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RESEARCH ARTICLE

Aqueous and n-Hexane Fractions of *Eruca sativa* Differentially Target Glycemic Control and Pancreatic Islet Protection in Diabetic Rats

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Abstract

BACKGROUND: The search for novel antidiabetic agents that simultaneously lower blood glucose and protect pancreatic β-cells is crucial. While *Eruca sativa* is known for its antidiabetic properties, the specific contribution of its solvent fractions to different therapeutic targets remains poorly understood. Therefore, this study was conducted to identify how different fractions selectively target glycemic control or pancreatic islet integrity.

METHODS: Twenty-five male Wistar rats were rendered diabetic by a single intraperitoneal injection of 45 mg/kg streptozotocin. Diabetic animals were divided into five groups (n=5): diabetic control, positive control (0.45 mg/kg glibenclamide), and three treatment groups receiving n-hexane, ethyl acetate, or aqueous fractions of 400 mg/kgBW *E. sativa* for 14 days. Phytochemical screening was performed to identify bioactive profiles. Blood glucose was monitored periodically, and pancreatic tissues were assessed using a histopathological scoring system (0–4) and islet area measurement.

RESULTS: Aqueous fraction showed the most potent antihyperglycemic activity, significantly reducing blood glucose (208.8±36.02 mg/dL) compared to the diabetic control (419.6± 117.11 mg/dL). Conversely, the n-hexane fraction provided superior pancreatic protection, maintaining the highest islet area (19,109.81±7,549.98 μm²) and the best histopathological score (2.8±0.8) among all treatment groups. Phytochemical screening revealed a distinct distribution of compounds, with flavonoids concentrated in the aqueous fraction and terpenoids in the n-hexane fraction.

CONCLUSION: This study demonstrates that therapeutic efficacy of *E. sativa* is fraction-specific, driven by its distinct phytochemical profiles. The aqueous fraction is the most effective for rapid glycemic control, significantly reducing blood glucose levels. Conversely, the n-hexane fraction provides superior pancreatic protection, as evidenced by the highest islet area and improved histopathological scores. These findings suggest that *E. sativa* possesses a dual-target potential; while the aqueous fraction excels in antihyperglycemic action, the n-hexane fraction is more potent for pancreatic islet preservation.

KEYWORDS: *Eruca sativa*, diabetes mellitus, histopathology, pancreatoprotective, solvent fractions, antihyperglycemic

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Introduction

Diabetes mellitus remains a critical global health issue, characterized by its chronic nature and the persistence of high blood sugar. Currently, the weight of this metabolic disorder is felt most heavily within developing countries.(1,2) The 2025 International Diabetes Federation (IDF) Diabetes Atlas highlights an alarming growth in metabolic disorders worldwide. While 589 million adults were estimated

to be living with diabetes in 2024, this demographic is anticipated to grow to 853 million by 2050, reflecting a sharp 45% increase that poses significant challenges for future clinical management. While pharmacological management exists, limitations such as adverse effects, cost, and accessibility constraints have driven the search for alternative therapies.(3,4) Medicinal plants, supported by World Health Organization (WHO) for research into chronic disease management, are thus a promising source of novel therapeutic compounds.(5)

Eruca sativa Mill. (arugula), a member of the Brassicaceae family, is an edible plant traditionally recognized for various medicinal properties, including potential antidiabetic effects.(6,7) Phytochemical studies have identified several bioactive constituents in arugula, such as flavonoids, alkaloids, terpenoids, and glucosinolates. These compounds are implicated in glucose homeostasis through mechanisms like enhancing insulin sensitivity, stimulating insulin secretion, and inhibiting digestive enzymes.(6,8) Although previous studies have demonstrated the antihyperglycemic potential of crude *E. sativa* extracts, the therapeutic activity is highly dependent on solvent polarity, which determines the yield and profile of bioactive compounds.(7,8) The extraction solvent significantly influences the concentration of specific metabolites; for instance, polar solvents typically yield higher concentrations of flavonoids, while non-polar solvents favor the recovery of terpenoids and steroids.

A critical unresolved issue is whether different solvent fractions of *E. sativa* leaf extract target distinct pathological facets of diabetes. Specifically, it remains unknown if polar fractions rich in compounds like flavonoids are primarily responsible for acute blood glucose reduction, while non-polar fractions containing terpenoids and steroids might be crucial for protecting and regenerating the insulin-producing pancreatic β-cells, a primary target of damage in DM. Previous studies have explored various natural agents to mitigate pancreatic damage and metabolic disturbances in streptozotocin (STZ)-induced models. (9,10) Research indicates that specific plant fractions can significantly improve islet histopathology and restore glucose homeostasis.(11) The efficacy of these fractions is fundamentally linked to the extraction yield and the chemical nature of the solvents used. Solvents with varying polarities, ranging from non-polar n-hexane to polar water, selectively extract different classes of phytochemicals, such as lipophilic terpenoids or hydrophilic flavonoids, respectively. These differences in extraction profiles are theorized to dictate the specific pharmacological targets of the plant. However, how these solvent-dependent yields in *E. sativa* differentially target glycemic control versus pancreatic protection remains to be elucidated. Addressing this question is essential for developing standardized, effective phytomedicines. Since STZ specifically targets pancreatic beta-cells through oxidative stress and DNA alkylation, leading to the structural collapse of the islets of Langerhans. We hypothesized that the biological effects would be fraction-dependent, with polar and non-polar fractions exhibiting divergent therapeutic profiles. Therefore, this study was conducted to evaluate and compare the effects of n-hexane, ethyl acetate, and aqueous fractions of E. sativa leaf extract on both glycemic control and pancreatic histopathology in STZ-induced diabetic rats.

Methods

Plant Material Collection and Authentication

Fresh leaves of *E. sativa* were harvested from a local farm in Berastagi, Karo Regency, Sumatera Utara, Indonesia. The plant specimen was authenticated at the Herbarium Medanense (MEDA), Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara (Specimen Voucher No. 794/MEDA/2025). This herbarium is a nationally recognized institution with the official authority to perform plant identification and authentication in North Sumatra, Indonesia.

Preparation of Crude Ethanol Extract

The collected leaves were thoroughly washed under running water to remove impurities and subsequently shade-dried at room temperature (25–30°C) for one week. The dried leaves were pulverized using an electric grinder and sieved through a 40-mesh screen to obtain a uniform powder. One kilogram of the powdered material was macerated in 96% ethanol at a ratio of 1:10 (w/v) for 72 hours with intermittent agitation. The mixture was filtered, and the solvent was removed under reduced pressure at 50°C using a rotary evaporator to yield a concentrated crude ethanol extract.(12,13)

Solvent Fractionation

Fractionation was performed using sequential liquid-liquid extraction following the standardized protocol that have been previously published.(14) Briefly, 100 g of the crude ethanol extract was dissolved in ethanol and partitioned successively with n-hexane, ethyl acetate, and distilled water. Each partitioning step was carried out in a separatory funnel by vigorously shaking the mixture for 1

minute, followed by 10 minutes of phase separation. The process was repeated three times for each solvent to ensure exhaustive extraction. The selection of solvents followed the order of increasing polarity to ensure systematic separation of bioactive constituents.

Phytochemical Screening

Phytochemical screening was performed to identify various bioactive compounds. Flavonoids were identified using magnesium powder and concentrated hydrochloric acid (Shinoda test). Alkaloids were verified using Meyer, Bouchardat, and Dragendorff reagents. The presence of saponins, tannins, glycosides, and steroids/triterpenoids was determined according to standardized procedures.(14–16)

Experimental Animals

Twenty-five adult male Wistar rats (200-300 g) were obtained and housed under standard laboratory conditions (12 h light/dark cycle, 25±2°C) with free access to standard pellet diet and water. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee of Universitas Prima Indonesia (No. 052/KEPK/UNPRI/V/2025). All procedures adhered to the guidelines for the care and use of laboratory animals.

Induction of Diabetes and Experimental Design

After a week of acclimatization, diabetes was induced by a single intraperitoneal injection of STZ (Sigma-Aldrich, St. Louis, MO, USA). The STZ solution was prepared by dissolving 0.24 g of STZ in 100 mL of ice-cold 0.1 M citrate buffer saline (pH 4.5) immediately before administration to ensure stability.(9) Forty-eight hours after induction, fasting blood glucose levels were verified. Animals with fasting blood glucose ≥200 mg/dL were considered diabetic and distributed into five experimental groups (n=5): the diabetic control (DC) received 0.5% Na-CMC vehicle, while the positive control (PC) was treated with 0.45 mg/kg BW glibenclamide. The remaining three groups G1, G2, and G3 were treated with n-hexane, ethyl acetate, and aqueous fractions, respectively, at a dose of 400 mg/kg BW. The dose of 400 mg/kg BW was selected based on previous pharmacological studies of *E. sativa* which demonstrated significant biological activity at this level without observable toxicity.(10). All preparations were administered via oral gavage once daily for a 14-day period.

Blood Glucose Monitoring

Blood glucose levels were measured at four time points: before STZ induction (baseline), 48 hours post-induction (confirmation of diabetes), and on day-7 and -14 of treatment. Measurements were performed using a standard glucometer based on the glucose oxidase method. Blood samples were obtained from the tail vein in the morning after the rats had been fasted for 8–12 hours (as fasting blood glucose).

Histopathological Examination

On day-15, all animals were anesthetized and euthanized. For histological examination, pancreatic samples were harvested and preserved in a 10% neutral buffered formalin solution. Following standard dehydration and paraffin infiltration, the tissues were cut into 4–5 µm sections using a microtome and subsequently subjected to Hematoxylin and Eosin (H&E) staining for structural analysis. Histopathological assessment of the islets of Langerhans was performed by a blinded observer using a light microscope Olympus CX23 (Olympus, Tokyo, Japan). Islet damage was scored on a semi-quantitative scale of 0–4 (17), based on architectural integrity, presence of necrosis, cell count, and morphology. The area of Langerhans islets was measured from five representative islets per animal using image analysis software, ImageJ (NIH, Bethesda, MD, USA). The histopathological changes in the pancreatic islets were assessed semiquantitatively using a scoring system of 0 to 4, representing the severity of vacuolization, necrosis, and inflammatory cell infiltration, based on established criteria.(18)

Statistical Analysis

Data were expressed as mean±SD. Statistical analysis was performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA). Normality and homogeneity of variance were assessed using Shapiro-Wilk and Levene's tests, respectively. For body weight analysis, a paired t-test was used to compare differences before and after treatment within each group. For parametric data (blood glucose, islet area), one-way ANOVA followed by Tukey‘s post-hoc test was used for intergroup comparisons. For non-parametric data (histopathological scores), the Kruskal-Wallis test followed by the Mann-Whitney U test was employed. A $p<0.05$ was considered statistically significant.

Results

Phytochemical Screening Results

The phytochemical analysis of *E. sativa* leaf extracts across different solvent polarities revealed a comprehensive profile of secondary metabolites. Qualitative testing confirmed

Table 1. Subjects' body weight before and after DM-induction based on the intervention groups.

Treatment Group	Body Weight (Mean±SD)		*p-value*
	Before Induction	After Induction	
DC	177.0±1.00.0	138.8±14.38	0.004*
PC	165.4±1.82	150.6±7.64	0.024*
G1	172.4±1.14	133.4±11.74	0.001*
G2	175.6±1.82	131.8±6.02	0.000*
G3	167.8±1.30	126.6±10.78	0.001*

*Significant if $p<0.05$; Tested with paired T-test.

that both n-hexane and ethyl acetate fractions contain a rich array of bioactive compounds, specifically flavonoids, alkaloids, glycosides, tannins, and steroids/triterpenoids. The phytochemical screening revealed a diverse distribution of bioactive compounds across the fractions. Flavonoids and alkaloids were consistently present in all fractions. However, a notable distinction in the phytochemical distribution was observed concerning saponins, which were only detected in the aqueous fraction. This group of compounds was exclusively detected in the ethyl acetate fraction, as evidenced by the formation of stable foam upon treatment with hot water and hydrochloric acid. Conversely, the n-hexane fraction yielded a negative result for saponins, indicating that these specific metabolites in *E. sativa* possess a higher polarity that favours extraction in ethyl acetate over non-polar solvents. These findings suggest that the leaves of arugula serve as a potent source of diverse phytochemicals with significant potential for pharmacological applications (Supplementary 1).

Evaluation of Body Weight Alterations

The administration of STZ resulted in significant body weight loss across all experimental groups, as evidenced by paired t-test $p<0.05$. The DC group exhibited the greatest absolute reduction (38.2 g), while the glibenclamide-treated PC group showed the smallest loss (14.8 g), suggesting a partial protective effect of the standard drug. The treatment groups receiving the n-hexane (G1), ethyl acetate (G2), and aqueous (G3) fractions of E. sativa extract experienced substantial weight loss (39.0 g, 43.8 g, and 41.2 g, respectively), comparable to or exceeding that of the DC group (Table 1). This indicates that, at the tested dose of 400 mg/kg, the extract fractions did not prevent the catabolic weight loss characteristic of uncontrolled, insulin-deficient diabetes in this model.

The blood glucose profiles of the experimental groups over the 14-day study period were summarized in Table 2. Prior to the induction of diabetes, all groups demonstrated comparable normoglycemic baseline levels, with no statistically significant differences observed ($p=0.925$). Following induction, a state of pronounced hyperglycemia was successfully established across all cohorts intended for intervention, as evidenced by elevated fasting blood glucose level. At this post-induction time point, no significant inter-group differences were detected ($p=0.164$), confirming a uniform diabetic state prior to the commencement of treatments. The therapeutic interventions elicited discernible effects on glycemic control over time.

Table 2. Blood glucose levels in STZ-induced diabetic rats treated with various intervention.

Time Stamp	Bloood Glucose (Mean±SD)					*p-value*
	DC	PC	G1	G2	G3	
Before Induction	97.60±5.94	96.40±6.84	96.40±5.64	97.40±3.91	97.40±6.95	0.925
After Induction	430.80±120.79	304.40±98.03	327.4±121.28	328.40±136.83	348.80±148.64	0.164
On Day 7	432.80±122.39	387.40±164.74	320.8±88.51	367.0±137.44	340.20±101.40	0.441
On Day 14	$419.6\pm117.11^{b,c,d,e}$	$152.0\pm22.46^{a,c,d,e}$	$319.0\pm48.15^{a,b,e}$	$308.8\pm115.19^{a,b,e}$	$208.8\pm36.02^{a,b,c,d}$	0.005*

Data expressed as mg/dL, mean±SD (n=5). Different lowercase superscript letters within a row indicate statistically significant differences based on one-way ANOVA followed by Tukey's post-hoc test. $^{a}p<0.05$ *vs.* DC group; $^{b}p<0.05$ *vs.* PC group; $^{c}p<0.05$ *vs.* G1 group; $^{d}p<0.05$ *vs.* G2 group, $^{e}p<0.05$ *vs.* G3 group.

While no significant differences were observed on day-7 (p=0.441), a highly significant divergence in fasting blood glucose emerged among the groups by the study endpoint on day-14 (p=0.005). Post-hoc analysis using Tukey's test revealed specific pairwise comparisons. The PC group, treated with the standard antidiabetic agent, exhibited the most substantial reduction in hyperglycemia, achieving a final blood glucose of 152.0±22.46 mg/dL. This value was significantly lower (p<0.05) than those of the DC group and all treatment groups receiving the *E. sativa* fraction (G1, G2, G3). In contrast, the untreated DC group maintained severe and persistent hyperglycemia throughout the experimental period, with a final blood glucose of 419.6±117.11 mg/dL, which was significantly higher than all other treated groups. Administration of the *E. sativa* leaf fraction resulted in a significant antihyperglycemic effect relative to the DC.

A clear dose-response relationship was apparent among the fraction-treated groups. G3, which received the highest dose, produced the most pronounced glucose-lowering effect, reducing blood glucose to 208.8±36.02 mg/dL. The blood glucose in the G3 group was not only significantly lower than in the DC group but also statistically distinct from the PC and G1 groups. Groups G1 (319.0±48.15 mg/dL) and G2 (308.8±115.19 mg/dL) also showed significant reductions compared to DC, with their values being statistically similar to each other yet significantly higher than that of the PC group. The temporal profile indicated a progressive decline in blood glucose level from day-7 to day-14 in the PC, G2, and G3 groups, suggesting a cumulative, time-dependent therapeutic action. The specific significant differences denoted by superscript letters in day-14 data comprehensively delineate the efficacy hierarchy among the interventions (Table 2).

Evaluation of Pancreatic Histopathology and Area of Langerhans Islets

Both the DC and PC groups received a score of 2, characterized by partially faded islet boundaries, a reduced number of cells, evidence of cellular degeneration, and some cells exhibiting unhealthy morphology. In contrast, the n-hexane fraction group of *E. sativa* leaf extract at 400 mg/kgBW (G1) showed the lowest pancreatic damage score (0.6±0.89), indicating superior pancreatoprotective effects, with intact islet borders, no necrotic cells, stable cell numbers, and well-preserved cellular morphology. The G2 and G3 at the same dose were assigned a score of 3, showing poorly defined islet boundaries, the presence of necrotic cells, reduced cell counts, and numerous cells displaying abnormal shapes. In the DC group, the mean area of the Langerhans islets was 5727.53±1819.43 µm², whereas the PC group exhibited a mean islet area of 9513.97±5332.30 µm². Meanwhile, the average area of Langerhans islets in the G1 was 10405.31±2520.23 µm², the G2 of was 9585.07±3710.25 µm², and the G3 was 9064.95±4811.56 µm² (Table 3, Figure 1).

STZ induction caused clear structural damage to pancreatic islets in the diabetic control group, which was reflected by an islet damage score of 2.4±1.14 and a reduced mean islet area of 5727.53±1819.43 µm². In rats treated with glibenclamide, islet injury was less pronounced, as indicated by a lower damage score (1.6±0.55) accompanied by an increase in islet area (9513.97±5332.30 µm²). Treatment with the n-hexane fraction (G1) resulted in the most distinct histopathological improvement. This group showed the lowest islet damage score (0.6±0.89) and the largest mean islet area (10405.31±2520.23 µm²), both of which differed significantly from the diabetic control (p<0.05). In contrast, animals receiving the ethyl acetate (G2) and aqueous (G3) fractions continued to display high degrees of islet damage, with scores of 3.0±0.71 and 3.0±1.00, respectively. Mean islet areas in these groups reached 9585.07±3710.25 µm² for G2 and 9064.95±4811.56 µm² for G3, but these increases were not accompanied by meaningful reductions in structural injury. Statistical testing confirmed significant differences among treatment groups for islet damage score (p=0.034) and mean islet area (p=0.044).

To further evaluate the relationship between structural damage and functional morphology, a pearson correlation analysis was conducted between the pancreatic histopathological damage scores and the area of the islets of Langerhans. The analysis revealed a statistically significant moderate negative correlation (r=-0.497; p=0.034). This

Table 3. Pancreatic histopathological assessment and Langerhans islet morphometry in STZ-induced diabetic rats treated with various intervention.

Treatment Group	Islet Damage Score (Mean±SD)	Mean Islet Area (µm²) (Mean±SD)
DC	2.4±1.14^{c,d,e}	5727.53±1819.43^{b,c,d,e}
PC	1.6±0.55^{a,c,d,e}	9513.97±5332.30^{a,b}
G1	0.6±0.89^{a,d,e}	10405.31±2520.23^{a}
G2	3.0±0.71^{a,b}	9585.07±3710.25^{a}
G3	3.0±1.0^{a,b}	9064.95±4811.56^{a,b}
p-value	0.034*	0.044*

Different lowercase superscript letters within a row indicate statistically significant differences based on one-way ANOVA followed by Tukey's post-hoc test. ^{a}p<0.05 *vs*. DC group; ^{b}p<0.05 *vs*. PC group; ^{c}p<0.05 *vs*. G1 group; ^{d}p<0.05 *vs*. G2 group, ^{e}p<0.05 *vs*. G3 group.

negative correlation indicated that lower histopathological damage scores (representing improved tissue integrity) were associated with larger islet areas. While the correlation was moderate, it provided statistical evidence that the reduction in cellular insults such as necrosis and vacuolization is a contributing factor to the preservation of the pancreatic islet mass. This finding supported the hypothesis that the n-hexane fraction (G1), which exhibited the lowest damage scores and relatively larger islet areas, worked through a pancreatoprotective mechanism that helps maintain the structural foundation of the endocrine pancreas.

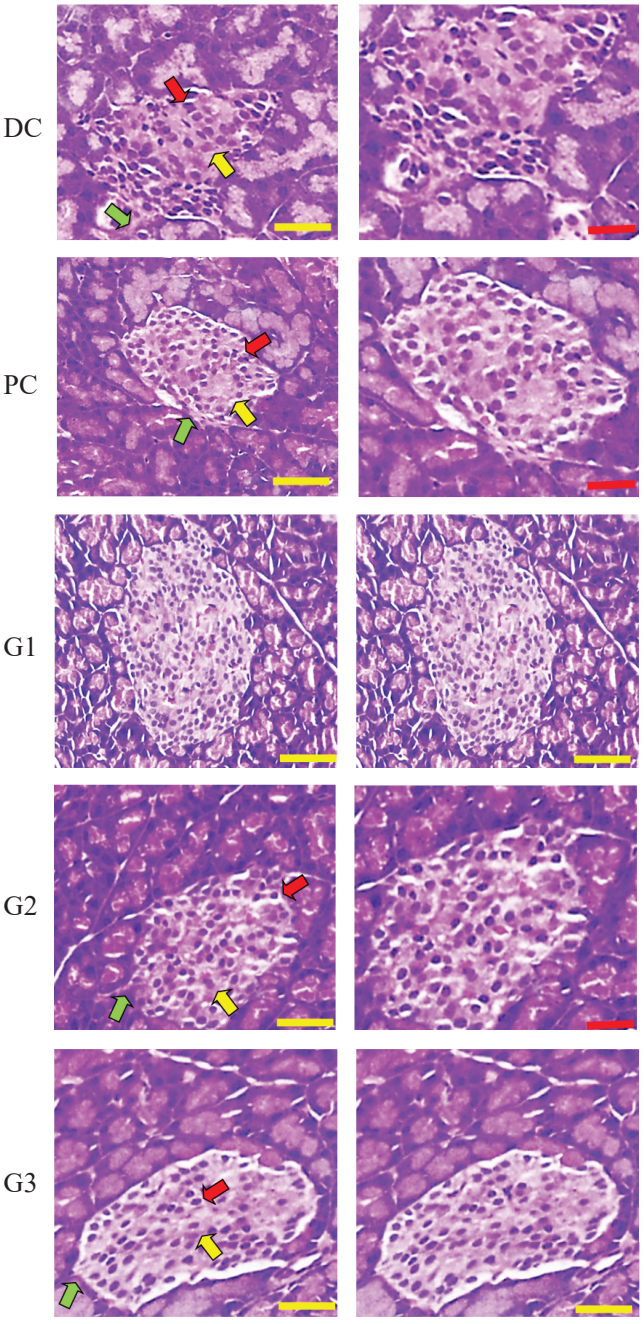

Figure 1. Pancreatic histopathology (left) and area of Langerhans islets (right) in STZ-induced diabetic rats treated with various intervention. Green arrow: Langerhans islet margins; Red arrow: cell morphology; Yellow arrow: degeneration and cell numbers. Red bar: 50 µm; Yellow bar: 100 µm. Surface number and length of surface number in the area of Langerhans islets are as follow: DC: (75) length 107536.58 nm and (76) 81136.76 nm; PC: (216) length 124064.40 nm and (217) length 92772.20 nm; G1: (63) length 221983.38 nm and (64) length 140055.53 nm; G2: (100) length 134981.70 nm and (101) length 105078.04 nm; G3: (184) length 140395.17 nm and (185) length 99941.04 nm.

Discussion

This study demonstrates a clear fraction-dependent duality in the therapeutic effects of *E. sativa* leaf extract on STZ-induced diabetic rats. The aqueous fraction exhibited significant antihyperglycemic activity, while the n-hexane fraction provided superior pancreatoprotection, validating the hypothesis of divergent therapeutic profiles based on solvent polarity. The weight loss observed across all experimental groups is characteristic of the catabolic state in insulin-deficient diabetes resulting from STZ-induced damage to pancreatic β-cells.(19) Although *E. sativa* flavonoids may contribute to weight modulation via appetite suppression, lipolysis enhancement, adipogenesis inhibition, and gut microbiota effects,(20) the comparable losses in treatment groups (G1–G3) to diabetic controls indicate the diabetic state dominated, rendering extract effects secondary in this acute model.

The differential therapeutic profiles of the fractions arise fundamentally from polarity-dependent extraction of phytochemicals, where solvent polarity influences the solubilization, quality, and quantity of secondary metabolites.(21,22) Non-polar n-hexane effectively extracts terpenoids, steroids, and fatty acids, which exhibit limited direct antihyperglycemic activity but provide superior pancreatoprotection, consistent with reports of n-hexane fractions prioritizing tissue recovery over glucose reduction.(23,24) In contrast, semi-polar ethyl acetate solubilizes flavonoids, alkaloids, and phenolics,(24,25) yet showed modest efficacy here, potentially due to suboptimal bioactive concentrations, dosing, or *E. sativa*-specific profiles.(26,27) Aqueous fractions, extracting highly polar compounds like flavonoids, saponins, tannins, alkaloids, and triterpenoids, demonstrated robust glycemic control through synergistic mechanisms including insulin sensitization, enhanced glucose uptake, reduced intestinal absorption, and enzyme inhibition.(28,29)

The n-hexane fraction's pancreatoprotective superiority aligns with its lipophilic constituents steroids

and triterpenoids which stabilize cell membranes, modulate anti-apoptotic pathways, protect β-cells via mitochondrial function preservation, and reduce endoplasmic reticulum stress.(30) This contrasts with aqueous fractions' hydrophilic profile, which excels in systemic antioxidant and enzyme-inhibitory effects but struggles with lipid membrane penetration for direct cellular repair.(31) Ethyl acetate's limited protection may reflect insufficient concentrations of repair-active compounds, differing from reports on other plants.(32,33) Notably, n-hexane treatment enlarged pancreatic islets, signaling β-cell regeneration and reduced apoptosis,(34,35) a benefit less evident in polar fractions despite their flavonoid-driven antioxidant potential.(36–38) These observations reinforce that polar solvents yield stronger hypoglycemic effects, while non-polar ones favor histopathological recovery.(39,40) Our findings challenge the assumption of uniform antidiabetic efficacy across *E. sativa* extracts, extending prior work on solvent-dependent bioactivity.(40) While methanolic extracts often show broad potency, fractionation reveals specialized profiles: aqueous for glucose homeostasis and n-hexane for β-cell integrity (Figure 2). This duality positions *E. sativa* favorably against single-target therapies, aligning with global trends in phytotherapy emphasizing polarity-tailored interventions for multifaceted diseases like diabetes. The distinct profiles suggest a combined aqueous-n-hexane formulation could holistically target hyperglycemia and pancreatic damage, surpassing single fractions by mimicking crude extract multifunctionality with dosing precision. This supports the development of standardized phytotherapeutics, potentially improving diabetes management in resource-limited settings like Indonesia. Several limitations that should be further improved including: the small sample size that limits the power and generalizability of this study; 14-day duration might requires chronic validation; single 400 mg/kg dose that omits response curves; male-only rats that overlook sex differences; and some fraction synergies untested. Hence, future studies should assess oxidative markers, insulin dynamics, dose ranges, sex effects, and hepatorenal of the extract safety.

Conclusion

This study demonstrates that the therapeutic efficacy of E. sativa is fraction-specific, driven by its distinct phytochemical profiles. The aqueous fraction, rich in flavonoids, is the most effective for rapid glycemic control, significantly reducing blood glucose levels in diabetic rats. Conversely, the n-hexane fraction, characterized by its terpenoid content, provides superior pancreatic protection by maintaining the highest islet area and improving histopathological scores.

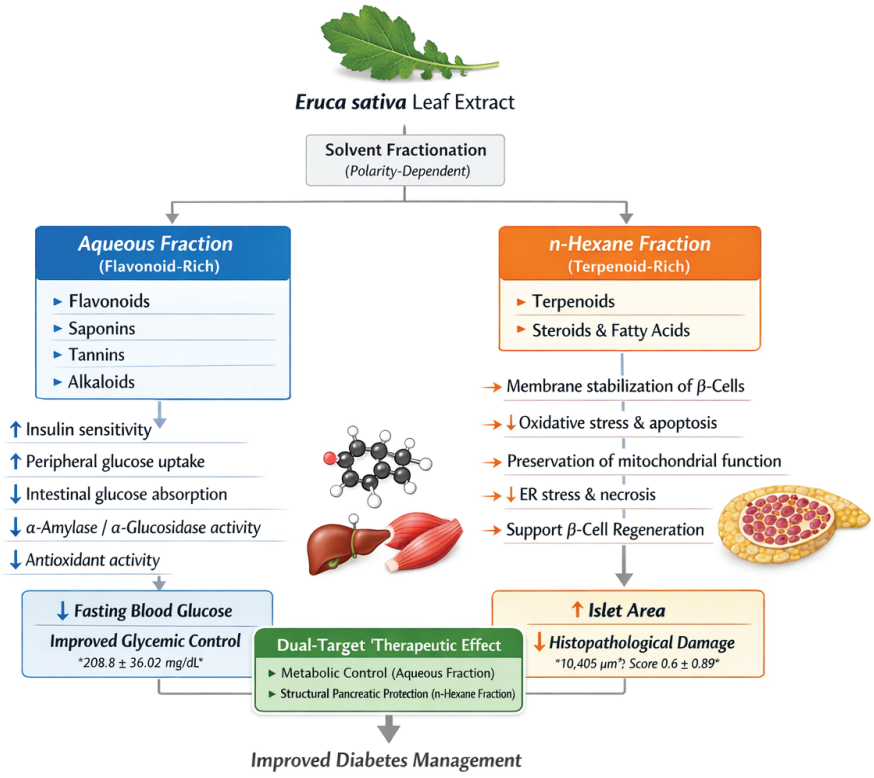

Figure 2. Conceptual schematic of the dual-target mechanism of *E. sativa* fractions in diabetes management.

These findings highlight a dual-target potential for *E. sativa*: the aqueous fraction excels in antihyperglycemic action, while the n-hexane fraction is more potent for preserving pancreatic islet integrity.

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Authors Contribution

SLRN contributed to the conceptualization and planning of the research. T and ASP were responsible for data collection, computation, and analysis. WYS drafted the manuscript and designed the tables. SLRN and S assisted in interpreting the findings. All authors provided comprehensive input to the manuscript and approved the final version.

Conflict of Interest

There are no conflicts of interest.

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