Tablet formulation of aqueous leaf extract of *Annona muricata* and its potential in the management of diabetes

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ABSTRACT

Background: Diabetes mellitus is a chronic and prevalent metabolic disease affecting individuals across all age groups. Studies show that plant-based antidiabetic medications are effective in the management of diabetes.

Objectives: The aim of this study was to develop a novel oral tablet formulation from the aqueous leaf extract of *Annona muricata* (AMALE), evaluate its physico-technical properties and blood glucose lowering capacity.

Methods: Powder blends of extract with Avicel®, corn starch/magnesium carbonate were prepared for direct tablet compression. Flow characteristics and moisture content of the blends were evaluated. Optimized compressed tablets were evaluated for uniformity of weight, hardness, friability and disintegration. Blood glucose lowering capacity of the AMALE and its tablet formulations were investigated in diabetic rats and compared with Glibenclamide.

Results: AMALE elicited 79.80 % reduction in blood glucose while Glibenclamide showed 68.84 % reduction. The combination of AMALE and Glibenclamide gave 56.59 % reduction. Powder blend of AMALE, Avicel® and corn starch was non-hygroscopic and free-flowing. Optimized formulated tablets had uniform weights, moderate hardness (3.78 kgF), low friability (0.17 %) and rapid disintegration (2.15 sec). The tablets gave 71.42 % reduction in blood glucose with minimal effect on body weight.

Conclusion: A unique tablet formulation of AMALE with significant blood glucose lowering potential has been successfully developed.

Keywords: *Annona muricata* leaf extract, blood glucose lowering capacity, Avicel®, tablet formulation, diabetic rats

Formulation en comprimés d'un extrait aqueux de feuilles d'Annona muricata et son potentiel dans la prise en charge du diabète

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RÉSUMÉ

Contexte: Le diabète sucré est une maladie métabolique chronique et répandue qui touche des personnes de tous âges. Des études montrent que les médicaments antidiabétiques à base de plantes sont efficaces dans la prise en charge du diabète.

Objectifs: Le but de cette étude est de mettre au point une nouvelle formulation de comprimé oral à partir de l'extrait aqueux de feuilles *d'Annona muricata* (AMALE), d'évaluer ses propriétés physico -techniques et sa capacité à réduire la glycémie.

Méthodes: Des mélanges de poudres d'extrait avec Avicel®, l'amidon de maïs/carbonate de magnésium ont été préparés pour la compression directe en comprimés. Les caractéristiques d'écoulement et la teneur en humidité des mélanges ont été évaluées. L'uniformité du poids, la dureté, la friabilité et la désintégration des comprimés optimisés ont été évaluées. La capacité hypoglycémiante de l'AMALE et de ses formulations en comprimés a été étudiée chez des rats diabétiques et comparée à celle du glibenclamide.

Résultats: L'AMALE a entraîné une réduction de 79,80 % de la glycémie, tandis que le Glibenclamide a entraîné une réduction de 68,84 %. L'association d'AMALE et de Glibenclamide a donné une réduction de 56,59 %. Le mélange de poudre d'AMALE, d'Avicel® et d'amidon de maïs était non hygroscopique et fluide. Les comprimés formulés optimisés avaient un poids uniforme, une dureté modérée (3,78 kgF), une faible friabilité (0,17 %) et une désintégration rapide (2,15 sec). Les comprimés ont donné une réduction de 71,42 % de la glycémie avec un effet minimal sur le poids corporel.

Conclusion: Une formulation unique de comprimés à base d'AMALE présentant un potentiel significatif de réduction de la glycémie a été mise au point avec succès.

Mots-clés: extrait de feuille *d'Annona muricata,* capacité à réduire la glycémie, Avicel®, formulation de comprimés, rats diabétiques

INTRODUCTION

Diabetes is a chronic and progressive metabolic disorder characterized by high levels of glucose in the blood which is caused by insulin resistance or defects in insulin secretion.[1] Diabetes can be classified into three (3) types; Type I is caused by deficient insulin production and is also called insulin-dependent diabetes. Type II is caused by inability of the body to use insulin effectively and is the most common of all types of diabetes, accounting for about 90 % of all diabetes cases worldwide.[1] The third type is the gestational diabetes which occurs as a result of pregnancy.[2] Epidemiological studies estimate that about 230 million people worldwide have diabetes and about 350 million would be affected by this disease by the year 2025.[3] In Africa, about 24 million adults currently live with diabetes and about 55 million would be affected by the year 2045.[1] Symptoms of diabetes include blurred vision, fatigue, frequent urination, unexplained weight loss among others, and if left untreated could lead to a mirage of problems including kidney failure, foot ulcers, nerve injuries and coronary heart failure.[4] Treatment of diabetes especially Type II diabetes include the use of insulin therapy and oral hypoglycaemic agents like; meglitinides, biguanides, sulfonylureas, and thiazolidinediones. Even though these have been successful to a large extent, they have been prone to adverse effects like weight gain, toxicity, hypoglycaemia and in some cases resistance to a specific active agent.[5] This has made researchers focus on getting alternative medications with better outcomes including investigations into natural products like herbal medicines. Folklore shows that some plants are effective in the management of diabetes, one of which is *Annona muricata*.

Annona muricata, belongs to the family Annonaceae, it is commonly called soursop, graviola and guanabana. It is widely cultivated for its edible fruits and is now being naturalized in tropical and subtropical parts of the world like South America, West Africa, Asia and Australia.[6,7] In Nigeria, the plant is called 'Ebo' in Yoruba, 'Tuwon biri' in Hausa, 'Shawshopu' in Igbo.[8] The fruit pulp is used to make flavoured sweets, sorbets and ice cream, as well as fruit nectars, cocktails and fruit juice drinks.[7] Apart from being of nutritional value traditionally, the fruit, seeds, leaves and tree bark have been shown to possess some medicinal value in treatment of diabetes, hypertension, skin diseases, cancer and parasitic infections, liver diseases, flu, cold, asthma, for pain relief.[9,10,11] The focus of this study is on the leaves of *Annona muricata* and its potential use in the management of diabetes.

Several scientific studies have demonstrated the potential of the leaf extracts of *Annona muricata* in lowering blood glucose[12,13,14,15] thereby confirming the folklore belief of its use in managing diabetes. However, taking such plant extracts in their unrefined forms are unaesthetic and unappealing to patients, as such, they can be developed into suitable dosage forms like tablets to improve their stability and acceptability.

Therefore, the aim of this study is to develop standardized tablet formulations from aqueous leaf extract of *Annona muricata,* evaluate the physico-technical properties of the formulations and assess the antidiabetic properties of the tablet formulations.

MATERIALS AND METHODS

Materials

Annona muricata leave were purchased from Ogbadibo Local Government Area of Benue State, Nigeria. Light liquid paraffin (CDH, Ltd India), Corn starch (BDH chemicals Ltd, UK), Avicel® PH 101 (BDH chemicals Ltd, UK), Alloxan monohydrate (Sigma Aldrich), Glibenclamide; 5mg (May&Baker Nigeria Plc), Cassava starch (extracted in the Laboratory of Bingham University Karu, Nasarawa State).

Animals

Wistar rats (150 - 200 g) of either sex was used for the experiment. The rats were obtained from the Animal Facility Centre of the Department of Pharmacology, Bingham University Karu, Nasarawa State, Nigeria. They were housed in standard cages under ambient conditions (temperature 24 ± 2 ^{o}C; 12 h light/dark cycle) with free access to food and water *ad libitum*. The study protocol was approved by the Animal Care and Ethics Committee of the Department of Pharmacology Bingham University Karu, Nasarawa state.

Collection and identification of plant material

Fresh leaves of *Annona muricata* were obtained from Ogbadibo Local Government Area in Benue State, Nigeria in the month of March (2023). The leaves were identified and authenticated in National Institute for Pharmaceutical Research and Development (NIPRD), Abuja by a Taxonomist (Mr. Akeem Lateef) with a voucher number (NIPRD/H/7380).

Preparation of *Annona muricata* aqueous leaf extract

The aqueous leaf extract of *Annona muricata* was prepared in the laboratory of National Institute for Pharmaceutical Research (NIPRD), Abuja, Nigeria. The leaves were separated from the plant stalk, washed, dried in the shade and pulverized to coarse powder. The powdered leaves were extracted by maceration in distilled water at the ratio of 1:5 for 48 h with intermittent stirring. Afterwards. The mixture was filtered through a muslin cloth to separate the marc, and the filtrate was concentrated on a water bath (E.Track Instrument, England; ET-4H) at 60 ^{o}C for 12 h. The resulting product (AMALE) which was sticky and hygroscopic was stored in an airtight container and placed in a desiccator until further use.

Physical evaluation of *Annona muricata* aqueous leaf extract (AMALE)

Organoleptic properties (colour, odour and texture) of AMALE were assessed using sensory organs. Qualitative solubility of AMALE was determined in water and ethanol at a concentration of 1 %w/v of the AMALE in the solvent.

Acute oral toxicity study

An earlier method[18] was adopted for the acute oral toxicity test. Twenty-four (24) male rats were used to investigate the acute toxicity of AMALE in two (2) phases. The animals were fasted for 4 h prior to the experiment but allowed free access to water. AMALE was suspended in water and doses of 10, 100, 1000, 1600, 2900 and 5000 mg/kg were prepared. In the first phase, the animals (n=3) were administered 10, 100 and 1000 mg/kg orally each using an oral feeding tube while in the second phase 1600, 2900 and 5000 mg/kg doses of the extract were administered to the animals (n=3) in a similar manner. The general behaviour of the animals was observed over a period of 24 h for signs of toxicity, onset of adverse effect or probably death.

Experimental design

Twenty-five (25) rats were randomly divided into five (5) groups of five (5) rats each. The groups were;

Group I: Non-diabetic rats given normal rat pellets and water (positive control)

Group II: Untreated alloxan-induced diabetic rats (negative control)

Group III: Alloxan-induced diabetic rats + Glibenclamide (5 mg/kg)

Group IV: Alloxan-induced diabetic rat + Glibenclamide 5mg/kg) + AMALE (100mg/kg)

Group V: Alloxan-induced diabetic rats + AMALE (100mg/kg)

Induction of diabetes in rats

Wistar rats were fasted overnight and administered 100 mg/kg of alloxan monohydrate dissolved in normal saline intraperitoneally. They were administered glucose solution (5 %) overnight ad libitum to prevent hypoglycaemia and observed for possible behavioural signs. After 72 h, blood samples were collected from the tail veins of the rats, blood glucose levels were determined using a glucometer. Animals with elevated blood levels above 200 mg/dL were considered diabetic and used to investigate the antidiabetic properties of AMALE and that of the AMALE tablets.

Treatment of diabetic rats

Treatment of the diabetic rats with AMALE, Glibenclamide or the combination of AMALE and Glibenclamide commenced after the rats were confirmed diabetic and continued consecutively for 14 days. Changes in blood glucose level and body weights of the rats were determined prior to diabetes induction and on Days 7, 10 and 14 after induction. Blood samples were collected from the tail veins of the rats and blood glucose levels were determined using a Fine test Glucometer and strip.

Preparation of *Annona muricata* aqueous leaf extract (AMALE) tablets

Due to the hygroscopic nature of the extract (AMALE), magnesium carbonate was incorporated into the tablet formulation to serve as an adsorbent while Avicel® and corn starch were also incorporated as adsorbent and binder. Tablets of AMALE were prepared by the direct compression method. A batch of 30 tablets was produced according to the composition in Table 1. The excipients were incorporated into the various batches at different concentrations. Batch A1 was prepared by weighing 250 mg of AMALE into a porcelain mortar and mixing it with Avicel® (25 %) and corn starch (25 %) in geometric measures to obtain a homogenous powder mix. Batches A2 and A3 were prepared with Avicel® and corn starch at concentrations of 33.4 % and 16.6 % respectively while batch A4 was produced with only magnesium carbonate (50 %). Batch A5 was prepared with corn starch (25 %) and magnesium carbonate (25 %), batch A6 was prepared with Avicel® (25 %), corn starch (20 %) and magnesium carbonate (5 %) while batch A7 was prepared with Avicel® (20 %), corn starch (20 %) and magnesium carbonate (10 %). The resulting powdered mix was compressed into tablets of 500 mg target weight at 10 Nm^{-2} compression pressure in a Manesty tableting machine (Shanghai, China) using a 10 mm punch and die set. The tablets produced were kept for 24 h before evaluation to allow for elastic recovery.

Table 1. Composition of ingredients for preparation of AMALE tablets

Ingredients	A1	A2	A3	A4	A5	A6	A7
AMALE (mg)	250	250	250	250	250	250	250
Avicel® (mg)	125	167	200	-	-	125	100
Corn starch (mg)	125	83	50	-	125	100	100
Magnesium carbonate (mg)	-	-	-	250	125	25	50
Total (mg)	500	500	500	500	500	500	500

Key: AMALE = Annona muricata aqueous leaf extract

Evaluation of *Annona muricata* aqueous leaf extract (AMALE) powdered mixture Moisture content

One (1) gram of the powdered mix was placed into a pre-weighed porcelain dish and dried to constant weight in the hot air oven (DHG-9050, China). The moisture content (MC) expressed as a percentage of the final weight (Fw) and initial weight (Iw) was computed using the equation below;

$$MC = Fw - Iw / Iw \times 100 \quad \text{..... (1)}$$

Angle of repose

The funnel method was used for this determination; 5 g of the powdered mix was poured through a funnel whose orifice had been plugged. The height and diameter of the heap formed upon opening of the orifice of the funnel was recorded and used to compute the angle of repose (AR) using the equation below;

$$MC = \tan^{-1} \text{height of heap} / \text{radius of heap} \quad \text{..... (2)}$$

Bulk and tapped densities

The volume occupied by 20 g of the powdered mix in a 100 mL measuring cylinder was recorded as the bulk volume. The measuring cylinder was tapped 50 times from a determined height and the volume occupied by the powdered mix after tapping was recorded as the tapped volume. Three (3) determinations of the bulk and tapped volume were done. Bulk and tapped densities were calculated as the ratio of the initial weight to the bulk volume and that of initial weight to the tapped volume respectively.

Hausner ratio (HR) and Carr's compressibility index (CI)

These were computed using data obtained from the bulk density (Db) and tapped density (Dt).

$$HR = Dt / Db \quad \text{..... (3)}$$

$$CI = (Dt - Db) / Dt \times 100 \quad \text{..... (4)}$$

Determination of true density

The liquid displacement method using pycnometer bottle was adopted. The bottle was cleaned and filled with the displacement fluid (liquid paraffin), the weight of the bottle at this point was recorded as "a". The bottle was emptied and cleaned, 2 g of the powdered mix (Wp) was placed into the bottle, filled with liquid paraffin and stirred with a glass rod to remove any bubbles; the weight of the bottle at this point was recorded as "b". True density (Td) was computed using the recorded data and the specific gravity of liquid paraffin (SG = 0.865 g/mL) in the equation below;

$$Td = Wp / ([a + Wp) — b]) \times SG \quad \text{..... (5)}$$

Porosity

Porosity of the powdered mix was computed using data from bulk density (Db) and true density (Td) in the equation below;

$$E = 1 – Dt) / Td \times 100 \quad \text{..... (6)}$$

Evaluation of *Annona muricata* aqueous leaf extract (AMALE) tablets

Determination of uniformity of weight

Ten (10) tablets randomly selected from the batch were weighed individually on an analytical balance (OHAUS, England). The average weight and deviation from the average weight were determined.

Determination of tablet hardness

Five (5) tablets randomly selected from the batch were crushed individually using the Hardness Tester (Monsanto DBK India), the values were recorded and the mean tablet hardness was determined.

Determination of tablet friability

Five (5) tablets randomly selected from the batch were collectively weighed (w1) and transferred into the friability apparatus (CS-3 Tablet friability tester). The apparatus was set to rotate at 25 rpm for 4 minutes after which the tablets were dusted and weighed again (w2). Friability (F) was computed using the equation below:

$$F = w1 – w2 / w1 \times 100 \quad \text{..... (7)}$$

Determination of disintegration time

Six (6) tablets randomly selected from the batch were placed in the compartments of the disintegration apparatus (BJ-3, Biosteller, Shanghai) containing distilled water maintained at 37 ± 0.5 ºC. The time taken for the tablet particles to pass through the compartment's mesh was recorded and the average time was calculated as the disintegration time.

Investigation of the diabetic property of optimized AMALE tablets

The optimized AMALE tablet was crushed and reconstituted with distilled water (2 mL) to obtain a dose of 100mg/kg body weight of the laboratory animals. Five (5) diabetic rats were given the reconstituted tablet (2 mL) daily for 7days. Blood samples were collected from the tail veins of the rats and blood glucose levels were determined using a Fine test Glucometer and strip. Changes in blood glucose level of the rats were determined prior to diabetes induction and on days 7, 10 and 14 after induction. Similarly, the body weight of the rats was taken before induction and on days 7, 10 and 14 after induction.

Statistical analysis

All the data were expressed as mean ± standard deviation and statistical significance was evaluated using the One-way analysis of variance (ANOVA) in SPSS Version 26; statistical values (p-values) less than 0.05 were considered significant.

RESULTS

The physical properties of the extract (AMALE) are presented in Table 2 and shows the colour, odour, texture, nature and solubility in water and alcohol. The extract was observed to be dark brown in colour with a characteristic odour, the texture rough and was found to be hygroscopic upon exposure to the atmosphere. AMALE was observed to be readily soluble in water and ethanol as determined qualitatively.

Table 2. Physical properties of AMALE

Parameters	Observations
Colour	Dark brown
Odour	Characteristic
Texture	Smooth
Nature	Hygroscopic
Qualitative solubility in water and ethanol	Readily soluble

Acute toxicity of the prepared extract as investigated in laboratory rats is presented in Table 3. It shows that there were no signs of toxicity after oral administration of the extract at all the experimental doses of AMALE. All the animals in both phases were observed to be physically stable and no death was recorded after 24 h of the study.

Table 3. Acute toxicity of AMALE

Experiment	Phase I		Phase II	
	Dose (mg/kg)	mortality after 24 h	Dose (mg/kg)	mortality after 24 h
	10	0/3	1600	0/3
	100	0/3	2900	0/3
	1000	0/3	5000	0/3
Control	0	0/3	0	0/3

Figure 1 shows the mean blood glucose levels of non-diabetic rats, untreated diabetic rats, diabetic rats treated with Glibenclamide, diabetic rats treated with the combination of Glibenclamide and AMALE and diabetic rats treated with AMALE alone at pre-induction, immediately after induction, 7, 10 and 14 days after induction. Blood glucose levels were observed to reduce progressively to varying degrees depending on the treatment agents administered.

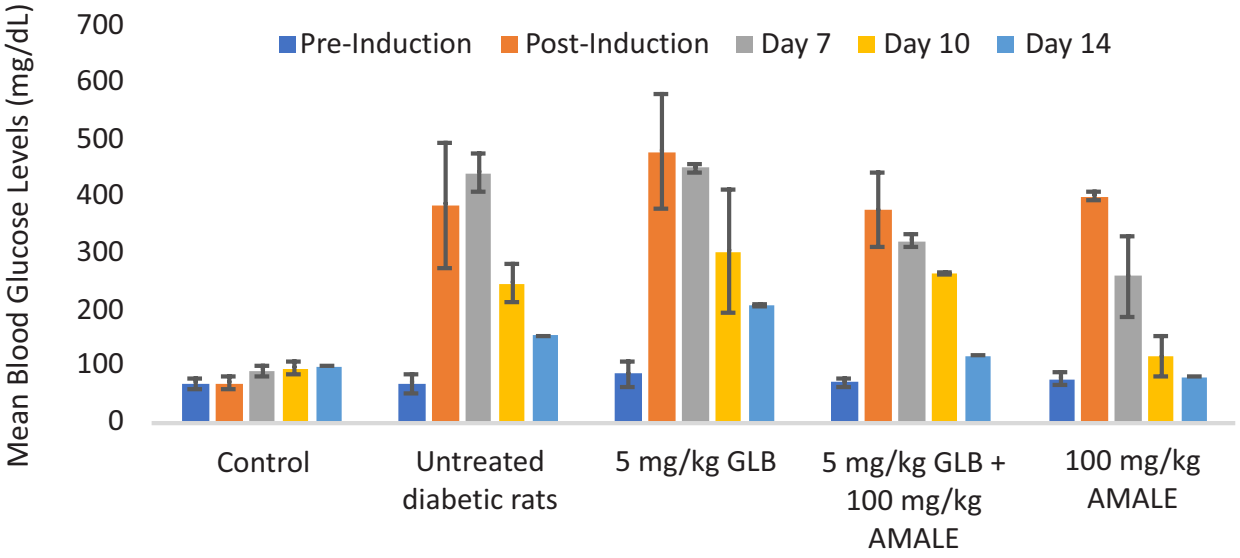

Figure 1. Mean blood glucose levels of diabetic rats treated with Glibenclamide alone, combination of Glibencalmide and AMALE, AMALE alone, untreated diabetic rats and the control.

The extent to which blood glucose levels reduced is further portrayed in Figure 2 which shows the percentage reduction in blood glucose levels. Administration of AMALE alone brought about 79.80 % reduction in blood glucose levels while the combination of Glibenclamide and AMALE brought about 68.54 % reduction and administration of Glibenclamide alone gave 56.59 % reduction which was the least significant among all the treatment agents. Figure 3 shows the percentage decrease in body weights of the experimental rats used in the study. The untreated diabetic rats had the least decrease in body weight (5.14 %) followed by those treated with the combination of AMALE and Glibenclamide (6.49 %) but there was no significant difference ($p>0.05$) in the body weights of these two groups. Those treated with the Glibenclamide alone had the most significant body weight change (16.14 %) while those treated with AMALE alone also showed considerable reduction in body weight (10.12 %).

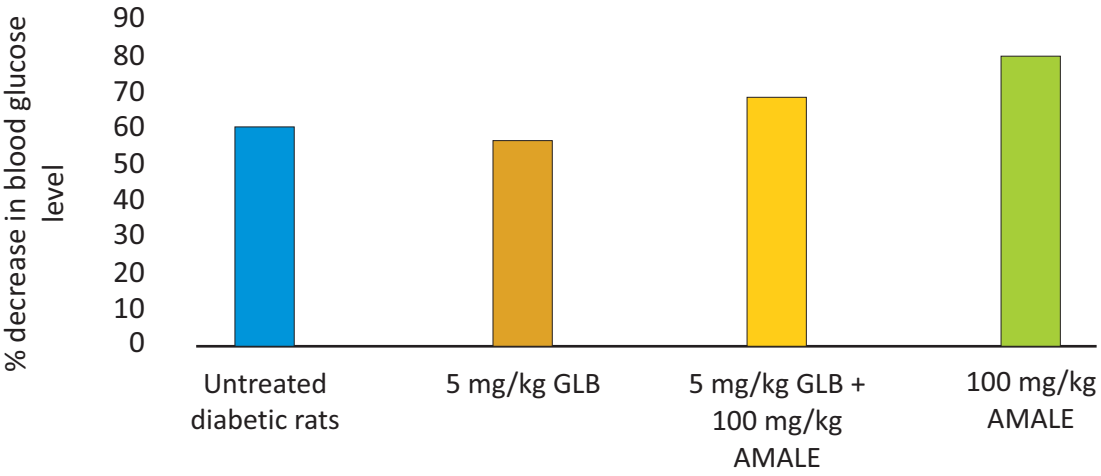

Figure 2. Percentage (%) decrease in mean blood glucose of diabetic rats treated with Glibenclamide alone, combination of Glibencalmide and AMALE, AMALE alone and the untreated diabetic rats.

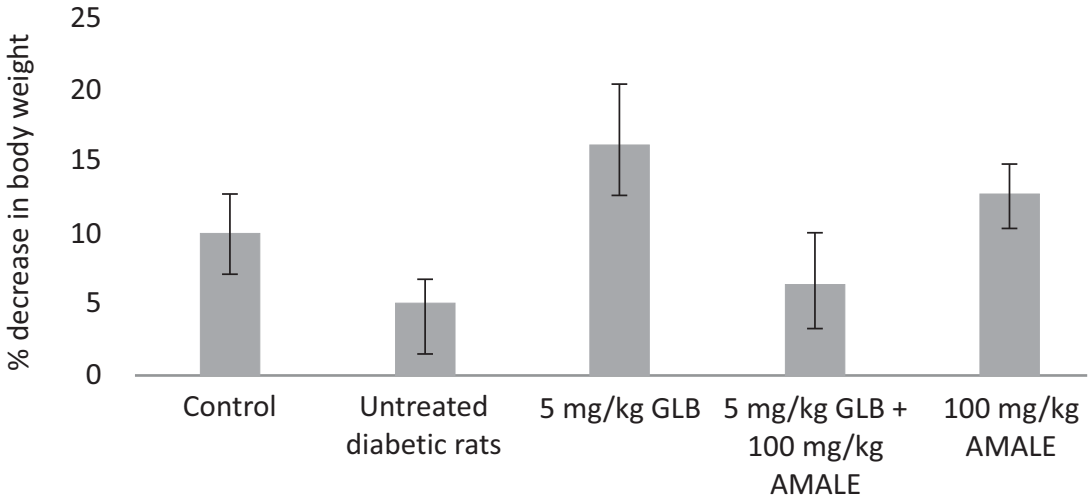

Figure 3. Percentage (%) decrease in body weight of diabetic rats treated with Glibenclamide alone, combination of Glibencalmide and AMALE, AMALE alone and the untreated diabetic rats.

The observations in Table 4 show powder mixtures containing the different excipients at different ratios. Results show that batches A1, A2, A4, A4, A5 and A7 were hygroscopic and non-flowing which made evaluation of the usual flow properties impossible. However, batch A3 was observed to be non-hygroscopic and free-flowing and was considered the optimized formulation for further investigations.

Table 4. Observations of batches of prepared AMALE tablet mixtures

Batches	Observations
A1	Hygroscopic, non-flowing
A2	Hygroscopic, non-flowing
A3	Non-hygroscopic, good flow
A4	Hygroscopic, non-flowing, caked
A5	Hygroscopic, non-flowing
A6	Hygroscopic, non-flowing
A7	Hygroscopic, non-flowing

Physical properties of the optimized AMALE mixture are presented in Table 5 and it shows low moisture content (7.18 %), angle of repose was 28.8o, bulk and tapped density were 0.63 and 0.73 g/mL respectively. Carr's compressibility index was 13.17 %, Hausner ratio was 1.10 while true density was found to be low (0.27) and porosity was 13.50 %.

Table 5. Physical properties of OPTZ AMALE mixture

Parameters	Observations
Moisture content (%)	7.18
Angle of repose (°)	28.8 ± 0.87
Bulk density (g/mL)	0.63 ± 0.01
Tapped density (g/mL)	0.73 ± 0.01
Carr's Index (%)	13.17 ± 0.58
Hausner ratio	1.10 ± 0.00
True density	0.27 ± 0.00
Porosity (%)	13.50

Some properties of the optimized (OPTZ) AMALE formulation are presented in Table 6. The average weight of the optimized tablet was 510.00 mg with minimal deviation from the average weight. Tablet thickness and diameter were 2.51 and 11.82 mm respectively with minimal deviation from the average. Hardness was minimum at a value of 3.78 kgF and friability was also low (0.17 %) and corresponding fast disintegration at 2.15 secs.

Table 6. Tablet properties of OPTZ AMALE tablet formulation

Parameters	Observations
Average weight (mg)	510. 00 ± 0.03
Thickness	2.51 ± 0.01
Diameter	11.82 ± 0.02
Hardness (kgF)	3.78 ± 0.02
Friability (%)	0.17 ± 0.09
Disintegration time (secs)	2.15 ± 0.02

Mean blood glucose levels of experimental animals that were administered OPTZ tablet were observed to reduce drastically by a factor of 3.5 after diabetic induction while there was minimal reduction in body weight.

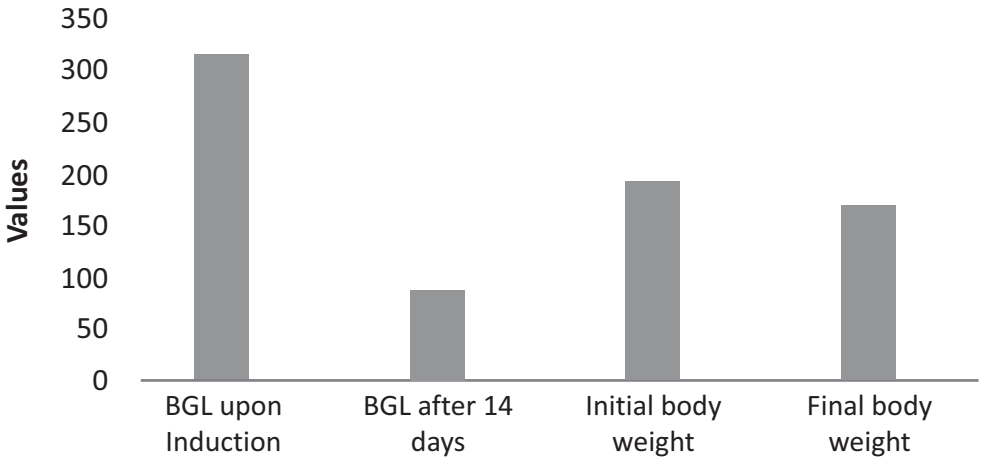

Figure 4. Mean blood glucose levels (BGL) and mean body weights of diabetic rats treated with OPTZ AMALE tablets.

DISCUSSION

The physical properties of the extract (AMALE) show its inherent characteristics which may be different when other solvents apart from water are used in the extraction process and when the plant is obtained at a location different from that reported in this study.

Acute toxicity study is important to ascertain that the extract or agent being investigated will not cause mortality upon ingestion. AMALE showed no signs of toxicity or death after oral administration at all the doses investigated. Similar reports have been documented about the extract in literature.[8,12,17]

Blood glucose levels at the pre-induction stage were observed to be different but insignificant ($p>0.05$) in all the treatment groups (Figure 1). However, significant increase ($p<0.05$) in blood glucose levels was observed after induction with alloxan in all group of animals. This is expected because alloxan causes a rise in blood glucose and is used to evaluate test agents with potential blood glucose lowering properties. There was significant decrease ($p<0.05$) in blood glucose levels in all the treated animals irrespective of the type of treatment received and this decrease was progressive over the 14 days of the study.

Treatment with the extract (AMALE) alone (group V) produced the most significant decrease in blood glucose levels (79.80 %) than its combination with the standard drug (Glibenclamide) (56.59 %) and produced the more significant decrease when compared with that of Glibenclamide alone (68.54 %). Other studies have also reported potential blood glucose lowering property of the extract of Annona muricata.[2,16,19]

At the end of the study, the body weights of the diabetic animals were observed to decrease to varying degrees depending on the treatments received. This may be attributed to the fact that alloxan causes high glucose levels which does not get into the cells where they can be used to produce energy, this causes the cells to compensate for energy by burning fats and muscles leading to weight loss.[20] Those treated with the Glibenclamide alone had the most significant body weight change while those treated with AMALE alone also showed considerable reduction in body weight. It may be inferred that AMALE may interfere with normal body metabolism leading to the observed changes in body weights. This suggests that one of the side effects of AMALE may be weight loss.

Selection of appropriate excipients is a major factor that influences the properties of active pharmaceutical excipients (APIs) and the final product; flowability, dissolution rate, stability and ultimately bioavailability can be impacted with the proper selection of excipients.[21] Table 1 shows the composition of the ingredients used to prepare AMALE tablet formulations intended for dry mixing for direct tablet compression. Microcrystalline cellulose, corn starch and magnesium carbonate were used as diluents, binder and absorbents respectively in different ratios. Our observations show that incorporation of high concentration of Avicel® may be responsible for the good physical property observed in batch A3 and this is because the polymeric material (Avicel®) has excellent binding and adsorbent properties. Therefore, Batch A3 containing Avicel® and corn starch (4:1) was taken as the optimized formulation in this study. The ability of powdered materials to remain stable upon storage is largely influenced by the presence of moisture; excessive moisture causes microbial degradation and consequent powder deterioration.[22] Low moisture content of the optimized (OPTZ) AMALE mixture suggests that the powdered mixture has low degree of moisture and may not require stringent storage conditions. Angle of repose measures the capability of materials to flow freely; values less than 30^o portray materials with excellent flow, values between 31 and 35^o denote good flow while those > 40^o signify poor flow.[23] Our results show the optimized formulation has excellent flow. Bulk and tapped densities are indirect measurements of material flow which determines the volume of material that would fill the die during tablet compression. These indices are used as basis for determination of Carr's Index (CI) which evaluates the ability of a material to deform under pressure and for determination of Hausner ratio (HR) which measures the cohesiveness of a powdered material by determining the degree of densification of that material.[24] Materials with values of CI below 10 %, between 11 and 15 % and those between 16 and 20 % are classified as having excellent, good and fair flow respectively while HR values below 1.10 and between 1.12 and 1.20 portray cohesive and less cohesive materials respectively.[25] Using these parameters, OPTZ AMALE mixture possess good flow and is not cohesive, implying that the mixture can easily flow into the die cavity, be easily compressed and ejected without sticking to the punches and dies. True density was low signifying its ability to promote even packing when confined into the tablet dies. Porosity value of 13.50 % suggests loose powder rearrangement which allows for good flow and ease of compaction of the powdered mixture.[26]

Uniform tablet weights is an important parameter because non-uniform tablets weights could lead to variations in bioavailability of the extract in the tablet. The OPTZ AMALE tablet formulation had uniform weight with deviation from the average weight of 500 mg below 5 % as specified in USP.[27] There were only minimal deviations from the average tablet diameter and thickness of OPTZ AMALE which were also below the specified requirement of ± 5 % of the average diameter and thickness.[28] This portrays that the tablet batch was of uniform thickness and diameter which will promote patient acceptability and facilitate adequate packaging.

The mechanical strength of a tablet can be evaluated by its hardness and friability which gives an insight into the ability of the tablet to withstand stresses of transportation, storage and use. Tablet hardness was at a value close to the limits of tablet hardness (4 to 8 kgF) which is considered optimum for uncoated immediate release tablet formulation.[27,29] OPTZ AMALE tablet showed ability to withstand fragmentation with low friability which is within the official specification of ≤1%.[27] We can put forward that OPTZ AMALE formulation produced compact and robust tablets. Disintegration describes the breaking up of tablets into smaller particles and the time taken for this process is the rate limiting step to the release of the active medicament for effective action. Official limit for disintegration of uncoated tablets is not greater than 15 min[27] and not greater than 30 min for herbal tablets. Our results show very rapid disintegration of OPTZ AMALE tablets suggesting rapid release of the extract from the tablet formulation.

Treatment of the diabetic rats with OPTZ AMALE tablet showed a significant reduction ($p>0.05$) in blood glucose level which was comparable to that of the extract (AMALE) alone. This buttresses the fact that the extract possesses blood glucose lowering properties and also corroborates its folklore use in the management of diabetes. The effect of the tablet on body weight of the tested animals was observed to be similar to that of the extract alone; where a decrease in body weight was observed. As earlier suggested, weight loss may be considered as one of the side effects of AMALE tablet formulation containing microcrystalline cellulose and corn starch as excipients.

CONCLUSION

Incorporation of extracts into tablet formulations is one of the means of making the use of herbal extracts presentable and acceptable to patients. However, in the presence of some process and formulation variables, the potency or efficacy of these extracts may decrease beyond therapeutic benefit. In this study, we have been able to produce robust and stable tablets of the aqueous leaf extract of the Annona muricata plant, which possesses excellent blood glucose lowering capability.

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