



Related Studies on the Efficacy of Organic and Synthetic Drugs Administration for Glucose Level Test: An Experimental Study on Laboratory Rats

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Abstract:

Diabetes mellitus is a chronic disease that causes imbalance in blood sugar levels that are abnormally high because the body can't produce enough insulin to meet the demands of our body processes. Rodents used as models in medical testing because their genetic, biological and behavior characteristics closely resemble those of humans, and many symptoms of human conditions can be replicated in mice and rats. The highlights of this research are drug-drug interactions between diabetic inducer drugs and treated drugs, efficacy of administered drugs on fasting blood glucose levels of rats, response of rodent models on induced drugs, and methods for blood sampling on rats. The objective is to determine the efficacy of different pharmaceutical drugs to fasting blood glucose levels of diabetic induced rats. The methods used were plant collection and extraction for organic drugs while synthetic drugs are obtained from pharmaceutical industries and hospitals at the location of the scientific analysis. Animals were procured from laboratories and medical institutes approved by the Ethics Committee of Laboratory Animal. Induction and assessment of diabetes was performed using Metformin, Streptozotocin and Alloxan as drug inducers of diabetic condition. Experimental design was constructed comprises groupings of animals (treated and untreated) with varying dosages and time frames. Different methods for blood sampling were introduced for final analysis. The results obtained were plant materials used as herbal drugs showed tolerance to glucose level test. Reduction to blood glucose level to certain period but as time passed by, normal conditions attained. Diabetic Alloxan Monohydrate induced rats once administered with synthetic drugs showed varied response to fasting blood glucose level. Hypoglycemic effects prevailed most compared to hyperglycemic effects but both showed adverse response. Efficacy of different drugs plays an important role to fasting blood glucose levels of laboratory rats. Standard drugs contribute effectively on treated drugs that can either alter its effect or to some extent be beneficial and important. Higher and lower dosages of administered drug showed adverse effects on the response of the drug under test. The mortality of rodents was observed during the course of the study. Different methods for blood sampling and glucose test were conducted. Comparative analysis on blood glucose level between normoglycemic and diabetic induced rats was performed. Experimental results were presented clearly and elaborately.

Keywords: Alloxan Monohydrate, Streptozotocin, Metformin, Fasting Blood Glucose Level Test, Diabetes Mellitus, Biochemical change

1. Introduction

A variety of lifestyle has tremendous impact on human health that is why different chronic diseases prevail as scientific breakthroughs and modernization gradually emerge. Blood chemistry analysis provides vital information about the functions of body's organs. Common panels of blood tests measure the levels of important electrolytes and other chemicals that play an important role in body processes. Glucose level or blood sugar of the body is one of the body's imbalance that undergoes blood test [1]. One of the chronic diseases which is very prominent since then is diabetes. Diabetes occurs when our body is unable to produce enough insulin for the regulation of blood glucose as diabetes aggravates and β -cell function deteriorates, the insulin level begins to fall below the body's requirements and causes prolonged and more severe hyperglycemia [2]. Chronic hyperglycemia is characterized by gradual loss of insulin gene expression considering other beta-cell specific genes; changes in mitochondrial number; chronic endoplasmic reticulum stress and oxidative stress; disruption in calcium homeostasis [3]. The proper way of assessing beta cell function is through closed interrelation of two variables, concomitant quantification of insulin secretion and insulin sensitivity [3].

Several synthetic drugs are used for the treatment of diabetes, but no drug is without side effects and, hence, there is need for alternatives in order to prevent detrimental response [3]. Scientists and researchers rely on mice and rats as a rodent model on formulating new cancer drugs and testing dietary supplements for several reasons. They are small, convenient to use, easily housed and maintained. The most important thing is that their genetics, biological and behavior characteristics closely resemble those of humans, and many symptoms of human conditions can be replicated by mice and rats [4]. Scientific experiments in pharmacokinetics and pharmacodynamics made possible with the help of albino rats as they response to the effects of different drugs they take [5,6]. Concomitant use of variety of drugs may sometimes produce interactions [7]. Safety precautionary measures and proper laboratory practices must be observed when dealing with rodent models. Drug interaction occurs when the effects of one drug is altered by another drug, food, drink or exposure to an environmental chemical. Drug interaction many times leads to adverse events [8]. Type-II diabetes mellitus is a dysfunction characterized by hyperglycemia that pertains to resistance in insulin action, inadequate insulin secretion, an excessive or inappropriate glucagon secretion. Treatment with

herbal drugs has an effect on protecting b-cells and smoothing out fluctuation in glucose levels. Most of these plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having antidiabetic effects [9]. Other drugs were also being used by different researchers such as alloxan and streptozotocin. Related studies from different journals were analyzed for drug response on glucose level of experimental rats.

hours and the treatment was started six weeks after the onset of diabetes because, in many studies, the duration of diabetes required to induce cardiac dysfunction in experimental rats [12, 13].

On the other hand, some researchers use Alloxan as an inducer of diabetic activity instead of streptozotocin. Alloxan induces diabetes in animals and impairs glucose induced insulin secretion from b cells of Islets of Langerhans of Pancreas. It has been reported that alloxan rapidly and selectively accumulates in b-cells in comparison with non-β cells [14].

The selected mice were weighed, marked for individual identification and fast for overnight. Alloxan monohydrate having rate of 150 mg/kg body weight were administered intraperitoneally. Blood glucose level of these mice were estimated 72 h after alloxan administration, diabetes was confirmed by blood samples collected from the tip of the tail using a blood glucometer [14]. Animals with blood glucose level equal or more than 200 mg/dl were declared diabetic and were used in entire experimental group [14]. The estimated hours of blood sampling and rate of Alloxan were varied to every research that was reviewed.

Both drugs have their own pharmacological approach, STZ uses 0.1 Citrate Buffer for stabilization while Alloxan uses sterile normal saline with the same purpose. Another thing, based from related studies, Alloxan exhibits rapid presence of diabetic even at greater dosage with respect to the mass of rats without being killed while streptozotocin is very sensitive to higher dosage intake.

2.1.2 Experimental Animals

The experimental rodents usually used are Wister albino rats and Sprague Dawley rats. They weigh approximately 150g-300g varies with the dosage of drugs being administered upon the conducted toxicity testing. They were housed at colony cages, polypropylene cages, bedded fine wood cages and cages that satisfy well ventilation and hygiene. They were allowed access to commercial grower mesh feeds, rat chow, pellet rich in proteins with water ad libitum. Standard temperature ranges from 22 °C - 36 °C for the housing and habitat. They were always maintained in a 12 hrs. light/dark cycle. The experimental procedures used in the present study were approved by the Ethic Committee of Laboratory Animals of the country where researchers reside.

2.1.3 Plant collection and extraction for organic drugs and acquisition of synthetic drugs.

Syzygium mundagam is known for its antidiabetic potential. Attempt to investigate the anti-oxidant property for controlling diabetic condition was conducted. Freshly collected leaves and bark were collected and cleaned to remove adhering dust and then dried under shed. 100 g of powdered form of plant material was extracted successively with petroleum ether, ethyl acetate, and methanol (300 mL) and the percent yield was obtained in terms of air dried form of plant material. [15]

The seeds of E. jambolana were collected from a local market in Midnapur town then underwent authentication by taxonomists in the department of Botany and Forestry, Vidyasagar University, Midnapore, where voucher specimens were preserved. Ethyl acetate fraction was prepared for the treatment of diabetic group with ethyl acetate fraction of seed

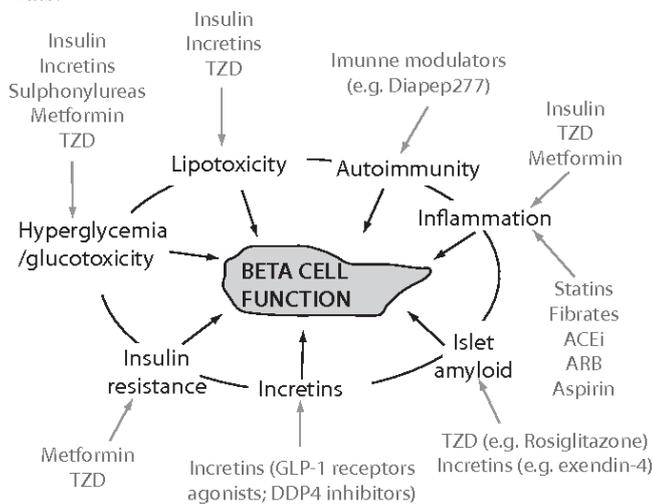


Figure 1: Main factors associated with progressive alteration of beta cell function and pharmacologic agents that influence them. TZD - thiazolidindione; GLP-1 - glucagon-like peptide-1; DPP4 - dipeptidyl peptidase-4; ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blocker. Image downloaded from <https://www.semanticscholar.org/paper/Diabetes-and-beta-cell-function%3A-from-mechanisms-to-Cernea-Dobreanu/94cdb9794fc6470ed2066b227162e467d48053a5>

2. Methodology

2.1 Materials and Methods

2.1.1 Drugs and Chemicals

All of drugs and chemicals for study are laboratory grade according to the reviewed journals. Other drug solutions incorporated were freshly prepared in distilled water and given intraperitoneally (i.p.) in appropriate doses. Diabetes was induced with a streptozotocin (Sigma Aldrich, St Louis, USA) injection at a dose of 40 mg/kg of body weight, which was dissolved then in 0.1 M citrate buffer (pH 4.5) [10]. This concentration of citrate buffer is preferred by researchers dealing with streptozotocin as inducer of Diabetes. Higher dosage of streptozotocin were reported to cause sudden death to rats while performing the procedure. The single dose of streptozotocin at a dose of 65 mg/kg intraperitoneally reported to have limitations [10]. The failure of obtaining diabetic rats was also due to a decline in blood glucose levels in some experimental animals after an increase in blood glucose levels >300 mg/dl [10]. Therefore, 40 mg/kg of rats exhibits significant diabetic condition compared to much higher dosage [10].

To overcome the drug induced hyperglycemia after the administration of streptozotocin, rats were given 10% glucose solution [9]. This was administered 6 hrs. of streptozotocin administration for the next 24 hrs. [11]. The animals showed 250 mg/dL confirmed as diabetic and preferred for experiment when time frame of 72 hours achieved [11]. Others used 300mg/dL of fasting blood glucose level after 96

of *E. jambolana* at the dose of 200 mg/2 mL distilled water/kg of body weight/d for 35 days at fasting state. [3]

Seeds of *T. lucida* were imported from Canada Company of Johnny's Selected Seeds-Superior Seeds & Gardening. Hypoglycemic effect of was investigated at a dose of 500 mg/kg (0.10 of LD50) (El-Newary et al., 2016). [23]

The tubers of *Chlorophytum alismifolium* were collected in July 2014 from a chosen river in Nigeria. The botanical identification and authentication was conducted. [16]

Ceiba pentandra (*C. pentandra*) has bark decoction that was used as diuretic, aphrodisiac, and to treat headache as well as type 2 diabetes. Fresh leaves were obtained and after that they were washed, blotted, and air dried for about two weeks. They are homogenized into fine power using a milling machine. 1500 g of fine powdered of *C. pentandra* was extracted with 300 mL ethanol using reflux method at 60°C and concentrated using rotary evaporator up to dryness in a water bath. 130.11 g was extracted and stored in a labeled sterile bottle. [17]

The turnips (*Brassica rapa*) were collected from a province in Iran around the month of December year 2011. *Brassica rapa* leaves were dried in shade at the room temperature. Afterwards the leaves were milled by an electric grinder for its powdered form. The powder was macerated in distilled water 1:10 (w/v) on a magnetic stirrer for a period of 2 days at room temperature. [18]

The *Moringa oleifera* leaves were harvested from Nsukka. Afterwards the leaves were dried in shade and pounded to yield a powder. The obtained powder was dispersed in 1% solution of sodium metabisulphate for 24 hours. [19]

The seed of *S. cumini* were procured from local market (Allahabad, U.P). Aqueous extract was made by dissolving it in distilled water using by mortar and pestle. The dose was finally made to 250 mg/kg body weight for oral administration after the LD50 estimation. [20]

Trigonella foenum graecum (Fenugreek) is an alkanoid trigonelline and an essential oil that shows hypoglycemic effects when used as a whole seed powder and cooked. A low dose of 2 g/kg and high dose of 8 g/kg were administered to thirty wistar albino rats. [21]

Mammea Africana is considered as a traditional medicine for treatment of different illness such as diabetes. Reduction of white blood cells has been reported in normal rats for 21 days of treatment. Stem bark of *Mammea Africana* was collected, dried at room temperature and ground into powdered form. An amount of 2 kg was macerated in 5 L of dichloromethane/methanol (1:1) for 24 hrs. The mixture was filtered, further concentrated yielding 450 g of brown viscous residue. [22]

Ginkgo biloba extract (GBE) was purchased from Hangzhou Greensky Biological Tech (Hangzhou, China) in powdered form. Different dosage of GBE used for the experimental design. (1) normal control group (N group), (2) STZ control group (D group), (3) GBE- (200 mg/kg) treated control group (N+G group), (4) GBE- (100 mg/kg) treated STZ group (D+LG), (5) GBE- (200 mg/kg) treated STZ group (D+MG), (6) GBE- (300 mg/kg) treated STZ group (D+HG), (7) glibenclamide- (5 mg/kg) treated STZ group (D+GLI group). [30]

The leaves of *E. variegata* were collected from Majhitar region of Sikkim State, India during 2009 of September. It is authenticated by a Taxonomist and the leaves used is in powdered form using the method of shade drying (24-26 °C) for 3-4 weeks. A 400g of powdered plant material was extracted with 95% methanol. It was filtered and evaporated to dryness (MEEV, 13.13 %). [31]

The collection of *Sargassum crassifolium* were from Drini seashore, Gunungkidul, Yogyakarta. The algae were extracted according to the Raysid method. The dried algae were washed with aquadest, filtered and bleached to obtain the desired form. [32]

The Daming capsule was consists of Solanaceae, Labiatae and *Acanthopanax gracilistylus*. These plant material were all collected from September to November. The sample were dried, powdered into fine and cased in capsule. [33]

Rosiglitazone is a drug use for treatment of diabetes particularly type 2. Whereas Intraconazole as an antifungal that increases the plasma concentration when it was used 200 mg per day on a period of 4 days with the effects of felodipine. Both drugs were prepared using 2 % w/v gum acacia as a suspending agent on a measurement of (720 µg/kg, p.o.) for Rosiglitazone while (9 mg/kg, p.o and 18 mg/kg, p.o) for Itraconazole. [4]

Clozapine can disturb the metabolism through the direction of body's mechanism in extracting energy from fat instead of carbohydrates and lead to the development of insulin resistance. The drug was suspended in 0.5% gum acacia and freshly delivered daily to rats. [24]

Topiramate is currently approved for marketing as an antiepileptic drug. However, the mechanism of action as an antiepileptic drug is unknown. Clinically reported that topiramate treatment reduced body weight and decreased fasting blood glucose of obese patients with or without type 2 diabetes. The solution of topiramate was prepared fresh by dissolving the powdered form of the drug in water. [25]

The nicorandil was administered almost simultaneously with glucose or glipizide in combined oral treatment. In nicorandil plus adrenaline group, after every 30 minutes the adrenaline was administer right after nicorandil. The right dosage of the drugs administered was on the basis of human therapeutic dose. [34]

Period of 13 consecutive days, all groups received the doses and at the end of the experimental an oral glucose tolerance test was conducted and blood glucose estimation was accomplished. [35]

Cassia kleinii was collected from Kanyakumari district of Tamil Nadu, India, in summer. A voucher specimen of the herb was identified by the taxonomists at Tropical Botanic Garden and Research Institute (TBGRI), Palode, Thiruvananthapuram Dist., Kerala, India and deposited in the herbarium of TBGRI, No. 47600. The extracts of dried root (suspension in water) and leaf (water, alcohol and n-hexane) were screened for their effects on serum glucose levels in glucose overloaded rats. The most active extract (alcohol extract of leaf) was tested for antidiabetes activity in alloxan-induced diabetic rats and for hypoglycaemic activity in normal fasted rats. [36]

Basella rubra plant was collected from the village area (Dindigul district) and raised in the university campus under normal climatic conditions (35 - 37°C). The plant was identified and authenticated (No.BSI/SC/5/21/04-05/Tech.367) from Botanical Survey of India (BSA), Tamil Nadu Agriculture University (TNAU) Coimbatore. [37]

Ficus hispida Linn. (Manipuri-Ashee-Haiboang; Sanskrit-Kakadumbura; Hindi – Konea-dumber) was authenticated by Dr. S.C. Sinha, Professor of Botany, Manipur University. Fresh barks of FH were collected during April-May from the Imphal area and dried under sunlight. [38]

The aerial part of Artemisia herba alba were collected in April 2016. Collecting was carried out according to good harvesting practices for medicinal plants recognised by OMS (2003). The plant taxonomic was identified by Azzedine Chefrour, a Professor of Botany at Badji Mokhtar University Annaba, Algeria. The plant was cleaned, dried in shade and powdered then stored in airtight container. [39]

Sitagliptin was obtained from Matrix pharmaceuticals, Hyderabad. Candesartan was obtained from Macs Biopharma, Hyderabad; Candesartan suspension was prepared using 0.5 % w/v sodium CMC as suspending agent. Alloxan-induced Diabetic model in rats has been used in this study. After induction of diabetes, sitagliptin (10mg/kg/p.o) and candesartan (5mg/kg/p.o) were administered orally for 7days. The Pharmacokinetic parameters like t_{1/2}, AUC, Clearance, T_{max} and C_{max} of sitagliptin with and without combination of candesartan treatment were determined. The blood glucose levels were estimated using Glucose Oxidase-Peroxidase (GOD-POD) method, creatinine by alkaline picrate method and albumin by BCG-dye method. [40]

2.2 Study design

Organic Drugs

a.) Grouping of rats for glucose test, b.) Method used for glucose level test c.) Method for blood sampling

Syzygium mundagam

- a.) 4 groups (6 animals each)
 - 1.) Control,
 - 2.) Syzygium mundagam bark (SMBM) (2 groups involved)
 - 3.) glibenclamide
- b.) Oral Glucose Tolerance test
- c.) Tail vein

E. jambolana

- a.) 4 groups (6 animals each)
 - 1.) Control
 - 2.) Diabetic
 - 3.) Ethyl acetate treated for diabetic
 - 4.) Glibenclamide treated diabetic group
- b.) Glucometer (Bayer'sAscensia Entrust)
- c.) Tail vein

T. lucida

- a) 6 groups [6 animals each]
 - 1.) Oral saline negative control
 - 2.) Tagetes extract positive control
 - 3.) glibenclamid positive control
 - 4.) STZ with tagetes extract as treated group
 - 5.) STZ treated with tagetes extract
 - 6.) STZ with glibenclamide
- b.) Glucose oxidase method
- c.) Tail vein and retro orbital plexus

Chlorophytum alismifolium

- a.) 6 groups [6 animals each]
 - 1.) Normal control group
 - 2.) Hyperglycaemic control group
 - 3.) Hyperglycaemic rats (150mg/kg CAE)
 - 4.) Hyperglycaemic rats (300 mg/kg CAE)
 - 5.) Hyperglycaemic rats (600 mg/kg CAE)
 - 6.) Hyperglycaemic rats (10 mg/kg CAE)
- b.) Glucose Oxidase Method
- c.) Jugular veins

Ceiba pentandra (C. pentandra)

- a.) 5 groups [20 rats each]
 - 1.) Normoglycemic
 - 2.) Diabetic untreated
 - 3.) Diabetic treated with standard drug (5 mg/kg body weight of glibenclamide)
 - 4.) Diabetic treated with 200 mg/kg body weight of crude ethanol extract of C. pentandra
 - 5.) Diabetic treated with 400 mg/kg body weight of crude ethanol extract of C. pentandra.
- b.) Glucometer
- c.) Tail vein puncture

Turnips (Brassica Rapa)

- a.) 6 groups [8 animals each]
 - 1.) saline (diabetic model)
 - 2.) MET50
 - 3.) MET100
 - 4.) 400 mg/kg AETL
 - 5.) 400 mg/kg AETL plus metformin at the dose of either 50 mg/kg
 - 6.) 400 mg/kg AETL plus metformin at the dose of either 100 mg/kg
- b.) Digital glucometer
- c.) Animal's heart through automatic biochemistry analyser

Moringa oleifera

- a.) 5 groups [6 animals each]
 - 1.) normal saline
 - 2.) 200 mg/kg tolbutamide
 - 3.) 100 mg/kg extract of Moringa oleifera
 - 4.) 200 mg/kg extract of Moringa oleifera
 - 5.) 300 mg/kg extract of Moringa oleifera

b.) 0- toluidine method

c.) Tail vein

S. cumini

a.) 3 groups [6 mice each]

- 1.) Control
- 2.) alloxan-induced diabetic control
- 3.) Diabetic mice given *S. cumini* seed extract

b.) Blood glucometer

c.) orbital sinus puncture method

Trigonella foenum graecum (Fenugreek)

a.) 2 groups [3 mice each]

- 1.) A (A1, A2, A3)
- 2.) B (B1, B2, B3) - Diabetic
A1 and B1- control
A2 and B2 – 2 kg/kg seed of *Trigonella foenum graecum* (Fenugreek).
A3 and B3 – 8 g/kg seed of *Trigonella foenum graecum* (Fenugreek).

b.) Dubowski's method

c.) Cardiac puncture

Mammea Africana

a.) 14 groups [5 animals each]

- 1.) Normal group
- 2.) Diabetic group
- 3.) normal rats treated with *Mammea africana* extract at different doses.
- 4.) normal rats treated with *Mammea africana* extract at different doses.
- 5.) normal rats treated with *Mammea africana* extract at different doses.
- 6.) normal rats treated with *Mammea africana* extract at different doses.
- 7.) normal rats treated with *Mammea africana* extract at different doses.
- 8.) normal (NGB) and diabetic (DGB) groups of rats treated with glibenclamide (10 mg/kg) as a standard hypoglycemic agent.
- 9.) were diabetic rats treated with the same doses of plant extract.
- 10.) were diabetic rats treated with the same doses of plant extract.
- 11.) were diabetic rats treated with the same doses of plant extract.
- 12.) were diabetic rats treated with the same doses of plant extract
- 13.) were diabetic rats treated with the same doses of plant extract.
- 14.) normal (NGB) and diabetic (DGB) groups of rats treated with glibenclamide (10 mg /kg) as a standard hypoglycaemic agent.

b.) Oral Glucose tolerance test

c.) Test strips (ACCUCHEK, Roche Lab. Pharm.).

Gingko biloba

a.) 7 groups (10 animals each)

1. Normal control group
2. STZ control group
3. GBE treated control group
4. GBE- (100 mg/kg) treated STZ group
5. GBE- (200 mg/kg) treated STZ group
6. GBE- (300 mg/kg) treated STZ group
7. Glibenclamide treated STZ group

b.) Oral glucose test (BIOSINO Bio-technology and Science INC, China)

c.) Tail vein

Tiger's Claw Erythrina variegata

a.) 7 groups (6 animals each)

1. Non-diabetic or normal group
2. Nondiabetic control (600 mg/kg)
3. Diabetic control
4. Diabetic Treatment (300 mg/kg)
5. Diabetic Treatment (600 mg/kg)
6. Diabetic Treatment (900 mg/kg)
7. Diabetic Treatment, glibenclamide (1ml/kg)

b.) Glucose-oxidase peroxidase

c.) Tail vein

Roflumilast

a.) 3 groups

1. Diabetic control
2. Glibenclamide group
3. Roflumilast group

b.) Capillary blood glucose testing

c.) Tail vein

Sargassum crassifolium

a.) 6 groups, 5 rats each

1. Normal rats (normal saline)
2. Diabetic rats (0.5% CMC-Na)
3. Diabetic rats (5mg glibenclamide)
4. Diabetic rats (200mg alginate)
5. Diabetic rats (400mg alginate)
6. Diabetic rats (600mg alginate)

b.) Diagnosis reagent kit (capillary glass tubes technique)

c.) Retro orbital plexus

Cassia Kleinii

a.) 4 groups (6 animals each)

1. Group I: 1 ml of 5% Tween 80, p.o. daily and served as control.
2. Group II was given alcohol extract daily (200 mg/kg, p.o.).
3. Group III: Received the same dose of the extract twice a day.
4. Group IV received insulin (5 U/kg, i.p., Knoll

Pharmaceuticals Ltd., India.) daily.

- b.) Oral Glucose Tolerance test
- c.) Tail vein

Basella rubra

- a.) 4 groups (6 rats each)
 - 1. Normal healthy control
 - 2. Streptozotocin (60 mg/kg body weight dissolved in 10 mM citrate buffer pH 4.5)
 - 3. STZ injected animals exhibited massive glycosuria and hyperglycemia
 - 4. Non diabetic rats treated with *B. rubra*.
 - 5. Diabetic rats administered with *B. rubra*.
- b.) Biochemical parameters by the method of Raghuramulu et al. (1983) respectively.
- c.) Analyzing the biochemical parameters

Ficus hispida (bark)

- a.) 3 groups (6 animals each)
 - 1. 3% aqueous Tween-80 (Loba Chem) suspension at a dose of 10 ml/kg.
 - 2. Aqueous suspension of water soluble portion of alcoholic extract of FH 6% w/v with 3% Tween-80 at a dose of 1.25 g/kg.
 - 3. aqueous suspension of glibenclamide (Hoechst) 0.01% w/v with 3% Tween-80 at a dose of 0.5 mg/kg.
- b.) Glucose Oxidase Method
- c.) orbital sinus

Artemisia herba alba

- a.) 4 groups (7 animals each)
 - 1. Normal control (NC) received saline solution at 9% given by intraperitoneal way
 - 2. Diabetic control (DC) was treated with 150mg Alloxan /[kg body weight] administered by intraperitoneal way.
 - 3. NCpAHA have received saline solution and treated with 400mg AHA/(kg body weight).
 - 4. DCpAHA were treated with alloxan and AHA
- b.) Blood glucometer
- c.) Single injection by Intraperitoneal way

Synthetic Drugs

a.) Grouping of rats for glucose test, b.) Method used for glucose level test and Method for blood sampling

Rosiglitazone and Itraconazole

- a.) 3 groups [6 animals per group]
 - 1.) treated with suspension of itraconazole (18 mg/kg, p.o)
 - 2.) Treated with rosiglitazone (720µg/kg) per oral respectively.
 - 3.) Treated with rosiglitazone (720µg/kg) per oral

respectively.

- b.) Glucose Oxidase/Peroxidase Method
- c.) retro orbital plexus

Clozapine

- a.) 2 groups [12 rats each]
 - 1.) Received clozapine orally at a dose of 10 mg/kg body weight daily for 6 weeks.
 - 2.) received the vehicle of clozapine throughout the course of the study and served as a normal control group
- b.) Spinreact kits according to the methods of Trinder and Abraham et al. respectively.
- c.) Decapitation

Topiramate

- a.) Two main groups
 - 1.) Diabetes was induced by a single intraperitoneal injection of freshly dissolved streptozotocin (STZ)
 - 2.) Control normoglycemic rats (30 rats)
*further division of rats occurred between the two groups based on the written journal. [25]
- b.) Glucose enzymatic-colorimetric assay test (Diagnosticum Rt.)
- c.) Retro-orbitalsinus

Nicorandil

- a.) 9 groups, 6 rats each
 - 1. Control A (2% gum acacia)
 - 2. Control B (normal saline)
 - 3. Nicorandil group
 - 4. Glucose group
 - 5. Nicorandil plus glucose group
 - 6. Glipizide group
 - 7. Nicorandil plus glipizide group
 - 8. Adrenaline group
 - 9. Nicorandil plus adrenaline group
- b.) Oral glucose test (Glucometer)
- c.) Lateral tail vein

Tramadol

- a.) 2 groups
 - 1. Diabetic treatment group (Tramadol)
 - 2. Diabetic control group
Glucose oxidase method
- b.) Daming capsule (DMC) Oral glucose test
- c.) Tail vein

Ramipril

- a.) 10 groups, 6 rats each
 - 1. Normal control group (sterile water)

2. Normal group (Ramipril)
3. Diabetic control
4. Diabetic treated (Ramipril)
5. Diabetic treated (Metformin)
6. Diabetic treated (Gliclazide)
7. Diabetic treated (Pioglitazone)
- 8-10. Positive control

b.) Oral glucose test

c.) Orbital sinus puncture

Sitagliptin and Candesartan

a.) 5 groups (5 rats each)

1. Normal control group treated with vehicle (0.5% Sod CMC)
2. Diabetic
3. Control
4. Sitagliptin (10mg/kg/p.o)
5. Candesartan (5mg/kg/p.o)

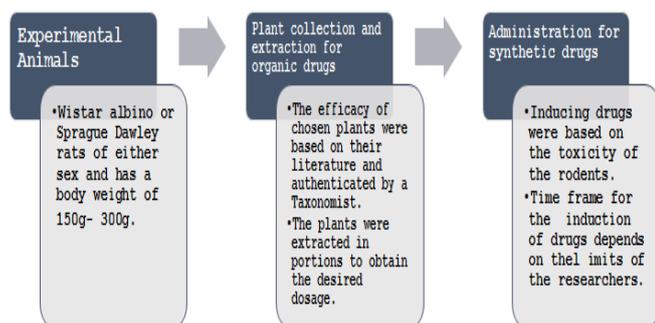
b.) Glucose Oxidase-Peroxidase (GOD-POD) method

c.) Retroorbital puncture

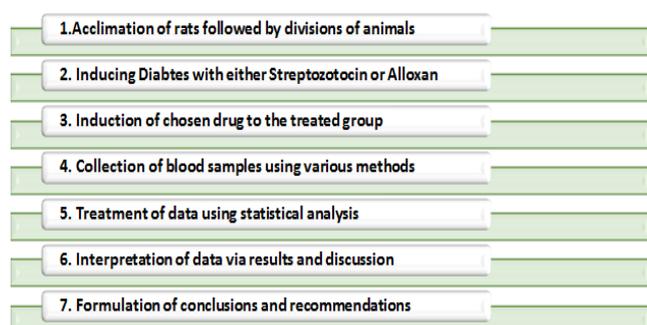
2.3 Statistical analysis

Every journal that was reviewed used similar statistical approach in presenting their respective data. All of the data were presented mean \pm standard error of the mean, for every rats in assigned groups. Comparative analysis between groups or points was featured through one-way analysis of variance followed by multiple comparison two-tail “t” test to analyze the significant of the study. Differences were considered significant for p-values that were less than 0.05.

2.4 Graphical abstract



2.5 Methodological framework



3. Results

Title:Antihyperglycemic activity of the bark methanolic extract of *Syzygium mundagam* in diabetic rats

Authors: Rahul Chandran, Thangaraj Parimelazhagan, Blassan P. George

Findings: The administration of extract doesn't affect the mortality of the test subjects which indicates the safety of the extract to a maximum dose. The treatment of *Syzygium mundagam* showed tolerance to glucose of the rats through glucose tolerance test. *Syzygium mundagam* has a good ability to reduced glucose level compared to control subject.

Title:Antidiabetic effects of *Eugenia jambolana* in the streptozotocin-induced diabetic male albino rat

Authors:Kishalay Jana, Tushar Kanti Bera, Debidas Ghosh

Findings:The antihyperglycemic activity of *E. jambolana* with respect to ethyl acetate was varied as indicated by a decrease to some period of time that increases as time passed by. The percentage of recovery of blood glucose level was much lower compared to glibenclamide treated group which both groups were under diabetic group. The serum level was restored to control levels with respect to ethyl acetate.

Title:In-vivo hypoglycemic and hypolipidemic properties of *Tagetes lucida* alcoholic extract in streptozotocin-induced hyperglycemic Wister albino rats

Authors:Samah A. Abdel-Haleema, Abeer Y. Ibrahima, Rasha F. Ismaila, Nermeen M. Shaffieb, S.F. Hendawya, E.A. Omera

Findings:*T. Lucida* extract showed reduction in blood glucose level on the earlier periods of analysis. However, as experimental period extended the blood glucose level returned to normal range. When the effects of *T. lucida* are compared to glibenclamide drug, there is a significant reduction in the blood glucose level during the experimental period. On the last period, there no change in the blood glucose level with respect to positive and negative control.

Title:Anti-hyperglycaemic activity of tuber extract of *Chlorophytum alismifolium* Baker in streptozotocin-induced hyperglycaemic rats of *Chlorophytum alismifolium* Baker in streptozotocin-induced hyperglycaemic rats

Authors:Abdulkhikim Abubakara, Nuhu M. Danjumaa, Ben A. Chindob, Abdullahi B. Nazif

Findings: The effect of methanol crude extract of *C. alismifolium* on blood glucose level of STZ-induced hyperglycemic rats showed glucose lowering effect all throughout the experimental period at a dosage of 600 mg/kg while a much lower dosage like 300 mg/kg, the lowering effect on glucose level was only significant to some periods not the entire experimental periods.

Title:Acute oral toxicity study of ethanol extract of *Ceiba pentandra* leaves as a glucose lowering agent in diabetic rats

Authors:Hadiza Lami Muhammad, Adamu Yusuf Kabiru, Musa Bola Busari, Abdullah Mann, Abubakar Siddique

Abdullah, Abdulrazaq Taye Usman, Usman Adamu

Findings:No behavioral changes observed at the administration of Ceiba pentandra leaves. All treated groups showed decrease in glucose concentrations compared to untreated groups that continued to elevates. In addition to that, treated groups greatly showed appreciation on body weight of rats compared to untreated diabetic groups.

Title:Co-administration effects of aqueous extract of turnip leaf and metformin in diabetic rats

Author:Moammadmehdi Hassanzadeh-Taheri, Mohammad Hassanpour-Fard,Mohammadreza Doostabadi, Hesam Moodi, Khadijeh Vazifeshenas-Darmany, Mehran Hosseini

Findings:Aqueous extract of turnip leaf reacts with metformin induced diabetic rats through a successive administration. All experimental groups showed gradual decrease in FBG levels when compared with Diabetic group for a certain period of time. Lower dosage of metformin only showed small difference on lowering FBG levels when compared with a higher one. Mixture of metformin and aqueous extract of turnip leaves showed highest level of lowering activity compared with experimental group and varied dosage of metformin. Normalization of FBG levels was achieved for a longer experimental period.

Title: Blood Sugar Lowering Effect of Moringa Oleifera Lam in Albino Rats

Authors: Edoga C. O., Njoku O. O., Amadi E. N., Okeke J. J.

Findings: The extract of Moringa oleifera greatly varies to dosage level for pronounced hypoglycemic condition. Alloxan-induced rats showed hypoglycemic effect that indicates reduction of glucose level. Finally, Moringa oleifera exhibits comparable effect with tolbutamide.

Title: Liver protective effects of aqueous extract of Syzygium cumini in Swiss albino mice on alloxan induced diabetes mellitus

Authors: Bhaskar Sharma, Md. Sufiyan Siddiqui, Shiv Shanker Kumar, Gurudyal Ram, Manisha Chaudhary

Findings: A sudden decreased in glucose level when aqueous extract of Syzygium cumini obtained. Alloxanization increased glucose concentration however when S. cumini incorporated the glucose concentration decreases which made an experimental analysis.

Title: Effect of Trigonella FoenumGraecum (Fenugreek) on Blood Glucose in Normal and Diabetic Rats

Authors: P. Khosla, D. D. Gupta and R. K. Nagpal

Findings: The administration of Fenugreek showed decrease in blood glucose level both in diabetic and controlled rats. Higher dose signifies hypoglycemic effect. The hypoglycemic effect of Fenugreek has not yet considered an effective cure for diabetes however it was considered a preventive approach for glucose level management.

Title: Hypoglycaemic effects of Mammea africana (Guttiferae) in diabetic rats

Authors: M.-C. Tchamadeu, P.D.D. Dzeufiet, C.C. Kouambou Nougou, A.G.B. Azebaze, J. Allard, J.-P. Girolami, I. Tack, P. Kamtchouing, T. Dimo

Findings: The effects of DCMM bark extract of Mammea africana on fasting blood glucose levels was varied between normal and diabetic drugs. Normal rats were unresponsive upon the accumulation of plant extract. When standard drug glibenclamide was introduced, hypoglycemic effect prevailed. Other case, diabetic rats considered dependable on the effects plant extract. inhibition of glucose intake-induced hyperglycaemia. Higher dosage produced a significant ($P < 0.01$) but milder reduction in blood glucose of diabetic rats. Glibenclamide plays a role in the fall of blood glucose level on a longer time interval.

Title:Anti- Hyperglycaemic Activity O Cassia Kleinni Leaf Extract in Glucose Fed Normal Rats and Alloxan-Induced Diabetic Rats

Authors: V. Babu, T. Gangadevi, A. Subramoniam

Findings: The plant leaves as well as its alcohol extract exhibited concentration dependent antihyperglycaemic effect in glucose loaded rats.

Title: Effect of Candesartan on Pharmacokinetics and Pharmacodynamics of Sitagliptin in Diabetic Rats

Authors:Syeda Munawar Khatoun, Tahseen Meraj and A. Rama Narsimha Reddy

Findings:The pharmacokinetic results showed similar sitagliptin plasma concentration when used in combination with candesartan and no change in the pharmacokinetic parameters were observed and no change in the blood glucose levels of sitagliptin was observed in the presence of candesartan indicates the no significant ($p > 0.05$) interaction.

Title:Hypoglycemic activity of Ficus hispida (bark) in normal and diabetic albino rats

Authors:R. Ghosh, Kh. Sharatchandra, S. Rita, I. S. Thokchom

Findings:The reduction in the blood glucose level was less than that of the standard drug, glibenclamide. FH also increased the uptake of glucose by rat hemidiaphragms significantly ($P < 0.001$).

Title:Hypoglycemic effect of Basella rubra in streptozotocin – induced diabetic albino rats

Authors:A. Nirmala, S. Saroja, H. R. Vasanthi and G. Lalitha

Findings:Streptozotocin causes selective destruction of cells of islets of pancreas and brings an increase in blood glucose levels.

Title:Mitigating effects of antioxidant properties of Artemisia herba alba aqueous extract on hyperlipidemia and oxidative damage in alloxan-induced diabetic rats

Authors:Omar Sekiou, Mahieddine Boumendjel, Faiza Taibi, Amel Boumendjel and Mahfoud Messarah

Findings: Diabetic rats showed a significant increase in blood glucose level compared to the normal rats ($p < .001$). As for the oral administration of AHA aqueous extract, it caused a significant decrease in blood glucose in treated rats from the second week compared to the beginning of the experimental protocol.

4. Discussions

The detrimental effects of diabetes and its corresponding complication believe to increase by occurrence of oxidative stress. Drugs possess antioxidant property can be used to combat diabetes. Extracts having antioxidants enhance the ability of tissues to uplift the glucose through the reduction of insulin resistance. [17]

Some biological processes reflect the extent of drug absorptions like gut lumen, metabolism of drug in the liver, and on the extend of its secretion into bile and urine. Modification of all the processes included concomitantly administered drug can alter the effects of oral antidiabetic drugs. [4]

In the course of this review, the induction of Streptozotocin cause pronounced disturbance of biochemical parameters. The most common lipid abnormalities that were presented by some results gathered from reviewed journals were Hypertriglyceridemia and hypercholesterolemia. Hyperlipidemia generally appears with diabetes upon the decrease of insulin which causes increment in lipolysis. [22].

The potency of medicinal plants as antidiabetic agents may be featured to one or more phyto-active components which primarily focus on glucose reduction. Some phytochemicals showed blood glucose lowering includes steroids, terpenoids and saponins. These phytochemicals play a role in in regeneration of damaged β cells following the administration of STZ and observe antihyperglycemic activity. [17]

Aerobic life and metabolism in biochemical processes constitute free radicals that are very fundamental and the most deleterious action is on DNA. The act of alteration can be part of diabetes mellitus. Every living organism has a cell responsible to fight against free radicals accompanied by enzymatic defense system like superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase etc. Promoting clinical and pre-clinical trials would lead to the emergence of novel natural drug that acts as insulin sensitizer to the tissues, insulin stimulant and protein inhibitors. [16]

5. Conclusion

Every human being tends to seek an alternative way on how to treat a specific disease with regards to its corresponding consequences that is why we can consider ourselves some kind of risk-takers. Life is very important not because it's a gift from God but a vital thing that we treasured most and cannot be forsaken or compromised no matter what. Diabetes Mellitus is one of the most prominent chronic disease around the that can easily be acquired because of lack of awareness and improper lifestyle. Scientists, Researchers and other individuals who are related in the field of science investigate a solution to this conflict through conducting sorts of analysis and test with the use of animals as a test subject. Rodent animals particularly rats are being used to examine the pharmacological property of a certain drug to some degree of lethality and preventive measures. Organic and synthetic

drugs exhibit unique properties and treatment that really differ to one other. In this study both drugs were present accompanying different constituents following certain procedures and incorporated parameters for the purpose of the study. After reviewing journal articles, some key points were gathered. Standard drugs contribute on the effectivity of treated drugs that can either alter its effect or to some extent be beneficial and important. Higher and lower dosages of administered drug showed adverse effect on the response of the drug under test. Another thing, the condition of rats as test subject affects the results obtained because mortality and behavioral changes interferes. Blood glucose levels can be analyzed through this kind of study design but we must consider the welfare of animals by abiding with the Ethics for animal care.

6. Conflict of interest

The authors declared conflict on the connectivity of every journal results interpreted in a cumbersome way. The aim of this review is to discuss and elaborate every information presented for the readers to convey it comprehensively.

7. Acknowledgement

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