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A Comprehensive Survey of Screening Models for Pharmacological Assessment of Diabetic Drugs.

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Abstract: A range of metabolic conditions include diabetes mellitus illnesses defined by insulin deficiency and its aggregate hyperglycemia. The condition has a high prevalence globally, impacting 2.8% of the world's population. Insulin use is necessary for type 1 diabetes, but insulin resistance characterises type 2 diabetes, can be treated with different therapeutic approaches. different in vivo and in vitro methods for insulin secretion have been used, either by genetic engineering (transgenic models) or chemical induction (disease-induced models). Rodents such as rats and mice are used in research as animal models for the antidiabetic effects of drugs. Advances in diabetes research require the development of more animal models and advanced techniques.

Objective: There are several models for determining the anti-diabetic activity of a pharmacological molecule at this time. This article's primary goal is to explain the importance of the numerous animal models that may be used to test antidiabetic effects.

Methods: The databases were used to perform a literature search Thermo Fisher, Springer Link, and PubMed with the aid of various keywords like “Antidiabetics”, “In vitro models” and “In- vivo models”. By using the necessary criteria, the search was adjusted to only return results that were relevant to the goal of this review article.

Result: There are numerous research and review articles based on the antidiabetic screening models for the determination of the antidiabetic activity of novel pharmacological compounds.

Conclusion: Based on the results of our investigation, we identified several helpful models for the antidiabetic activity of medications and hypothesised that, if we combine in-vitro and in-vivo methodologies, we may acquire the most relevant outcome in our field of study.

Keywords: Antidiabetics, animal models, in vitro, in vivo, Alloxan

Introduction: Often referred to as diabetes mellitus (DM), diabetes is a metabolic disease characterised by consistently high blood sugar levels. Acute consequences include hyperosmotic hyperglycemia, diabetic ketoacidosis, and even fatality. Serious long-term consequences include cardiovascular disease, stroke, chronic renal failure, and foot ulcers [1]. Type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is an autoimmune condition in which antibodies kill the beta cells in the islets of Langerhans. Typically, young toddlers and teens are affected (hence the name juvenile diabetes). Non-insulin-dependent diabetic mellitus, often known as type 2 diabetes (NIDDM), first appears in adults. Most patients are obese. There is reduced tissue sensitivity to insulin, dysregulation of insulin secretion [2] and type 3 gestational diabetes.

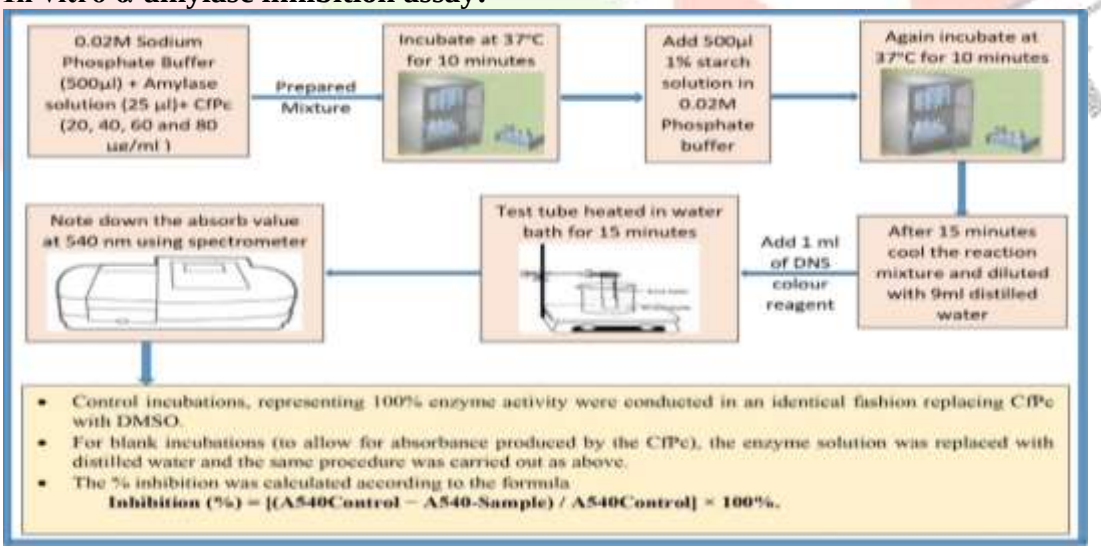
Around 10% of people worldwide have diabetes, and 90% of those cases are type 2 diabetes [3]. India, China, and the United States are predicted to have the biggest populations by 2030 with diabetes [4]. Also, according to the IDF's estimation [5], up to 183 million individuals do not know they have diabetes. The scientific community has tended to be interested in examining unprocessed or isolated natural products in experimental investigations due to the tremendous interest in creating new medications to lessen the burden of this illness, although most has not been clinically tested in humans [6,100,101]. Diagnosis of diabetes in asymptomatic patients should not be based on abnormal blood glucose levels. When a diabetes diagnosis Before rendering a diagnosis, the doctor must be confident about it has been completed. This is because the impact on individuals is significant and lifelong [7]. Diagnosis of diabetes mellitus includes urinary glucose, blood glucose, Renal glucose threshold, renal glucosuria, a dilated glucose tolerance curve, a corticosteroid challenge glucose tolerance test, an increase in glucose tolerance, and intravenous glucose tolerance are all terms used to describe different aspects of tolerance for glucose. One of the exams is the oral glucose tolerance test. [102-107]. Treatment goals for developing diabetes mellitus may be done by: 1. Bringing the dysfunctional metabolism of diabetics closer to normal as long as it is comfortable and safe.2. to reduce both the short- and long-term hazards of illness and to stop or delay their course. 3. to provide patients the information, inspiration, and tools they need to carry out this specially enlightened treatment. Experimental induction of diabetes mellitus It is crucial to do research in animal models to increase our knowledge and comprehension of many elements of its aetiology and, eventually to the search for new and therapeutic modalities. Diabetes animal models are very valuable in biomedical research because they bring novel insights into human diabetes. Experimental diabetes has been analysed utilising a range of techniques, including genetic, surgical, and pharmacologic interventions [8]. It is crucial to choose the right animal models for testing novel drugs and other treatments of diabetes [9]. The current review focuses on documented models of secondary complications of diabetes, compiles a variety of experimental models, including types 1 and 2, evaluates the strengths and weaknesses of each model, and identifies erroneous results. It is intended to emphasise the safety measures to take After the use of these models [10,87, 88]. Many popular plants with anti-diabetic properties include:

S. NO.	Plants Name	Family	Part used	Type of extract	References
1	Alangium lamarckii	Alangiaceae	Leaves	Alcoholic	11
2	Albizia odoratissima	Mimosaceae	Bark	Methanol	12
3	Axonopus compressus	Poaceae	Leave	Methanol	13
4	Berberis vulgaris	Berberidaceae	Root	Aqueous	14
5	Brassica juncea	Cruciferae	Seed	Aqueous	15
6	Caesalpinia digyna	Fabaceae	Root	Methanol	16
7	Catharanthus roseus	Apocynaceae	Leaf	Methanol	17
8	Centaurium erythrea	Gentianaceae	Leaf	Aqueous	18
9	Chaenomeles sinesis	Rosaeae	Fruits	Ethyl acetate	19
10	Cocos nucifera	Arecaceae	Leaf	Hydro-methanol	20
11	Costus speciosus	Costaceae	Rhizome	Hexane	21
12	Cyclocarya poliurus	Cyclocaryaceae	Bark	Aqueous, PE, Chloroform	22
13	Dillenia indica	Dilleniaceae	Leave	Methanolic	23
14	Embelia ribes	Myrsinaceae	Berries	Hexane	24

15	Hybanthus enneasperms	Violaceae	Whole plant	Alocoholic	25
16	Lippa nodiflora	Verbenaceae	Whole plant	Methanolic	26
17	Lithocarpus polystachyus	Fagaceae	Leave	Ethaanol & Aqueous	27
18	Marrubium culgare	Lamiaceae	Aerial part	Methanol	28
19	Ocimum sanctum	Lamiaceae	Aerial part	Hydroalchoholic	29
20	Opuntia streptacantha	Cactaceae	Leave	Ethanol	30
21	Psidium guajara	Myrtaceae	Fruits	Ethanol	31
22	Semecarpus anacardium	Anacardiaceae	Nut	Milk	32
23	Prosopsis glandulosa	Fabaceae	Whole plant	Jelly	33
24	Setaria italic	Poaceae	Seed	Aqueous	34
25	Viscum schimperi	Viseaceae	Aerial part	Methanolic	35

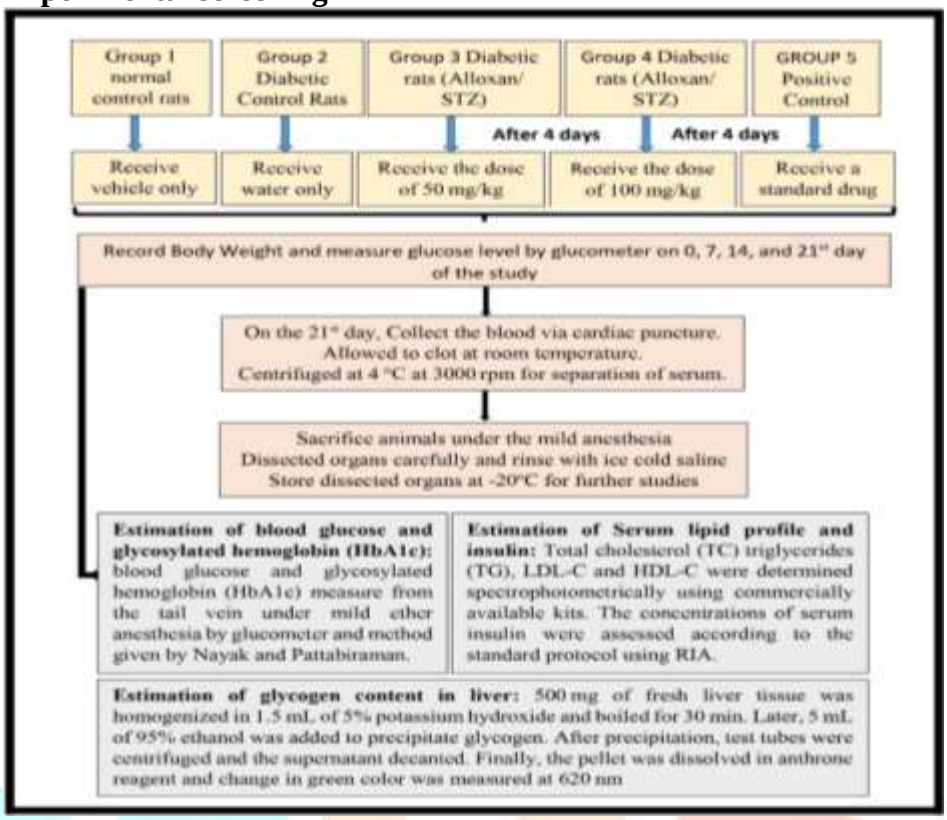
Material and Methods: Using a mix of distinct keywords, a literature search was carried out in multiple database sources (Science Direct, PubMed, etc.) antidiabetic drug, in vivo, in vitro animal model, and alloxan. Searches have been tailored by using the proper criteria to find the most relevant articles that fit the review's goals. To determine the antidiabetic activity of newly synthesized drugs. There are numerous publications on anti-diabetic models of newly synthesized drug to determined antidiabetic activity.

In vitro α-amylase inhibition assay:



In vivo antidiabetic activity:

Experimental screening



a. **Diabetic retinopathy in streptozotocin-induced diabetic rats :** Adult in good health Wistar rats weighing 250 to 300 g are kept on a conventional lab food and tap water with a 12-hour light/dark cycle. a single dose of streptozotocin between 50 and 70 mg/kg causes diabetes [39,102,103]. Same sized vehicle (3 mM citrate buffer, pH 4.5) is administered simultaneously to the control group. After 10 days, animals are monitored for plasma glucose and The study included rats with blood sugar levels over 300 mg/dl. After 2 weeks, rats can be examined for diabetic retinopathy. The following paradigms can be evaluated to assess etiology, etiology, and preventive and therapeutic interventions in this model. Diabetic retinopathy that is proliferative thought to develop due to the release of vasogenic factors from ischemic and hypoxic retinal areas following the retinal vascular bed is blocked. Vascular occlusion in diabetic retinopathy may be brought on by the deposition of glycoprotein compounds that are periodic acid-Schiff positive on the retinal artery walls. To investigate Expression of type VI collagen, fibronectin, and laminin and VEGF in regions with retinal capillary blockage, periodic acid-Schiff staining and immunohistochemistry are helpful.

b. Blood Glucose Monitoring: Rats in the control, normal, and test groups had different blood glucose levels. can be estimated at regular intervals. A little quantity of blood, around 0.05 ml, is extracted from the strip and placed to the tail vein. Blood sugar levels are assessed with a digital glucometer.

c. Blood HbA1c, Hb-AGE measurement: According to this method, under light ether anesthesia, whole blood of rats is collected into heparinized tubes from the tail vein. Prepare hemolysate and prepare purified hemoglobin using standard procedures. Hemoglobin content is measured with Drabkin's reagent and HbA1c levels are measured using standard chromatographic methods. AGE-modified haemoglobin may be evaluated using an ELISA that is unique to AGE (Hb-AGE) [40]

d. Fluorescein Angiography: Clinical manifestations of pathology can be monitored by fluorescein angiography. The fluorescent dye is injected into the leg vein of the rat. The dye will go all over your body, including your eyes. A special camera designed to photograph the retina is used to observe the retinal vessels and photographically record how the dye flows through the retinal vessels [41].

e. Visualization of vascular leakage: Increased vascular permeability is a useful marker and can be assessed 2 weeks after induction of hyperglycemia. Evans blue, a dye that has the ability to bind plasma albumin, is used to test for blood flow and vascular leakage, if any. Briefly, follow this protocol: 200 l of 2% (w/v) Injection of Evans blue into the femoral vein after being dissolved in a sterile physiological solution of 200 g rats confined on a heating platform at 37 °C for 20 minutes while under deep anaesthesia.

Animals are returned to the warming plate for a further 20 minutes before being sacrificed. Retinas are immediately isolated, fixed flat, kept in 10% formaldehyde, inspected, and photographed under fluorescent lighting (excitation filter 546 nm, blocking filter 590 nm). Modifications to standard protocols are also widespread. Retinol vascular leakage can also be measured by intravenous injection of FITC-BSA. Rats were given a tail vein injection of 100 mg/kg FITC-bovine serum albumin after the administration of anaesthesia, and 20 minutes later the animals were slaughtered and their eyeballs were removed. Collect plasma at the same time and analyze fluorescence with a fluorescence spectrophotometer Based on a healthy rat plasma FITC-BSA standard curve. We acquire frozen retinal slices (6 m thick) and observed under a fluorescence microscope [42].

f. Antioxidant activity: Retinas were treated at 50 mM under cryogenic conditions using a handheld homogenizer to measure thiobarbiturate-reactive substances (TBARS), antioxidant enzymes (reduced glutathione, catalase, superoxide dismutase). Homogenized in PBS.

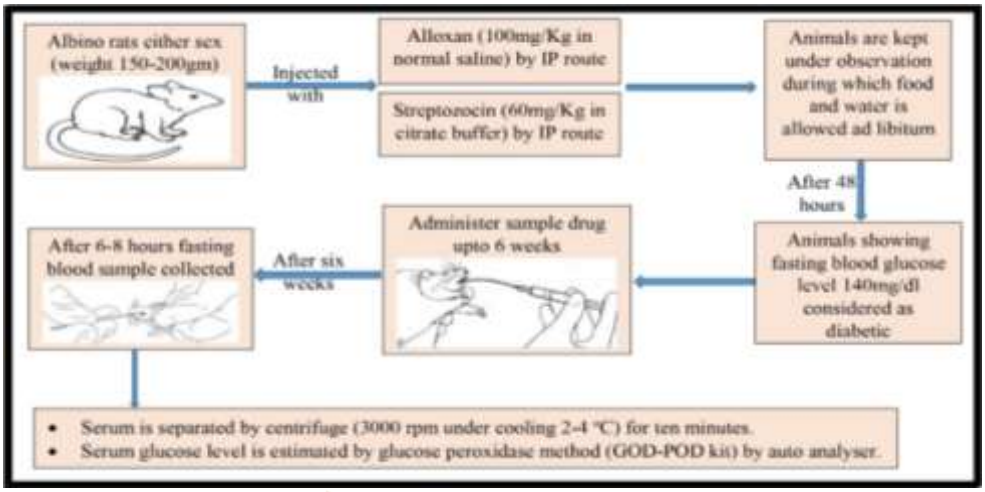
1. IDDM

a. Alloxan-induced diabetes: 5, 5-Dihydroxypyrimidine-2, 4, 6-trione, often known as alloxan, is a chemical compound cytotoxic glucose analogue, a urea derivative, and a carcinogenic molecule. Streptozotocin and alloxan are the most commonly used diabetogenic agents. All other drugs such as high fructose load, anti-insulin serum, dithizone, gold thioglucose, monosodium glutamate, and high glucose load. Our literature Alloxan review and secondary meta-analysis and streptozotocin use in diabetes research experiments conducted over the past 5 years (021). Some animal species, including cats, dogs, mice, monkeys, rabbits, and rats, may develop an insulin-dependent diabetic condition known as alloxan-induced diabetes. Alloxan has a very narrow diabetogenic dose range, with sometimes low doses causing toxicity in many animals and ultimately leading to animal loss.High doses cause renal tubular necrosis toxicity. Dosages of alloxan vary between studies and range from 90 mg/kg to 200 mg/kg and may be given via a number of different ways. including subcutaneous, intravenous and intraperitoneal. Alloxan doses of 65 mg/kg are most commonly administered intravenously, but intraperitoneal and subcutaneous alloxan doses should be elevated for diabetogenic effects. However, many studies have shown that alloxan dosing is most effective at 170-220 mg/kg body weight. The mechanism that causes diabetes is less clear. Alloxan is a very reactive chemical that may be quickly converted into diuretic acid. After the autoxidation of diuretic acid back to alloxan, free radicals are produced. These free radicals damage beta cells' DNA, leading to their demise. The capacity of alloxan to interact protein SH groups, particularly membrane proteins on cells like glucokinase, is his second theory for how the substance functions, leading to cell necrosis in the process. Alloxan responses vary greatly across species, leading to significant mortality in rats, animal ketosis brought on by the creation of free fatty acids, and other adverse effects. and some species such as guinea pigs exhibit resistance activity to its diabetogenic effects.

b. Streptozotocin Induced Diabetes: 2-Deoxy-2(3-methyl-3-nitrosourea) 1-D-glucopyranose, commonly known as streptozotocin, is a broad-spectrum antibiotic produced by chromogenic actinomycetes. It is a chemotherapeutic alkylating agent. It causes beta-cell damage by three mechanisms: the first is through methylation processes, the second is through the production of free radicals, and the third is through increased nitric oxide production. The amount of streptozotocin needed to cause diabetes varies on a number of variables, including the method of administration, nutritional status and animal species. Via the glucose transporter GLUT2, it reaches pancreatic beta cells and triggers alkylation of deoxyribonucleic acid. Moreover, it triggers pancreatic enzymes to activate polyadenosine diphosphate-ribosylation and produce nitric oxide. streptozotocin beta cells destroyed by necrosis. The most common dose of streptozotocin -induced diabetes is 60 mg/kg, although higher doses can be used if needed. Less than 40 mg/kg is ineffective by any route of administration. An animal is considered diabetic two days after his streptozotocin administration if the animal's tail blood glucose level exceeds 200–300 mg/dl.

Intraperitoneal therapy or intravenous tail vein method are two ways to cause type 2 diabetes. For diabetes, STZ has almost fully replaced alloxan induction due to its high selectivity for β-cells, low mortality and delayed or ongoing development of diabetes. It also causes oxidative stress, kidney damage, endothelial dysfunction, and inflammation. Yet it has no impact on diabetes in guinea pigs or rabbits. Multiple doses of low doses of his STZ promote hyperglycemia and rats with immune-mediated insulitis. The ability of STZ to cause diabetes is increased when cyclosporin-A is also administered. One instance of hyperglycemia was

caused by STZ when it was combined with a full Freund's adjuvant, CFA, an insufficient Listeria monocytogenes, Freund's adjuvant, Mycobacterium butyricum, a component of CFA, or endotoxin (25 mg/kg) that was given 24 hours before STZ and for the following three weeks. Fasting for 48 hours (24 hours before STZ injection and 24 hours after his) also causes hyperglycemia. Four doses of CFA or STZ alone do not produce sustained hyperglycemia.



c. **Hormones- induced Diabetes Mellitus:** NIDDM is produced with Dexamethasone is a long-acting glucocorticoid. When dexamethasone is injected intraperitoneally at levels of 2 to 5 mg/kg, NIDDM-type diabetes develops. administered twice day in rats for a number of days [54]. diabetes brought on by insulin antibodies. Anti-insulin antibodies are created when guinea pigs are given bovine insulin together with CFA. Rats' When rats take Blood glucose levels rise to 299.99 mg% when 0.26-1.1 ml of guinea pig anti-insulin serum is administered intravenously. in a dose-dependent manner. Insulin antibodies' ability to neutralise endogenous insulin underlies their special ability to affect guinea pig anti-insulin sera. It continues for as long as there is still insulin in circulation and the antibodies are still able to react with it. The impact is prolonged over many hours by a gradual intravenous or intraperitoneal infusion. The diabetic state is reversible within hours, but high-dose and prolonged treatment are linked to ketosis, ketonuria, diabetes, and acidosis, which are fatal for low-dose animals [55].

2. Models for NIDDM

a. Neonatal STZ Model of NIDDM (Chemically Induced Diabetes): STZ (80-100 mg/kg i.p.) is administered to newborn Wistar or Sprague-Dawley strain rats within the first five days after delivery or at birth. Pancreatic beta-cells are extensively damaged and this is followed by diminished pancreatic insulin reserves and increased plasma glucose levels. Nevertheless, treated neonatal -cells partly regrow in contrast to STZ-treated adult rats. At three weeks of age, newborn rats treated with STZ achieve normoglycemia after an initial rise in plasma glucose. The proliferation of cells from the ducts causes -cell counts to rise in the weeks that follow; the amount depends on the age at which the animals received STZ treatment as well as the kind of treated rat [56-57].

b. Other Chemically Induced NIDDM Models: Adrenaline (0.1 mg/kg s.c.) is one of the substances used to cause NIDDM in rabbits. After an hour, the maximum hyperglycemic impact kicks in and lasts for up to four hours. The rise of blood glucose is 120-150mg/100ml, and oral hypoglycemic medicines may be evaluated in this method. The chelating agent's 8-hydroxyquinolones and biphenylthiocarbazines may also cause diabetes in animals. It has been discovered that EDTA causes diabetes in rats with incomplete pancreas. Mice develop diabetes when antiserum against oxinsulin is injected into guinea pigs or lambs. Rats with spontaneous hypertension (SHR)

An major a contributing factor to the onset of diabetes retinopathy is inflammation. or pathophysiology. Hypertension is the primary secondary risk factor connected to DR. Hereditary hypertension in early retinitis in experimental diabetes has been studied [58]. They induced diabetes in both fully hypertensive rats and rats that developed hypertension along with age-matched normotensive Wistar-Kyoto (WKY) rats. They concluded that onset of hypertension and full-blown hypertension lead to early onset of diabetic retinal inflammation.

c. **Genetic Models of NIDDM**

Transgenic Vascular Endothelial Growth Factor Mouse Model: The pathophysiology of DR and the function of vascular endothelial growth factor (VEGF)[59,86] motivated the investigation into if transgenic mice have modest levels of VEGF expression in photoreceptors (trVEGF) underwent alterations mimicking diabetic retinopathy and looked at whether the condition worsened over time. According to analysis of human VEGF (Hvegf), serum glucose levels, changes that resembled diabetic retinopathy, and if the problem became worse over time and the number of hVEGF165 expression is briefly elevated in acellular capillaries. is thought to cause progressive retinopathy. The next procedure may be used to produce mice.

Procedure: A DNA construct is microinjected to produce mice. incorporating a truncated mouse rhodopsin promoter and the hVEGF165 gene confining transgene expression to the eye. Backcrossing with C57BL/6J mice produces fifth and sixth-generation heterozygous Age-matched wild-type littermates and mice. These animals have a modest increase in hVEGF165, low retinal injury, and few neovascular alterations; and help in the examination of early pathological changes [54-55].

The rat model of streptozocin one of the most well-liked models for lengthy investigations is induced diabetes. Retinal lesions seen in rats have similarities to the initial process of DR in men [60, 83, 84, 85]. However, mice can be genetically manipulated and provide the opportunity to study the molecular pathways the onset of diabetic retinopathy. Transgenic mice help in the investigation of various causes that influence the first phases of diabetic retinopathy and to test early therapeutic interventions. The models describe above vary from each other in some aspect or the other having unique benefits and drawbacks. The selection of the appropriate experimental model therefore has a prime importance in execution of one's study.

d. **Monogenic Models of obesity and NIDDM:** The hallmarks of this condition include obesity, hyperinsulinemia, transitory or chronic hyperglycemia, and hyperlipidemia characteristics of the monogenic rodent models. The following animal models were employed: (The Agouti Mouse) Yellow Mouse Because of its vivid hair colour, the agouti mouse is said to have initially arisen in China, where people considered it as a curiosity. The South American rat Dasyprocta agouti, which has a banded pattern of hair colour, was called after the agouti locus, which was discovered as a consequence of investigations on coat colour pigments. When a man is 4 to 5 weeks old, hyperinsulinemia, hyperglycemia, insulin resistance, and NIDDM are discovered. [61-65]

In vitro methods on Isolated Organs, Cells and Membranes:

Isolated Pancreas of Rat: We can evaluate a drug's impact on the production of insulin, glucagon, and somatostatin without being confounded by changes to other organs thanks to in vitro perfusion of isolated pancreas.

Procedure: The rats utilised are male Wistar rats weighing 200-250g. The animals are continuously fed. The pancreas is harvested while being anaesthetized 50 mg/kg i.p. pentobarbital, is used. Once the pancreas is withdrawn at a rate of 1.74 ml/min, Krebs- Ringer bicarbonate buffer containing 2.1% bovine albumin and 5.6 mmol/l glucose is perfused into the body. At a pressure of roughly 100 mmHg, the perfusion fluid is injected while being held at a temperature of 37.5 oC. During 30 minutes, the perfusate is removed once per minute. Adding a test chemical after the first five minutes of perfusion and perfusion is continued until the fifteenth minute (conc. Of test compound being 0.05-0.5 mM). 5.5 mM and 16.6 mM of glucose are perfused at the 16th and 30th minutes, respectively. The samples are stored in a freezer at -20oC. The hormones somatostatin, glucagon, and insulin are estimated radioimmunologically. An absolute minimum of three tests are performed on each concentration. The effect of the test substance on the hormones released by the pancreas in response to high glucose levels is assessed in comparison to the control. [66]

Isolated Rat Pancreatic Islets

Procedure: The pancreas is given to two male Wistar rats, each weighing 200–250g while being administered. The anaesthetic pentobarbital is employed. The collagenase method is utilised to remove the islets seen stereomicroscopically. Up to 10 chambers, each holding a maximum of 15 islets, may be used in a test. Cut-off Perfusion chambers are created by securing microfuge tubes with Tuohy-Borst adapters. The adapter is used to put two Teflon catheters with small diameters and thick walls into the chamber. Both catheters extend to the adapter cone's bottom edge, with one reaching the base of the chamber and acting as an exit. A multichannel peristaltic pump connected to the latter moves the perfusate a fraction gatherer. The perfusate flow rate is 0.2 ml/min, and the chamber has a capacity of 0.15 ml. The Krebs- Ringer bicarbonate

buffer, Bovine albumin, 0.26% glucose, and 5.1 mmol/l theophylline make up the perfusate. A 37°C water bath is used to keep the chambers, intake catheters, and perfusate storage containers immersed. After an hour-long pre-perfusion phase, a 46-minute period of minute-by-minute perfusate collection occurs. From the second to The test substance is given between 0.1 and 2.5 mol/l at the 18th minute, and the glucose level rises to 20.1 mol/l from the 33rd to the 45th minute. Insulin determination is done using radio-immunological methods. As soon as an experiment is over, a choice is made. [67-70]

Modifications: Pancreatic islet free cell suspensions from mice have been tried where the response to glucose is lower than that of pristine, uninhabited islands. As a model for investigating long-term regulation of -cell function, adult rat islets of Langerhans were cultured in a monolayer for an extended period of time. [71-76]

Isolated Rat Liver

Procedure: Hexobarbital 149 mg/kg is administered to male Wistar rats weighing 200 to 250g. intravenously to induce anaesthesia before having their livers removed and being rinsed with physiological saline solution for three minutes at 37°C. Following that, The oxygenated medium is delivered by tubing that is attached to a portal vein cannula as the preparation is transported to the perfusion device. Krebs-ringer bicarbonate buffer, 1.6% bovine serum albumin, and 22.5 mmol/L Na-L-lactate are all used at a flow rate of 30 ml/min are perfused. For recirculation, 70 ml are eaten over the course of two hours. The test chemical is injected into a 40–100 mol/l concentration of the perfusate medium. A variable CO2/O2 combination is used for gassing, and the ratio used depends on the pH of the perfusate. Each minute, a 70 cc gas mixture is bubbled into the perfusate. A detergent must be added to the perfusate in order to prevent foam formation. The samples are obtained through catheter and used for analysis. [77-82]

Conclusions and considerations: Second, to validate the presence of antidiabetic activity in newly synthesized or discovered drugs that physicians use to treat hyperglycemia or increased diabetes, the antidiabetic properties of synthesized drugs It is imperative to examine In recent years, different antidiabetic drug screening models have been developed in different parts some of which are extremely nice and some of which are not, of the globe. Every model comes with its own setbacks and adaptations. This review's primary goal is to provide a summary of popular antidiabetic models. to investigate antidiabetic research. After research, we found that the above models are now widely used according to pharmaceutical needs. In vitro models are used less frequently than in vivo models. Our study shows that using in vitro and in vivo models together provides an opportunity to enhance the potency of the results, which can aid in finding better antidiabetic activity of new drug molecules.

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