	4.00 ± 0.73	3.35 ± 0.59
Formula 2 (25:25 g)	3.40 ± 0.50	3.35 ± 0.67	3.00 ± 0.65	3.75 ± 0.72
Formula 3 (20:30 g)	3.00 ± 0.73	3.15 ± 0.81	3.70 ± 0.57	2.40 ± 0.50

RESULTS AND DISCUSSION

Sensory Acceptance of Cookies

The hedonic evaluation was conducted to determine the sensory acceptance of cookies containing chayote flour and milkfish bone flour. The evaluated attributes included taste, colour, texture, and odour. The mean scores of the hedonic test are presented in Table 2.

Formula 1 showed the highest acceptance scores for taste, colour, and texture, with mean scores of 4.00, 3.90, and 4.00, respectively. These scores indicate that Formula 1 was generally categorized as “like” or “tend to like” by the panelists. This result may be related to the higher proportion of chayote flour and lower proportion of milkfish bone flour in Formula 1. Chayote flour may contribute to a milder taste and lighter colour, whereas high levels of fish bone flour may increase fishy odour and affect the visual appearance of the product. Formula 2 showed the highest odour score, suggesting that the balanced ratio between chayote flour and milkfish bone flour may reduce the dominance of fishy odour while still maintaining the characteristic odour of the cookie.

Formula 3, which contained the highest proportion of milkfish bone flour, had the lowest scores for taste, colour, and odour. The odour score of Formula 3 was 2.40, indicating that the panelists tended to dislike its odour. This finding suggests that increasing the concentration of milkfish bone flour may reduce sensory acceptance, especially due to the stronger fishy odour. This result is consistent with previous findings indicating that fish bone flour can be used as a calcium-rich ingredient in food products, but its concentration needs to be controlled because excessive addition may affect sensory quality, particularly odour, colour, and taste (Simamora & Hidayat, 2024).

Overall, the sensory evaluation showed that all formulations were still acceptable, but Formula 1 provided the most balanced sensory profile. This finding is important because functional food products should not only provide potential health benefits but also have acceptable sensory characteristics to support consumer compliance.

Blood Glucose Levels in Alloxan-Induced Mice

The antihyperglycemic activity of the cookie formulations was evaluated in alloxan-induced mice. Blood glucose levels were measured before alloxan induction, after alloxan induction, and on days 7 and 14 of treatment. The mean blood glucose levels are shown in Table 3.

Alloxan induction increased blood glucose levels in all groups, indicating the successful establishment of a hyperglycemic animal model. Alloxan is widely used to induce experimental diabetes because it selectively damages pancreatic β-cells through glucose transporter-mediated uptake and reactive oxygen species generation, leading to impaired insulin secretion (Ighodaro et al., 2017; Lenzen, 2008). In this study, the F4 group showed a progressive increase in blood glucose levels from 166.8 ± 36.2 mg/dL after alloxan induction to 289.0 ± 118.0 mg/dL on day 14. This result indicates that the cookie base without chayote flour and milkfish bone flour did not prevent the progression of hyperglycemia.

In contrast, the positive control and all treatment groups showed a decrease in blood glucose levels after 14 days of treatment. Formula 1 reduced blood glucose levels from 182.2 ± 33.2 mg/dL after alloxan induction to 92.8 ± 10.5 mg/dL on day 14. Formula 2 showed the greatest numerical reduction, from 200.6 ± 66.4 mg/dL to 82.2 ± 14.8 mg/dL, corresponding to a 59.0% reduction. Formula 3 also reduced blood glucose levels from 176.2 ± 32.6 mg/dL to 93.6 ± 13.4 mg/dL. These results indicate that cookies containing chayote flour and milkfish bone flour have antihyperglycemic potential in alloxan-induced mice.

The blood glucose profile during the treatment period is illustrated in Figure 1. The F4 group showed a progressive increase in blood glucose levels, whereas the positive control and all cookie formulation groups showed a gradual decrease after 14 days of treatment. As shown in Figure 1, the F4 group demonstrated a progressive increase in blood glucose levels after alloxan induction and during the 14-day observation period. In contrast, the positive control group and all cookie formulation groups showed a gradual decrease in blood glucose levels after treatment. The decrease was already observed on day 7 and continued until day 14, indicating that the cookie formulations contributed to improved blood glucose profiles in alloxan-induced mice. Formula 2 showed the lowest mean blood glucose level on day 14, followed by the positive control, Formula 1, and Formula 3. However, the overall pattern indicates that all formulations containing chayote flour

Table 3. Blood glucose levels of alloxan-induced mice after cookie treatment

Group	Baseline (mg/dL)	Post-alloxan (mg/dL)	Day 7 (mg/dl)	Day 14 (mg/dL)	% Reduction to day 14 (%)
Positive Control	81.2 ± 19.9	153.0 ± 21.9	130.2 ± 10.7	84.8 ± 11.1	44.6
Formula 1	75.6 ± 10.2	182.2 ± 33.2	132.8 ± 22.6	92.8 ± 10.5	49.1
Formula 2	84.6 ± 28.6	200.6 ± 66.4	123.8 ± 12.6	82.2 ± 14.8	59.0
Formula 3	94.2 ± 17.4	176.2 ± 32.6	139.2 ± 19.8	93.6 ± 13.4	46.9
Formula 4	93.8 ± 15.6	166.8 ± 36.2	273.8 ± 140.9	289.0 ± 118.0	-73.3

and milkfish bone flour produced a better glucose-lowering profile than the F4.

The decrease in blood glucose levels may be associated with the fiber and bioactive compounds contained in chayote. Dietary fiber can delay gastric emptying, reduce the rate of carbohydrate digestion, and slow intestinal glucose absorption. Recent systematic evidence supports the role of dietary fiber interventions in improving glycemic control in individuals with diabetes or at risk of diabetes (Giuntini et al., 2022). Soluble fiber may also be fermented by gut microbiota into short-chain fatty acids (SCFAs), which are associated with lower fasting insulin concentrations and improved insulin sensitivity as indicated by improvement in HOMA-IR (Nitzke et al., 2024; Pham et al., 2024).

In addition to fiber, chayote contains flavonoids and other phenolic compounds that may contribute to antihyperglycemic activity. A recent systematic review and meta-analysis reported that *Sechium edule* has hypoglycemic effects in clinical and preclinical studies, although it should be regarded as a complementary dietary approach rather than a replacement for standard therapy (Arista-Ugalde et al., 2025). These findings are supported by clinical evidence showing that powdered *Sechium edule* concentrate may reduce HbA1c and oxidative stress markers in older adults with metabolic syndrome (Arista-Ugalde et al., 2022). The antioxidant and anti-inflammatory properties of *S. edule* may also support metabolic regulation, as supplementation with chayote has been reported to improve oxidative and inflammatory markers in older adults with metabolic syndrome (Gavia-García et al., 2023). Flavonoids may reduce blood glucose by inhibiting α-amylase and α-glucosidase, the key enzymes involved in carbohydrate digestion, thereby reducing postprandial glucose absorption. This mechanism is supported by a systematic review showing the potential of flavonoids as dual inhibitors of α-glucosidase and α-amylase (Lam et al., 2024).

The addition of milkfish bone flour may

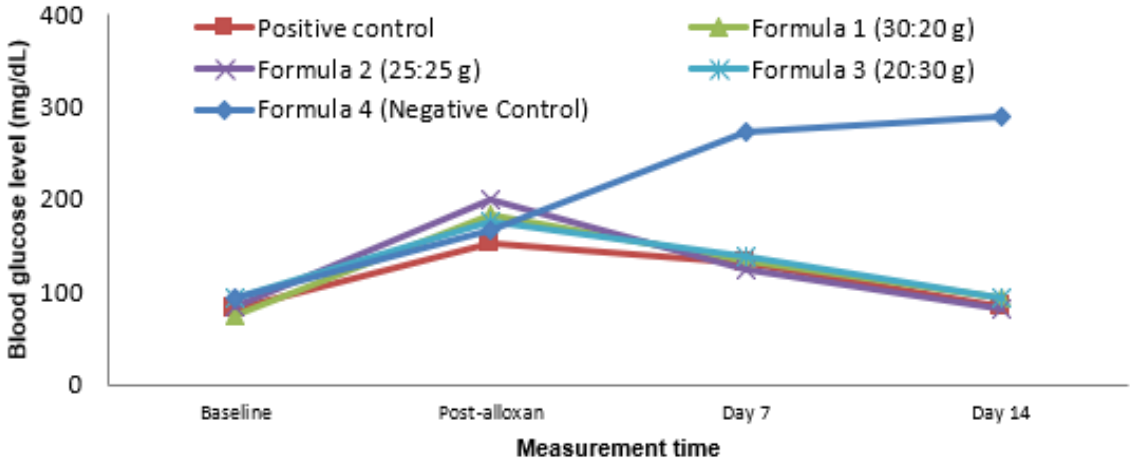

Figure 1. Blood glucose level profile of alloxan-induced mice during 14 days of treatment.

also support the functional value of the cookies. Milkfish bone is rich in minerals, particularly calcium and phosphorus, and its incorporation into cookies has been reported to increase the nutritional value of the product (Simamora & Hidayat, 2024; Wahid et al., 2024). The use of milkfish bone flour as a calcium fortificant has also been reported in snack products, where its incorporation improved the calcium value but required concentration control to maintain sensory acceptability (Probowati et al., 2024). Calcium is an important intracellular signal in pancreatic β-cells. In glucose-stimulated insulin secretion, increased intracellular ATP closes ATP-sensitive potassium channels, induces membrane depolarization, opens voltage-dependent calcium channels, and increases intracellular Ca^{2+} concentration, which triggers insulin granule exocytosis. Current evidence confirms that Ca^{2+} is a critical second messenger involved in β-cell insulin exocytosis (Magnuson & Osipovich, 2024). Therefore, the mineral contribution of milkfish bone flour may be relevant to metabolic regulation, although the present study did not directly measure calcium content or insulin levels.

Statistical analysis using the General Linear Model with repeated measures showed a significant effect of measurement time on blood glucose levels ($p<0.001$), indicating that blood glucose changed significantly during the observation period. The between-subjects effect was also significant ($p=0.001$), indicating differences among treatment groups. The LSD post hoc test showed significant differences between the F4 group and the positive control, Formula 1, Formula 2, and Formula 3 groups ($p<0.05$). However, no significant differences were observed among the positive control and the three cookie formulations. This finding suggests that all cookie formulations produced comparable

antihyperglycemic effects and were significantly better than the negative control (F4).

Althought Formula 2 showed the lowest mean blood glucose level on day 14 and the greatest numerical reduction from post-alloxan levels, the difference between Formula 2 and the other formulations was not statistically significant. Therefore, Formula 2 may be considered the most promising formulation based on numerical blood glucose reduction, while Formula I may be considered the most acceptable formulation based on sensory evaluation. This distinction is important because the best functional food formulation should ideally balance biological activity and sensory acceptability.

The findings of this study support the potential development of chayote and milkfish bone cookies as functional food candidates for supporting blood glucose control. This is in line with recent evidence showing that the glycaemic index of shortbread cookies can be modulated by incorporating functional ingredients, such as fruit pomace, indicating that cookie-based products can be redesigned to provide a more favourable glycaemic response (Raczkowska et al., 2024). Similar findings were reported in functional cassava pulp flour cookies, where increasing substitution improved dietary fiber and resistant starch content and produced cookies categorized as low glycemic index food (B. Hidayat et al., 2023). The novelty of this study lies in combining chayote flour as a source of dietary fiber and flavonoid-rich bioactive compounds with milkfish bone flour as a calcium-rich fishery by-product in a cookie formulation. This approach provides two advantages: the development of a local functional food product and the valorization of fishery waste into a value-added ingredient. However, this study has several limitations. The proximate composition, calcium content, fiber content, total flavonoid content, and glycemic index of the cookies were not measured. In addition, insulin levels, pancreatic histopathology, and product stability were not evaluated. Further studies are needed to confirm the nutritional profile, mechanism of action, storage stability, and safety of the formulated cookies.

CONCLUSION

Chayote (*Sechium edule*) flour and milkfish bone (*Chanos chanos*) flour can be formulated into functional cookies with acceptable sensory characteristics and antihyperglycemic activity in alloxan-induced mice. The cookie formulations significantly reduced blood glucose levels compared with the negative control (F4), indicating the potential contribution of chayote fiber and bioactive compounds as well as milkfish bone minerals in

supporting blood glucose control. Formula showed the greatest numerical reduction in blood glucose levels, while Formula 1 demonstrated the most favourable sensory acceptance. Further studies are needed to evaluate the proximate composition, fiber and calcium content, glycaemic index, product stability, safety, and mechanism of action of the formulated cookies.

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