REVIEW ARTICLE JPAR 2018

Journal of Pharmaceutical Advanced Research
(An International Multidisciplinary Peer Review Open Access monthly Journal)
Available online at: www.jparonline.com

Various models used to induce Diabetes: A comprehensive review

Bimala Tripathy[1]*, S. Satyanarayana[2], K. Abedulla Khan[3], K. Raja[4]

[1]St. Mary's Pharmacy College, Deshmukhi (V), Ramoji Film city, Greater Hyderabad - 508284, Telengana, India.
[2]Avanthi Institute of Pharmaceutical Sciences,Vizianagaram, Andhra Pradesh, India.
[3]Department of Clinical Pharmacy and Pharmacology, IBN Sina National College for Medical Studies, Al Mahjar, Jeddah-22421, K.S.A, India.
[4]Executive, Microbiology - QC, M/s. Jodas Expoim Private Ltd, Hyderabad, India.

Received: 17.03.2018 Revised: 23.03.2018 Accepted: 25.03.2018 Published: 31.03.2018

ABSTRACT: Diabetes mellitus is one of the most common endocrine metabolic disorders. It is a silent disease which damages the blood vessels – capable of leading to microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications. Animal models in diabetes research are very common where rats are the first choice of use, comprising over 85% of these models. In recent years, a various pharmacological agents, chemical agents, large number of new genetically modified animals, hormone induced DM, insulin antibodies-induced diabetes, diabetes induced by viral agents, surgically induced diabetes; genetic models have been conducted for the study of Type 1 diabetes mellitus for understanding the pathogenesis complications and its management. The animal models of Type 2 diabetes can be obtained either spontaneously or induced by chemical or dietary or surgical manipulations or by combination of that. Currently, large number of new genetically modified animal models include transgenic, generalized knockout and tissue specific knockout mice have been used for the study of diabetes.

Corresponding author*
Ms. Bimala Tripathy
St. Mary's Pharmacy College,
Deshmukhi (V), Ramoji Film city,
Greater Hyderabad - 508284,
Telengana, India.
E. Mail ID. bimalatripathy09@gmail.com
Tel. No. +919848245865.

Key words: Diabetes Mellitus, Insulin antibodies-induced diabetes, Transgenic and Knockout mice.

INTRODUCTIONS:

India is anticipated to be the diabetic capital of the world, with 50.8 million diabetics. Diabetes mellitus is a lifestyle disorder. It is an independent risk factor for the development of coronary artery disease, myocardial infarction, hypertension and dyslipidemia. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8 % in 2000 and 4.4 % in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The

ubiquity of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. For study details about diabetes *in vivo* and *in vitro* suitable models are used extensively. Rodents (Rat and mouse), guinea pig, rabbits, hamster are mostly used as experimental models. They are used for natural development of study. At present time easiest and rapid way to induce diabetes is with use of chemicals (Alloxan, Streptozotocin, Dithizone, Monosodium glutamates etc.), Hormone, Insulin Antibodies, Viruses, Surgically induced diabetes and genetic models are enormously used for diabetes study.

Various types of animal models of type 2 diabetes derived either spontaneously or induced by treating with chemicals or dietary or surgical manipulations and combination. Currently genetic engineering or molecular biological techniques including transgenic and knockout mice has used for diabetic research. Transgenic animals are suitable model for gaining proper knowledge about gene regulation and development, pathogenesis and discover new targets for treatment of different diseases and its complications [1-5].

TYPES OF DIABETES [4,5]:

Type-1 diabetes:

It is also called as Juvenile diabetes and insulin-dependent diabetes mellitus (IDDM). It results from the autoimmune destruction of the insulin-producing beta cells in the pancreas. Type 1 diabetes is a life-long condition that affects the body processes food and then turns it into energy. Pancreas stops producing insulin, a hormone that allows our body's cells to take in the glucose for energy. It's rare. Only about 5% to 10% of people with diabetes have type 1. It affects men and women equally. Although the disease usually starts in people under 20, it can happen at any age.

Type-2 diabetes:

It is also called as Insulin resistance, adult onset diabetes and Non- insulin dependent diabetes mellitus (NIDDM). It results from insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism. Type 2 diabetes makes up about 90 % of cases of diabetes. The primary cause is excessive body weight and not enough exercise.

Type- 3 diabetes:

It accurately reflects the fact that Alzheimer's disease (AD) represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 and type 2 DM and research also showed that AD was treatable with insulin sensitizing agents.

Type- 4 diabetes:

It is also called as gestational diabetes. It occurs when pregnant women without a previous history of diabetes develop high blood sugar levels. This type of diabetes is observed in approximately 4-5% of all pregnancies, due to placental hormones that promotes insulin resistance. Gestational diabetes usually resolves after the birth of the baby.

MODEL FOR INSULIN DEPENDENT DIABETES MELLITUS (IDDM):

Chemical causes diabetes:

Alloxan: Chemically induced type 1 diabetes is the most commonly used animal model of diabetes. Chemical agents specifically damage β-cell, cause temporary inhibition of insulin production and secretion and diminish the metabolic efficacy of insulin in target tissues. It is a cyclic urea analog, was the first agent which was reported to produce permanent diabetes in experimental animals such as rabbits, rats, mice and dogs with different grade of pathological alloxan dose was used severity [1]. Alloxan (2, 4, 5, 6 - tetraoxypyrimidine; 2, 4, 5, 6 - pyrimidinetetrone) is an organic compound. It is a beta cell toxic glucose analogue with a molecular shape similar to glucose, a very hydrophilic compound. Chemically instable in buffer solution with a half life of 1.5 min at pH 7.4 and at 37 ^{0}C decomposes to alloxanic acid. It stable at acid pH (0.01 M HCl).

It is a toxic thiol reagent, reduced to dialuric acid in the presence of GSH and other thiols. During redox cycling between alloxan and dialuric acid, new alloxan is formed continuously, so that toxic ROH species can be generated intracellular over a long time period (>1h). Phases of diabetes induction are alloxan induces triphasic blood glucose response when injected into experimental animals. The first phase is the transient hypoglycemic phase starts within very few minutes of alloxan injection administration. It is lasts maximum for 30 min [2,3]. This hypoglycemic response has been identified by stimulation of insulin secretion which

confirmed by an increase of the plasma insulin concentration [4]. The 2nd phase identify one hour after administration of alloxan leads to rise in blood glucose concentration. Furthermore, when the pancreatic beta cells come in contact with the alloxan toxin first hyperglycemic phase was identifying. The plasma insulin concentrations continuously decrease in this phase up to 2-4 h [5,6]. The 3rd phase is again producing a hypoglycemic condition after alloxan injection up to 4-8 h, which continuous for several hours. The concentration of insulin increase in circulation by alloxan-induced secretary granule and cell membrane rupture resulting in severe transitional hypoglycemia [7,8]. Mechanism of action of alloxan is a highly reactive molecule that is readily reduced to dialuric acid, which is then auto-oxidized back to alloxan resulting in the production of free radicals.

These free radicals damage the DNA of β-cells and cause cell death. Another mechanism proposed for alloxan is its ability to react with protein-bound sulfhydryl (-SH) groups, especially the membrane proteins like glucokinase on the β-cells, finally resulting in necrosis [9].

Streptozotocin (STZ): STZ is one diabetogenic agent inhibits insulin secretion and causes a state of insulin dependent diabetes mellitus by induce a selective necrosis of the pancreatic β cells [10]. STZ [2-deoxy-2-(3-methyl-3-nitrosourea) 1-D-glucopyranose] is a broad-spectrum antibiotics, which is produced from *Streptomyces achrmogen*.

It is a glucosamine derivative and is having cytotoxic methyl nitrosourea moiety attached to the glucose molecule. It is also one alkylating agent and hydrophilic in nature. Relatively stable at pH 7.4, temperature 37 ^{0}C [11]. The mechanism of action of STZ is attachment of the methyl nitrosourea moiety to the 2 carbon of glucose as a carrier molecule streptozotocin is selectively accumulated in pancreatic β- cell and become a β-cell toxic and causes alkylation of DNA. Further STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release which destroyed pancreatic β-cells by necrosis and finally induced insulin dependent diabetes [12,13].

Hormone-induced diabetes mellitus:

Growth hormone induced diabetes: The permanent diabetes produced by more prolonged administration of growth hormone, there was loss of pancreatic islet tissue and beta cells. Repeated administration of growth hormone in cats and adult dogs induces diabetes with all symptoms of diabetes including severe ketonuria and ketonemia [14].

Corticosteroid induced diabetes:

The hormones of the adrenal cortex are well known for their diabetogenic effects and are responsible for most steroid diabetes. The most common glucorticoids which cause steroid diabetes are dexamethasone and prednisolone. Glucocorticoids oppose insulin action and stimulate gluconeogenesis, especially in the liver, resulting in a net increase in hepatic glucose output and induce insulin resistance, hyperglycemia, and hyperlipidemia [15].

Insulin Antibodies-induced diabetes:

Administration of bovine insulin along with CFA (Complete Freund's adjuvant) to guinea pigs produces anti-insulin antibodies. Intravenous injection of 0.25-1.0 ml of guinea pig anti-insulin serum to rats induces a dose dependent increase in blood glucose levels up to 300 mg/dl. This unique effect to guinea pig anti-insulin serum is due to neutralization of endogenous insulin by the insulin antibodies. It persists as long as the antibodies are capable of reacting with insulin remaining in the circulation. Its effect is prolong for more than few hours when use slow i.v infusion or i.p injection. High doses and prolonged administration may lead to ketonemia, ketonurea, glycosuria and acidosis which are harmful to animals [16].

Surgically induced diabetes:

Induction of diabetes mellitus can be achieved through the surgical removal of all or part of the pancreas. Total removal of the pancreas results in an insulin dependent form of diabetes, and insulin therapy is required to maintain experimental animals. Researchers used this technique for evaluate the effect of medicinal plants with different animal species such as rats, rabbits, pigs, dogs and primates. By the help of this model 80% pancreatectomized rats is require to obtain mild to moderate hyperglycemia [17,18].

Diabetes induced by viral agents:

Various human viruses used for inducing diabetes include RNA picornoviruses, Coxsackie B4 (CB4), encephalomylocarditis 9EMC-D and M variants), Mengo-2T, as well as two other double stranded RNA viruses, reovirus and lymphocytic choriomeningitis virus (LMCV). These human pathogenic agents are must be

adapted for growth either by inoculation into suckling mice, or by passage in cultured mouse β-cells [19,20]. Viruses may produce diabetes mellitus by infecting and destroying of β-cells in pancreas, it produces damage to the β-cells by eliciting immune autoreactivity. Viruses not directly affect the β-cells but produce systemic effect. Currently proved that 2 viruses are reported first is D-variant of encephalomyocarditis (EMC-D) and another is Coxsackie virus, causes type 1 diabetes [21,22].

D-Variant Encephalomyocarditis:

EMC- D virus can infect and destroy pancreatic beta cells in certain inbred strains of mice and produce insulin dependent hyperglycemia. Pre-treatment with a potent immunosuppressive drug, cyclosporine-A increases severity and incidence of diabetes in ICR Swiss mice [23]. In 1992 Utsugi et al demonstrated the clone of EMC-D virus known as NDK25. Intraperitoneal injection of NDK25 develops non- insulin dependent diabetes mellitus [24].

Coxsackie Viruses:

Coxsackie viruses are also a possible cause of diabetes in mice; it can infect and destroy pancreatic acinar cells while leaving the adjacent islets of Langerhans intact. Coxsackie B4 virus is strongly associated with the development of insulin-dependent diabetes mellitus in humans. Diabetes induced by Coxsackie virus infection is a direct result of local infection leading to inflammation, tissue damage, and the release of sequestered islet antigen resulting in the re-stimulation of resting auto reactive T cells, further indicating that the islet antigen sensitization is an indirect consequence of the viral infection [25,26].

Genetic model:

NOD mouse: The most commonly used autoimmune models of type 1 diabetes are the non-obese diabetic (NOD) mouse and the Biobreeding (BB) rat. The NOD mouse was developed at the Shionogi Research Laboratories in Osaka, Japan in 1974. NOD mice develop insulitis at around 3–4 weeks of age. In this pre-diabetic stage, the pancreatic islets are infiltrated by predominately $CD4^+$ and $CD8^+$ lymphocytes, although B cells and NK cells are also present, which can develop up to 30 weeks of age. When these mice become overtly diabetic, they rapidly lose weight and require insulin treatment [27].

BB rats: BB rats were derived from out bred Wistar rats and they are usually developing diabetes just after puberty and have similar incidence in males and females. Around 90 % of rats develop diabetes between 8 and 16 weeks of age. The diabetic phenotype is quite severe, and the rats require insulin therapy for survival. Although the animals have insulitis with the presence of T cells, B cells, macrophages and NK cells, the animals are lymphopenic with a severe reduction in $CD4^+$ T cells and a near absence of $CD8^+$ T cells. Marked hyperglycemia, glycosuria, and weight loss occur within a day of onset and are associated with decreased plasma insulin that if untreated will result in ketoacidosis within several days [28].

MODEL FOR NON INSULIN DEPENDENT DIABETES MELLITUS (NIDDM):

The animal models of type 2 diabetes can be obtained either spontaneously or induced by chemicals or dietary or surgical manipulations or by combination of that. Currently, large number of new genetically modified animal models include transgenic, generalized knockout and tissue specific knockout mice have been used for the study of diabetes.

Chemically induced type 2 non obese models:

Alloxan and Streptozocin induced adult diabetic animals. Alloxan is a Uric acid derivative and is highly unstable in water at neutral pH, but reasonably stable at pH 3. Alloxan acts by selectively destroying the pancreatic islets leading to insulin deficiency, hyperglycaemia and kitosis [29]. The Alloxan [ALX) treated animal exhibit severe hyerglycaemia, glucosuria, hyperlipidaemia, polyphagia, polydypsia and also develop various complications such as neuropathy, cardiomyopathy, retinopathy and others [30]. Streptozotocin (STZ) is an antibiotic. Its nitrosourea moiety is responsible for beta cell toxicity, while deoxyglucose moiety facilitates transport across the cell membrane. STZ causing alkylation or breakage of DNA strands and a consequent increase in the activity of poly-ADP- ribose synthetase, an enzyme depleting NAD in beta cells finally lading to energy deprivation and death of beta cells and produce diabetes. STZ is more preferable than ALX [31-33].

Neonatal STZ diabetic rats: Single high dose of STZ injection, which can produce type-1 diabetes in adult rats, when STZ injected neonate age or immediately after birth, rats develop tye-2 diabetes in the adult age. Single dose of STZ injection range of 80-100 mg/kg (i.v./ i.p./ s.c.) to one or two or five days old wistar or

Sprague- Dawley neonatal rats has been reported to produce type-2 diabetic conditions. This model is one of the best model for understanding of the mechanism associated with regeneration of the beta cells and the function of cells and the emergence of defects in insulin action. Some investigators have also developed neonatal type-2 diabetic models by injecting ALX 200 mg/kg, i.p. to male neonatal rats at age of 2, 4 or 6 day after birth and it is useful for the investigation of long term complication of type-2 diabetes [34].

Surgical diabetic animals:

VMH lesioned dietary obese diabetic rats: This model has been developed by experimental surgical manipulation of genetically normal animals without the reduction in pancreatic beta cell mass resembling type-2 diabetes by combaining bilaterial electrolytelesion of VMH and feeding of high fat and high sucrose diets termed as VMH dietary obese rats [35]. It is characterized by marked obesity, hyperinsulinaemia, hypertriglyceridaemia, insulin resistance, impaired glucose tolerance, moderate to severe fasting hyperglycaemia and defective regulation of insulin secretory response despite extremely high insulin secretory capacity. Significant hyperphagia is observed despite increased leptin levels (leptin resistance) in these VMH lesioned rats.

Non obese partial pancreatectomized diabetic animals: Usually 90 % dissection of pancreas has been reported in various animal species mostly in dogs, pigs, rabbits, and also rats [36,37]. It does not cause severe form of diabetes. For better degree of glycaemia or stable form of diabetes for long duration can be achieved by the combination of pancreatectomy with chemicals like alloxan (ALX) and Streptozotocin (STZ) injection in animal such as dog, pig, monkey and others [38]. Currently, stable form type-2 diabetes has been produced by combination of 50 % partial pancreatectomy along with NAD (350 mg/kg) and STZ (200 mg/kg) treatment in BALB/c mice [39]. Advantage of this combination procedure as it minimizes the risk of unnecessary adverse effect of chemicals on body [40].

Transgenic and knockout animal model for type 2 diabetes:

Transgenic animals are generally helpful in giving proper knowledge about gene regulation and development, pathogenesis and finding new targets, treatment of disease and its complications. Especially mice are mostly used as transgenic animal model which created by transferring and altering the site or level of expression of functional gene (transgene) or by deleting specific endogenous genes (knockout) or changing its place under the control of alternate promoter regions [41]. The transgenic/knockout animal models of type 2 diabetes are used to study the role of genes and their effects on peripheral insulin action such as peroxisome proliferator activated receptor γ (PPAR-γ), tumour necrosis factor-α (TNF-α), insulin receptor, IRS-1, IRS-2, glucose transpoter (GLUT-4) along with insulin secretion such as GLUT-2, glucokinase (GK), islet amyloid polypeptide (IAPP) and GLP-1 and in hepatic glucose production (expression of PEPCK) associate with development of type -2 diabetes [42-45]. The transgenic/knockout animal models are recently used for the mechanistic study in diabetes research but it is more complicated and expensive model.

CONCLUSION:

Animal models of diabetes mellitus are regarded as very useful tool for studying many anti-diabetic drugs and research is going on for more effective drug discovery of antidiabetic drugs with new models and it may help to elucidate effects of medicinal plants employed in the treatment of diabetes mellitus. In this review research different models are used to induce diabetes along with their chemical properties and mechanism of action. Care must be taken in interpretation and extrapolation of the result obtained from these animal models to humans. For screening of anti-diabetic drugs some particular animal models are suitable to screen particular class of compounds.

ACKNOWLEDGEMENTS:

Authors wish to thanks their respective Institution for providing library facility to carry out this review study.

REFERENCES:

1. Iranloye BO, Arikawe AP, Rotimi G, Sogbade AO. Anti-diabetic and anti-oxidant effects of Zingiber officinale on alloxan-induced and insulin-resistant diabetic male rats. Niger J Physiol Sci, 2011; 26(1): 89-96.
2. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia, 2008; 51(2): 216-226.
3. Wrenshall GA, Williams CJ, Best CH, J. Initial changes in the blood sugar of the fasted anesthetized

dog after alloxan. Am J Physiol, 1950; 160: 228-246.
4. Kliber A, Szkudelski T, Chichłowska J. Alloxan stimulation and subsequent inhibition of insulin release from in situ perfused rat pancreas. J Physiol Pharmacol, 1996; 47(2): 321-328.
5. Goldner MG, Gomori G. Studies on the mechanism of alloxan diabetes. Endocrinol, 1944; 35: 241-248.
6. West E, Simon OR, Morrison EY. Streptozotocin alters pancreatic beta-cell responsiveness to glucose within six hours of injection into rats. West Indian Med J, 1996; 45(2): 60-62.
7. Tasaka Y, Inoue Y, Matsumoto H, Hirata Y. Changes in plasma glucagon, pancreatic polypeptide and insulin during development of alloxan diabetes mellitus in dog. Endocrinol Jpn, 1988; 35(3): 399-404.
8. Munday R. Dialuric acid autoxidation: Effects of transition metals on the reaction rate and on the generation of active oxygen species. Biochem Pharmacol, 1988; 37(3): 409-413.
9. Viana GS, Medeiros AS, Lacerda AM, Leal LK, Vale TG, Matos FG. Hypoglycemic and anti-lipemic effect of the aqueous extract from *Cissus sicyoides*. BMC Pharmacol Toxicol, 2004; 8: 4-9
10. Herr RR, Jahnke JK, Argoudelis AD. The structure of streptozotocin. J Am Chem Soc, 1967; 89(18): 4808-4809.
11. Rakieten N, Rakieten ML, Nadkarni MV. Studies on the diabetogenic action of Streptozotocin (NSC 37917). Cancer Chemother Rep, 1963; 29: 91-98.
12. Wang Z, Gleichmann H. GLUT2 in pancreatic islets: crucial target molecule in diabetes induced with multiple low doses of streptozotocin in mice. Diabetes, 1998; 47 (1): 50–56.
13. Schnedl WJ, Ferber S, Johnson JH, Newgard CB. STZ transport and cytotoxicity, Specific enhancement in GLUT2-expressing cells. Diabetes, 1994; 43(11): 1326–1333.
14. Wrenshall GA, Williams CJ, Best CH. Initial changes in the blood sugar of the fasted anesthetized dog after alloxan. Am J Physiol, 1950; 160: 228-246.
15. Heather A, Ferris C, Kahn R. New mechanisms of glucocorticoids-induced insulin resistance: make no bones about it. J Clin Invest, 2012; 122: 3854-3857.
16. Moloney PJ, Coval M. Antigenicity of insulin: diabetes-induced by specific antibodies. Biochem J, 1955: 59: 179-185.
17. Duff GL, Murray EGD. The pathology of the pancreas in experimental diabetes mellitus. Am J Med Sci, 1945; 210: 81-95.
18. Kaufmann F, Rodriguez RR. Subtotal pancreatectomy in five different rats strains incidence and course of development of diabetes. Diabetologia, 1984; 27: 38-43.
19. Yoon JW. The role of viruses and environmental factors in the induction of diabetes. Curr Top Microbiol Immunol, 1990; 164: 95-123.
20. Szopa TM, Titchener PA, Portwood ND, *et al*. Diabetes mellitus due to viruses-some recent developments. Diabetolgia, 1993; 36: 687-695.
21. Anturlikar SD, Gopumadhavan S, Chauhan BL and Mitra SK. Effect of D-400, a herbal formulation, on blood sugar of Normal and Alloxan- induced Diabetic Rats. Indian J Physiol Pharmacol, 1995; (39)2: 95-100.
22. Gamble DR, Kinsley ML, FitzGerald MG, Bolton R, Taylor KW. Viral antibodies in diabetes mellitus. Br Med J, 1969; 3(5671): 627-630.
23. Gould CL, McMannama KG, Bigley NJ, Giron DJ. Virus-induced murine diabetes Enhancement by immunosuppression. Diabetes, 1985; 34(12): 1217-1221.
24. Utsugi T, Kanda T, Tajima Y, Tomono S, Suzuki T, Murata K, *et al*. A new animal model of non-insulin-dependent diabetes mellitus induced by the NDK25 variant of encephalomyocarditis virus. Diabetes Res, 1992; 20(4): 109-119.
25. Lansdown AB, Brown JD. Immunization of mice against Coxsackie virus B3 and prevention of foetal growth retardation. Br J Exp Pathol, 1976; 57(5): 521-524.
26. Horwitz MS, Bradley LM, Harbertson J, Krahl T, Lee J, Sarvetnick N. Diabetes induced by Coxsackie virus: initiation by bystander damage and not molecular mimicry. Nat Med, 1998; 4(7): 781-785.
27. Leiter EH. NOD mice and related strains: origins, husbandry, and biology. In: Heiter EH, Atkinson MA, editors. Nod mice and related strains: Research Applications in Diabetes, AIDS, Cancer, and other Diseases. Austin: RG Landes; 1998. pp. 1-15.
28. Chappel Cl, Chappel WR. The discovery and the development of the BB rat colony; and animal

model of spontaneous diabetes mellitus. Metab Clin Exp, 1983; 32: 8-10.
29. Rerup CC. Dugsproducing diabetes through damage of the insulin secreting cells. Pharmacol Rev, 1970; 22: 485-518.
30. Battell ML, Yuen VG, Verma S, McNeil JH. Other models of type-1 diabetes. In: McNeil JH, editor. Experimental models of diabetes. Florida, USA: CRC Press LLC; 1999. pp. 219-229.
31. Ozturk Y, Atlan VM, Yildizoglu AN. Effects of experimental diabetes and insulin on smooth muscle functions. Pharmacol Rev, 1996; 48: 69-112.
32. Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin. Proc Soc Exp Biol Med, 1967; 126: 201-205
33. Ho E, Chen G, Bray TM. Alpha- phenyl-tert-butylnitrone (PBN) inhibits NF kappa B activation offering protection against hemically induced diabetes. Free Redical Biol Med, 2000; 28: 604-614
34. Kodama T, Iwase M, Maki Y, Yoshinari M, Fujishima M. A new diabetes model induced by neonatal alloxan treatment in rats. Diabetes Res Clin Pract, 1993; 20: 183-189.
35. Axen KV, Li X, Fung K, Sclafani A. The VMH-dietary obese rat: a new model of non-insulin-dependent-diabetes mellitus. Am J Physiol, 1994; 266 : R921-928.
36. McNeil JH. Experimental model of diabetes. Florida, USA: CRC Press LLC; 1999.
37. Ibanez CR, Meckes LM, Mellado CV. The hypoglycaemic effect *Opuntia streptocanthe* studied I different animal experimental models. J Ethnopharmacol, 1983; 7: 175-181.
38. Kurup S, Bhonde RR. Combained effect of nicotinamide and streptozotocin on diabetic status in partially pancreatectomized adult BALB/c mice. Horm Metab Res, 2000; 32: 330-334.
39. Risbud M, Bhonde PR. Models of pancreatic regeneration in diabetes. Diabetes Res Clin Pract, 2002; 58: 155-165.
40. Livingston J. Genetically engineered mice in drug development. J Intrn Med, 1999; 245: 627-635.
41. Kadowaki T. Insights in to insulin resistance and type-2 diabetes from knockout mouse models. J Clin Invest, 2000; 106: 459-465.
42. Gray SL, Dalla Nora E, Vidal-Puig AJ. Mouse model of PPAR-gamma deficiency: dissecting PPAR- gamma's role in metabolic homoeostasis. Biochem Soc Trans, 2005; 33: 1053-1058.
43. Butler AE, Jang J. Gurlo T, Carty MD, Soeller WC, Butler PC. Diabetes due to progressive defect in beta-cell mass in rats transgenic for human islets amyloid polypeptide (HIP Rat): a new model for type 2 diabetes. Diabetes, 2004; 53: 1509-1516.
44. Nandi A, Kitamura Y, Kahn CR, Accili D. Mouuse models of insulin resistance. Physiol Rev, 2004; 84: 623-647.
45. Plum L, Wunderlich FT, Baudler S, Krone W, Bruning JC. Transgenic and knockout mice in diabetes research novel insights into pathophysiology, limitations and perspectives. Physiol, 2005; 20: 152-161.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Tripathy B, *et al*. Various models used to induce Diabetes: A comprehensive review. J Pharm Adv Res, 2018; 1(2): 88-94.