

Antihyperglycemic Activity of Oregano (*Origanum vulgare*) and Mango (*Mangifera indica* L.) Leaf Extract Mixture on Alloxan-Induced Diabetic Rats

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood sugar levels caused by insulin deficiency or resistance.

Objective: The goal of this study was to assess the antihyperglycemic effects of mango (*Mangifera indica* L.) and oregano (*Origanum vulgare*) leaf extracts (OMX) on female albino rats with alloxan-induced diabetes, through the determination of median effective dose (ED₅₀) and approximate effective dose (AED).

Methods: Twenty-one (21) rats were divided into seven groups. Five groups received varying doses of OMX (1 mg/kg, 4.98 mg/kg, 20.78 mg/kg, 83.88 mg/kg, and 335.08 mg/kg of body weight); one group received acarbose (32.28 mg/kg) as the positive control, and another received normal saline solution as the negative control. Blood glucose levels were measured before treatment and 1 hr, 4 hrs, 6 hrs, 24 hrs, 48 hrs, and 72 hrs after treatment. ED₅₀ and apparent effective dose were calculated.

Results: The ED₅₀ of the OMX mixture was 12.94 mg/kg body weight, while the AED required to achieve a glucose reduction equivalent to acarbose (70.66%) was 1,330.85 mg/kg. Compared to acarbose, the OMX extract demonstrated a noticeable blood sugar-lowering effect, although it was descriptively less potent.

Conclusion: The rats treated with OMX generally showed a decline in blood glucose levels, suggesting a potential benefit. However, the differences between the treatment groups were not statistically significant during the observation period. While the extract shows potential, the findings emphasize the need for more investigation. Future research should focus on identifying the exact active chemicals, improving the extraction method,

and investigating the effects over a longer treatment time. This will aid in understanding its potential as an alternative or supportive treatment for diabetes.

Keywords: *Antihyperglycemic activity, Oregano, Mango, Median Effective Dose, Approximate Effective Dose, Philippines*

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INTRODUCTION

Concerns have risen regarding unwanted side effects and adverse effects of drugs globally, and turning to natural products in addressing this issue has been a gateway to finding new medications and treatments for diseases that require constant pharmacologic interventions (Moukette et al., 2017). As in the case of diabetes mellitus, where lifelong treatment is necessary to maintain and relieve the patient's condition, side effects can affect compliance and adherence to treatment. According to the World Health Organization in 2024, more than half of the population with diabetes were non-compliant to their treatments in 2022, and in 2021, approximately 2 million deaths were caused by diabetes and kidney diseases caused by unmanaged diabetes. These concerning numbers impel researchers to investigate other ways to manage chronic diseases, like diabetes, in hopes of reducing the mortality caused by noncompliance with medications.

Following the trials of traditional medicines, studies involving plant extracts have provided scientific evidence for the use of herbal medicines as adjuvants and even as alternative treatments for chronic diseases (Wang et al., 2012). Research into a combination of plant extracts with similar pharmacological effects have been conducted, in hopes of achieving synergistic effects and fewer adverse side effects. In Africa, mixtures of specific plant extracts traditionally used in the management of diabetes have been shown in research to have significant hypoglycemic, antioxidant, and hypolipidemic properties, suggesting their potential as a polyherbal treatment (Moukette et al., 2017). Another study from Pakistan also finds that a polyherbal extract combination can alleviate diabetes symptoms in in-vitro and in-vivo testing (Gardezi, 2022).

Herbal medicine may not be an official mainstream treatment for various diseases in the Philippines, yet its potential for integration into clinical practice is being encouraged for exploration. This is due to their popularity, especially in rural and far-flung communities, where accessibility and the financial capacity to adhere to allopathic treatment are challenges (Maramba-Lazarte, 2020). Thus, local plants are being investigated for their potential as herbal treatments for ailments that contribute significantly to the country's mortality rate. With diabetes mellitus ranking fourth among causes of death in 2021 (Philippine Statistics Authority, 2023), studies on potential treatments derived from the country's rich botanical and agricultural resources are ongoing. A study in Metro Manila involving the antihyperglycemic activity of the flavonoid extract of *Ficus benjamina* L. *Moraceain* showed results indicating a capacity comparable to that of acarbose, a standard hypoglycemic drug that inhibits the alpha-glucosidase enzyme (Gorospe et al., 2014).

With such, *Origanum vulgare* and *Mangifera indica*, two plants found in urban and rural areas, have shown promising potential in treating diabetes. Oregano leaves have been shown to have glucose-lowering capacity through inhibition of alpha-glucosidase in in-vitro and in-vivo studies, mediated by the pharmacodynamic effects of the phenolic compounds in their leaf extract (Gutierrez-Grijalva et al., 2022). Meanwhile, extracts of mango leaves have also been shown to have activity against diabetes, as evidenced by the presence of mangiferin in the extracts in in vitro and in vivo setups (Kumar et al., 2021).

Despite the established antihyperglycemic effects of the individual extracts, the antihyperglycemic activity of the combination of mango and oregano leaf extracts has not yet been studied. As such, this study aims to determine the antihyperglycemic activity of the combined *Mangifera indica* and *Origanum vulgare* leaf extracts (OMX) in alloxan-induced diabetic female albino rats through the determination of its median effective dose (ED₅₀) and approximate effective dose (AED), and to assess its effect in reducing blood glucose levels in comparison with acarbose. Since previous studies have associated the glucose-lowering activity of mango and oregano leaf extracts with alpha-glucosidase inhibition, acarbose was selected as the comparator for the present study.

MATERIALS AND METHODS

Research Design

This study followed an in-vivo experimental design. In-vivo experiments are conducted on living organisms, specifically female rats. To gain information about the effects on the animals' biological processes animal models are used to study biological responses in a controlled environment (Lewis, 2024). In this study, diabetes was induced in female rats using alloxan to determine the median effective dose and the approximate effective dose of OMX. As the study aims to determine the glucose-lowering effect of OMX, the data collection follows a biological sample analysis: blood is collected from treated rats to measure serum glucose levels.

Animal Procurement and Handling

Rats are used in this research for their physiological similarities to the human pancreas and glucose metabolism. Alloxan, which destroys pancreatic β -cells, is a frequent diabetogenic drug used in experimental animals. Necrosis and oxidative stress are outcomes of β -cells producing more reactive oxygen species (ROS) via the GLUT2 glucose transporter. Like type 1 diabetes, this results in insulin deficiency and persistent hyperglycemia.

This study used female albino rats as the experimental subjects. Although studies have traditionally employed male rats because of the apparent hormonal variability in female rats, mounting evidence suggests that using female rodents can ensure sex inclusivity and reveal potential sex-specific effects (Beery & Zucker, 2011). Alloxan-induced diabetes reliably elicits physiological responses in female albino rats, making them appropriate for pharmacological research.

Twenty-one (21) female Albino rats from the San Pedro College Animal Lab and Research Hub, Ulas, Davao City, weighing 130-165 grams, were used for this experiment. These test animals were acclimatized and kept at the Animal Research Facility of the University of Immaculate Conception.

Plant Collection and Authentication

The plant collection of *Origanum vulgare* was done at Barangay Kapayawi, Libungan, North Cotabato. The varieties of *Mangifera indica* (carabao and apple mango)

were collected at Purok Mahogany, Barangay Cogon, Digos City. After collecting the plant samples, they were authenticated at the Office of the Provincial Agriculturist in Digos City for verification of the plant material.

Plant Material Preparation

Maceration. Following the plant collection, the fresh leaves of mango and oregano were meticulously washed with tap and distilled water, respectively, three times each, and then air-dried. To ensure moisture is removed, the leaves underwent a dehydration process at 40 °C for 4 hours using a dehydrator. Then, the leaves (100g of both plants) were macerated together with enough volume of ethyl acetate and left to stand for 1 week with shaking and agitation being done every day to ensure proper mixing and maceration.

Extraction. The marc was removed from the macerate using simple gravity filtration with Whatman filter paper number 1. The filtrate of the macerate underwent a thorough rotary evaporation process using the rotary evaporator at 50°C.

Determination of Baseline (initial) Blood Glucose Level

Blood extraction and measurement. The process was carried out in a warm environment, with a tuberculin syringe needle, a blood sample taken from the rat's tail, withdrawn and put into a test strip, then inserted in the glucometer. The results were ready after a couple of seconds, and the baselines were recorded.

Induction of diabetes with Alloxan. Female albino rats were kept in standard conditions with free access to standard food and water, at $23 \pm 1^\circ\text{C}$, $55 \pm 5\%$ humidity, and a 12-hour light:12-hour dark cycle. Alloxan was injected intraperitoneally to cause diabetes in the rats; a blood sugar level of ≥ 200 mg/dL is considered diabetic. All pharmacological experiments were conducted following approval from the Institutional Animal Care and Use Committee of the University of the Immaculate Conception.

Preparation and Administration of Treatments. The study involves 7 treatment groups of female albino rats, with 3 rats per group. Five of these groups received different doses (1 mg/kg, 4.98 mg/kg, 20.78 mg/kg, 83.88 mg/kg, and 335.08 mg/kg of body weight) to assess the approximate effective doses of OMX that exhibit antihyperglycemic effects compared with the standard drug, acarbose (32.28 mg/kg). A negative control group was also used and only normal saline solution was given.

Blood extraction and measurement. This process was carried out in a warm environment to dilate the rats' veins. The needle was inserted at the caudal $\frac{1}{3}$ length of the tail through the skin and into the lateral veins. The blood sample is collected and placed on the test strip for measurement with a glucometer.

This study analyzed data collected from days 1 to 3 after treatment administration. Blood glucose levels were normalized relative to before treatment baseline to generate a graph for convenient interpretation. The results of actual blood glucose levels from the seven treatment groups were analyzed using the Hill equation to determine the median effective dose (ED₅₀). To determine the approximate effective dose, the mean percent reduction in blood glucose from acarbose treatment was used as a benchmark and substituted into a modified Hill equation for OMX's AED determination. To assess the effectiveness of the OMX treatments in reducing blood glucose over time, a repeated-measures ANOVA was used.

Ethics Statement

This study was submitted to the Research Ethics Committee of the University of the Immaculate Conception for ethical review under the protocol code UG-EX-01-25-

0155. A certificate of exempt was provided after review of the study protocols and procedures. Furthermore, the study was also subject to review from the Institutional Animal Care and Use Committee (IACUC) of the University of the Immaculate Conception. Conduct of animal laboratory work was not done unless approval and clearance from the IACUC was obtained.

RESULTS

To determine the median effective dose (ED50) of the combined mango and oregano leaf extracts, this study used the Hill Equation Method, a four-parameter logistic model that predicts cooperativity and generates dose-response curves. This tool is used to assess the characteristics of varying doses of combined OMX and its antihyperglycemic effect in induced diabetic rats.

Figure 1 presented below shows the % normalized blood glucose levels of the rats after administration of treatment interventions. Figure 1.A provides comparison between the positive control group (acarbose) and negative control group (normal saline solution). Figure 1.B shows the comparisons between OMX treatments. From this figure, acarbose had a lower blood glucose level compared to NSS and the OMX treatments. Furthermore, OMX treatment groups had more variability relative to concentration and duration of observation. At each time point, OMX treatments did not show concentration dependent manner of blood glucose reduction.

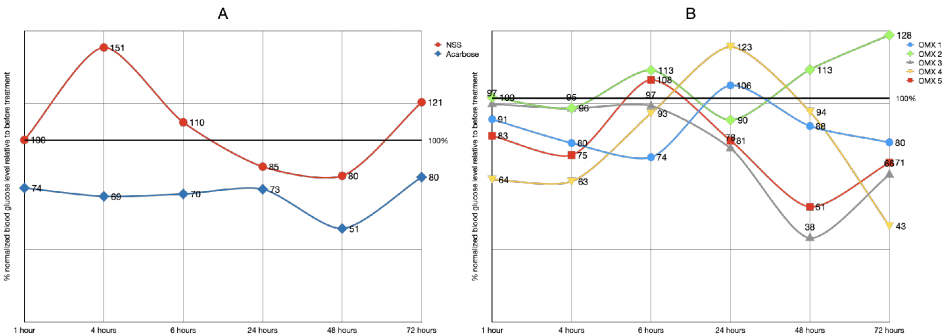


Figure 1. Normalized blood glucose levels of female rats (A) under the negative, positive control group, and (B) treatment groups. Normalization is relative to before the treatment (100%). Concentrations for OMX1, OMX2, OM3, OMX4, and OMX5 are 1 mg/kg, 4.98 mg/kg, 20.78 mg/kg, 83.88 mg/kg, and 335.08 mg/kg of body weight, respectively.

Table 1 presents the numerical output of the Hill method used to fit the dose-response relationship. The estimated median effective dose was 12.94 mg/kg body weight, which corresponds to 50% of the maximum antihyperglycemic effect of the extract in diabetes-induced rats. This implies that, between 1 mg/kg BW and 335.08 mg/kg, the dose that may achieve half the maximum glucose-lowering effect of the OMX extract is 12.94 mg/kg BW.

Table 1. Estimated ED₅₀ and Hill coefficient of the OMX treatment.

Parameters	Combined OMX Treatment
ED ₅₀ (mg/kg BW)	12.94
Hill Coefficient	0.1897

The Hill coefficient indicates the slope or steepness of the dose-response curve and reflects the cooperativity of ligand binding or the system's responsiveness. From the data gathered, the Hill coefficient was calculated at 0.1897, a significantly lower value than 1.0, the pharmacodynamic comparison point. The determined value indicates a shallow response or negative cooperativity, suggesting that a gradual increase in OMX dosing results in a modest increase in its effect. This value will then be used to assess the approximate effective dose of the OMX combination.

To determine the Approximate Effective Dose (AED) of the combined mango (*Mangifera indica* L.) and oregano (*Origanum vulgare*) leaf extract (OMX) that produces an antihyperglycemic effect, comparable to that of the standard drug, acarbose. The AED was estimated by identifying the OMX dose required to elicit a glucose-lowering response equivalent to that of Acarbose.

The calculation is performed using the Hill coefficient and rearranging the Hill equation to compute the required dose, in this case, the AED to achieve a predefined biological response. The predefined biological response in this scenario is the benchmark set by the mean percent reduction in blood glucose observed in the acarbose-treated group.

As shown in Table 2, the positive control group achieved a mean percent reduction in blood glucose of 70.66%. This value is used in the transposed Hill equation to determine the approximate effective dose of the OMX extract.

Table 2. Approximate Effective Dose of Combined Oregano and Mango Leaf Extract.

Parameter	Result
Positive control and dose	Acarbose (32.28 mg/kg BW)
Mean blood glucose reduction of positive control	70.66 % ± 9.40 %
Calculated OMX AED	1,330.85 mg/kg BW
<i>Note:</i> AED = approximate effective dose; BW = body weight; OMX = combined oregano and mango leaf extract.	

The direct calculation of AED resulted in a dose of 1330.85 mg/kg BW for the OMX extract. It posits that, to achieve the pharmacologic efficacy of the 32.38 mg/kg acarbose dose in lowering blood glucose levels, OMX would require a 1330.85 mg/kg BW dose. This result shows a significant difference in therapeutic performance between the two treatments. Despite the potential therapeutic relevance of the OMX treatment, the magnitude of the disparity between the two treatments only underscores the key limitation of crude plant extracts in terms of potency.

Despite this limitation, the findings remain promising. The OMX mixture demonstrated the ability to induce a measurable antihyperglycemic effect, and the calculated AED serves as a reference point for further research. It also illustrates why

further attempts to enhance, such as component separation, synergistic optimization, or formulation changes, are required to boost efficacy at lower dose levels.

The data gathered during the experimentation showed glucose-lowering activity for the OMX treatment; the statistical insignificance of the results can be attributed to the low dose range used relative to the approximate effective dose. The vast difference between the ED₅₀ and AED shows that greater dosing for herbal medications is required to make a significant effect that can be comparable to drugs that are formulated specifically for therapeutic treatments. The 1,330.85 mg/kg AED indicates the need for a higher dose to match the performance of the standard treatment, acarbose. This is understandable, as formulated drugs are curated to contain specific bioactive components in scientifically based concentrations and forms to be efficient in treating the illnesses they are intended to treat.

DISCUSSION

The estimated ED₅₀ of 12.94 mg/kg BW indicates that the combined oregano and mango leaf extract (OMX) produced a measurable antihyperglycemic response within the tested dose range of 1–335.08 mg/kg BW. This finding is generally consistent with previous studies demonstrating the glucose-lowering activity of the individual plant extracts. Saleem et al. (2019) reported significant reductions in postprandial blood glucose in diabetic mice administered mango leaf extract at 500, 750, and 990 mg/kg, with effects comparable to glibenclamide. Similarly, Thành et al. (2022) observed a significant reduction in fasting blood glucose following administration of 500 mg/kg ethanolic mango leaf extract for seven days, while Lemhadri et al. (2004) reported a significant reduction in blood glucose following a single 20 mg/kg dose of aqueous oregano leaf extract. The present ED₅₀ therefore supports the established antihyperglycemic potential of both plants, although direct numerical comparison should be made cautiously because the previous studies differed in plant preparation, extraction solvent, animal model, endpoint, and treatment duration.

The differences in response may partly be explained by the extraction procedures used in the respective studies. The present investigation utilized crude extracts obtained separately through ethyl acetate maceration and rotary evaporation before combining the extracts, whereas the cited studies employed aqueous or ethanolic preparations. Differences in solvent polarity can influence which phytochemicals are recovered and, consequently, the biological activity of the resulting extract. This is particularly relevant because mango contains mangiferin and other phenolic compounds associated with α -glucosidase and α -amylase inhibition, while oregano contains phenolic constituents such as carvacrol and thymol that have been associated with glucose metabolism and insulin sensitivity (Gutiérrez-Grijalva et al., 2022; Kumar et al., 2021). Thus, although the present results support the proposed pharmacodynamic basis of OMX, the composition and concentration of active constituents may differ from those of extracts used in previous studies.

The findings also provide partial support for the theoretical rationale of polyherbal therapy proposed by Parasuraman (2014), in which combinations of medicinal plants may provide complementary pharmacological effects. Previous studies have reported enhanced antihyperglycemic activity from combinations of plant extracts, including *Mangifera indica* with *Azadirachta indica* and other polyherbal formulations (Omeodu et al., 2022;

Perumal et al., 2022). However, the present study cannot establish true pharmacological synergy between mango and oregano because the individual extracts were not evaluated as separate treatment groups. The observed activity can therefore only be interpreted as evidence that the combined preparation possesses antihyperglycemic potential, rather than definitive evidence that the two extracts act synergistically.

In contrast to the relatively low ED₅₀, the calculated AED of 1,330.85 mg/kg BW was substantially higher than the highest administered OMX dose of 335.08 mg/kg BW and considerably exceeded the 32.28 mg/kg BW dose of acarbose, which produced a mean glucose reduction of 70.66%. This disparity indicates that, although OMX demonstrated antihyperglycemic activity, the crude extract was considerably less potent than the standard drug under the conditions of the experiment. Similar differences between botanical preparations and conventional drugs have been attributed to the complexity of phytochemical mixtures, the presence of inactive constituents, and differences in bioavailability (Li et al., 2008; Wagner & Ulrich-Merzenich, 2009).

The AED should nevertheless be interpreted cautiously because it was derived from the Hill equation rather than directly observed experimentally. The low Hill coefficient of 0.1897 indicates a shallow dose-response relationship, meaning that increasing the dose within the tested range produced relatively modest changes in response. More importantly, the estimated AED lies beyond the highest dose actually administered; therefore, 1,330.85 mg/kg BW represents an extrapolated model-based estimate rather than a dose whose efficacy was directly demonstrated in the animals. The large difference between the ED₅₀ and AED may also explain why no statistically significant difference was detected among the OMX, acarbose, and normal saline groups during the 72-hour observation period.

The lack of statistical significance should also be considered in relation to the experimental model and duration of treatment. Alloxan-induced diabetes can produce variable hyperglycemic responses, including delayed development of diabetes and spontaneous recovery at some doses, which may increase variability among experimental animals (Ighodaro et al., 2017). The present study used alloxan at 150 mg/kg, a dose at which variability has previously been reported. In addition, only a single administration of OMX was given and the primary statistical analysis covered the first 72 hours. This differs from studies such as Thành et al. (2022) and Omeodu et al. (2022), which used repeated treatment over seven and fourteen days, respectively. Overall, the findings indicate that OMX possesses measurable antihyperglycemic activity but is substantially less potent than acarbose under the conditions tested. The results are consistent with previous evidence supporting the antidiabetic properties of mango and oregano, while the differences in magnitude of response highlight the influence of extraction method, phytochemical composition, animal model, dosage, and treatment duration. The findings therefore provide preliminary evidence for the antihyperglycemic potential of the combination, but further studies using standardized extracts, individual-extract controls, repeated administration, longer observation periods, and phytochemical characterization are necessary to determine whether the combination provides a genuine synergistic advantage and to establish its reproducible therapeutic dose.

CONCLUSION

Based on the findings, it can be concluded that OMX treatment exhibits half the maximum antihyperglycemic effect at 12.94 mg/kg BW and has an approximate effective

dose of OMX of 1330.85 mg/kg BW. These results support the ayurvedic notion that polyherbal formulations require higher dosing to elicit the same effect when compared to synthetic or conventional drugs. These results contribute to the search for alternative treatments for diabetes, particularly with polyherbal formulations. Admittedly, the data gathered in this study require further confirmation due to limitations encountered, such as single-dose administration and 72-hour post-treatment analysis, but the findings demonstrate the glucose-lowering effect of OMX treatment in alloxan-induced diabetic rats.

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