WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Volume 3, Issue 2, 1150-1164. Review Article ISSN 2278 – 4357

ANIMAL MODELS OF HYPERTENSION, DIABETES AND DIABETIC HYPERTENSION: AN OVERVIEW

***GB Jadhav[1], RB Saudagar[1] and CD Upasani[2]**

[1]Department of Pharmacology, KCT's R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India, 422 213.

[2]Department of Pharmacology, SSDJ College of Pharmacy, Chandwad, Nashik, Maharashtra, India.

Article Received on
20 November 2013,
Revised on 26 December 2013,
Accepted on 28 January 2014

***Correspondence for Author:**
GB Jadhav,
Department of Pharmacology, KCT's R.G.Sapkal College of Pharmacy, Sapkal Knowledge Hub, Maharashtra, India.

ABSTRACT

Hypertension is the most common cardiovascular disease and is a major public health issue in developed as well as developing countries. Changes in human behavior and lifestyle over the last century have resulted in dramatic increase in the incidence of diabetes worldwide Hypertension is twice as prevalent in people with diabetes as in the general population. Both hypertension and diabetes are independent risk factors for micro vascular and macrovascular disease. There is need to search new techniques for evaluation of efficacy of new drugs on diabetic hypertension. The objective of the present review was to study various animal models of experimental induced diabetic hypertension in animals. Though there are some research papers and reviews available on the animal models of diabetic hypertension, the aim of this review, however, is highlight on overview on the currently available animal models of diabetic hypertension with respect to their origin/source, characteristic, advantages, and disadvantages in in human. Further, it especially deals with the appropriate selection and usefulness of different animal models in testing various classes of new chemical entities (NCEs) and other therapeutic modalities for the treatment of diabetic hypertension.

Keyword: Animal models, Diabetes, hypertension, DOCA, STZ.

INTRODUCTION

Hypertension is the most common cardiovascular disease and is a major public health issue in developed as well as developing countries [1]. In more than 95% of cases specific underlying

cause of hypertension is remain unknown, such patients are said to have essential hypertension. Changes in human behavior and lifestyle over the last century have resulted in dramatic increase in the incidence of diabetes worldwide [2]. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in 2025. Hyperglycemia and hyperlipidemia are important risk factors in the development of cardiovascular disease and metabolic disorders. [6]

It is estimated that 30% of the adult population may have arterial hypertension and that 30-60% of diabetic patients have associated hypertension [8].Hypertension is twice as prevalent in people with diabetes as in the general population. Both hypertension and diabetes are independent risk factors for micro vascular and macrovascular disease. Some of the factors which are thought to contribute to the genesis of hypertension in the diabetic patients are insulin resistance, hyperinsulinemia, kallikrein kinin system, rennin angiotensin aldosterone system and the sympathetic system[9]. There is a need to increase awareness of these facts among all health professionals involved in the care of hypertension and diabetes in developing countries, as well as health policy makers of these countries. Efforts at cost reduction should have the family as its focus as the largest share of costs is being borne by patients and their families and relieving the family of this financial burden needs to be prioritized. The Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have shown that strict control of hyperglycaemia reduces the incidence of diabetic micro-vascular disease[10].The economic and social costs of hypertension and diabetes are enormous, both for health care services and through loss of productivity. In developed countries, 10% or more of the total health budget is spent on the management of hypertension, diabetes and its complications.Generally, current therapeutic strategies for type 2 diabetes are limited and involve insulin and four main classes of oral antidiabetic agents that stimulate pancreatic insulin secretion (sulphonylureas and rapid-acting secretagogues/insulinotropics *e.g.*, glibenclamide,glipizide, rapaglinide), reduce hepatic glucose production (biguanides *e.g.*, metformin), delay digestion and absorption of intestinal carbohydrate (a-glucosidase inhibitors *e.g.*, acarbose) or improve insulin action [thiazolidinediones (TZDs) *e.g.*, pioglitazone, rosiglitazone]. number of serious adverse effects. Thus, there are wide variety of newer therapeutic agents/strategies being examined for the treatment of type 2 diabetes, most of all currently under preclinical and early clinical stages of drug development.

Though there are some research papers and reviews available on the animal models of diabetic hypertension.The aim of this review, however, is highlight on overview on the currently available animal models of diabetic hypertension with respect to their origin/source, characteristic, advantages, and disadvantages in in human. Further, it especially deals with the appropriate selection and usefulness of different animal models in testing various classes of new chemical entities (NCEs) and other therapeutic modalities for the treatment of diabetic hypertension.

ANIMAL MODELS OF DIABETIC HYPERTENSION [3, 4]

Hypertension and DM are common chronic condition, which frequently coexist and can significantly affect individual health care needs [12]. Hypertension and diabetes mellitus are known to occur simultaneously frequently [13]. Streptozotocin diabetic rats have long been used in laboratory to study the effects of antihypertensive agents on cardiac complications, hypertension and dyslipidaemia [15]. It has been reported that the antihypertensive agents prevent STZ indued hypertension in diabetic rat. Vasodilators like hydralazine, angiotensin converting enzyme inhibitors like enalapril and calcium channel blockers like nifedipine have been shown to prevent STZ induced cardiomyopathy, cardiac dysfunction and hyperlipidaemias[16]. It is also reported that STZ diabetic DOCA hypertensive rats may be a useful model for the clinical conditions in humans in which diabetes mellitus, hypertension and atherosclerosis can occur simultaneously [17]. Sevak and Goyal (1996) were studied the effect of chronic treatment with lisinopril on cardiovascular complications in STZ induced diabetes and DOCA induced hypertension in rats. Blood sampling by orbital puncture is a controversial technique. The puncture of the orbital venous plexus is often performed in tail-less animals, e.g. hamsters. This technique is also used in rats and mice, when larger volumes are required which cannot be obtained from the tail vein[18].

Antihypertensive Effect of Herbal Medicine

Numerous drugs from plants have also been used in the treatment of hypertension. The extract from root of *Solanum sisymbriifolium* (Solanaceae) produced a significant decrease in BP in anaesthetized hypertensive (adrenal regeneration hypertension + DOCA) rats[19].Vasorelaxant and antihypertensive effect of *Cocos nucifera* Linn. endocarp was studied on isolated rat thoracic aorta and DOCA salt induced hypertensive rats. Aqueous extract of the calyx of *Hibiscus sabdariffa* significantly exhibit antihypertensive effect on experimentally induced hypertension in laboratory animals[21].

The antihypertensive effect of a methanol extract of seeds of *Trigonella Fonenum-greacum* and its methanol fraction was studied in DOCA-salt-induced and fructose-induced hypertensive rats and exhibits a significant antihypertensive effect. Several herbal medicines were used for determining antihypertensive activity. The antihypertensive effects of the flavonoids extracted from *Spergularia purpurea* were studied both in normotensive rat (NTR) and spontaneously hypertensive rats (SHR) [22]. Antihypertensive effects of treatment with the aqueous extract of *Croton schiedeanus* was investigated in anaesthetized SHR[23].*Bidens pilosa* extract was able to prevent the establishment of hypertension and lower elevated blood pressure levels. The extract also reduced the highly elevated plasma insulin levels provoked by the high fructose diet. These results suggest that the leaf methanol extract of *Bidens pilosa* exerts its antihypertensive effect in partly by improving insulin sensitivity [24].Tetrandrine an alkaloid isolated from the Chinese herb Radix of *Stephaniae tetrandrae* was not only an anti-hypertensive drug but also an excellent drug to reverse cardiac and vascular remodeling[25].Treatment with Abana a polyherbal formulation (PHF) reduced the BP of unilaterally nephrectomized (UNF) DOCA salt-treated hypertensive rats[26].

ANIMAL MODELS OF HYPERTENSION

Mineralocorticoid Induced Hypertension (Endocrine Hypertension)

Mineralocorticoid-induced hypertension is thought to be due to the sodium retaining properties of the steroid causing increases in plasma and extracellular volume. The hypertensive effect is increased by salt loading and unilateral nephrectomy in rats [27].DOCA is an agent commonly used to induce hypertension in experimental animals [28].Hypertension induced by DOCA is due to retention of Na and water[29].was the first to demonstrate that DOCA produces hypertension in rats. There is increased DOCA-induced reabsorption of salt and water leading to increased blood volume and hence increased BP. There is also increased secretion of vasopressin leading to water retention and vasoconstriction. In addition, altered activity of Renin angiotensin- aldosterone system (RAAS) leads to increased sympathetic activity. Rats, especially female and young, are prone to DOCA-salt induced hypertension[29].This type of hypertension can also be produced in dogs and pigs. Other mineralocorticoids (*e.g.,* aldosterone) and glucocorticoids can also produce this type of hypertension[29]. DOCA induced hypertension is salt dependent since neither administration of DOCA nor partial removal of renal mass is effective in increasing BP when applied without salt administration[30].To produce hypertension, rats weighing about 100 g are kept on a diet high in sodium chloride and drinking water is replaced by 2% sodium chloride solution

ad libitum. After they attain a weight of about 250 g, they are given DOCA dissolved in sesame seed oil at a dose of 10 mg/kg, twice weekly for 43 days[33]. In another method, UNF is performed followed by DOCA administration[32].can be produced by the following methods: All operated rats receive an injection of ampicillin (10 mg/kg, i.m.) daily for 5 days and local application of Neosporin-H to prevent infection. A week later, DOCA (25 mg/kg/wk, s.c. for 5 wk) dissolved in cottonseed oil, is injected into nephrectomised rats. Alternatively, nephrectomised rats could receive DOCA from silicon rubber implants (200 mg/rat) implanted subcutaneously. NaCl (1.0%) solution is substituted for drinking water and given ad libitum[33].

Fructose Induced Hypertension

Insulin resistance and hyperinsulinemia are two metabolic defects that have been demonstrated to be frequently associated with both clinical and experimental hypertension[34].Increases in dietary carbohydrate intake can raise blood pressure in experimental animals. The increased intake of either sucrose or glucose was shown to enhance the development of either spontaneous hypertension or salt hypertension in rats[36].investigated the fructose-Induced Insulin resistance and hypertension in rats. The results indicate that metabolic changes associated with fructose-induced hypertension are unlikely to be secondary to an increase in sympathetic activity. [39].investigated the antihypertensive effects of *Dorstenia psilurus* extract in fructose-fed hyperinsulinemic, hypertensive rats. The results suggest that, *Dorstenia psilurus* treatment could prevent and reverse high blood pressure induced by a diet rich in fructose probably by improvement of plasma insulin levels[40].studied the concentration and duration-dependence of fructose-induced hypertension in rats. Insulin resistance has been documented in several models of experimental hypertension, including the fructose hypertensive rat[41]. Rodents fed sucrose or fructose-enriched diets can develop hypertension that is also related to insulin resistance and hyperinsulinemia[43].The fructose hypertensive rat model represents an acquired form of systolic hypertension, where in feeding normal wistar rats a fructose-enriched diet results in hyperinsulinemia, insulin resistance, hypertrygliceridemia and consequently hypertension[44].If these metabolic abnormalities were responsible for the development of hypertension, then drug interventions that combat or moderate these defects may also decrease high blood pressure.

Cadmium Induced Hypertension

Cadmium has been reported to be a possible risk factor of hypertension in experimental studies[45].It has been shown that cadmium produced hypertensive effect in rats following repeated exposure to cadmium (1 mg/kg, i.p; 5 days) caused hypertensive response in anesthetized rats.The specific mechanism responsible for cadmium produced hypertension has several hypothesis including an increase of Na retention, interaction with Ca channels, activation of sympathetic nervous system. It is also reported that sub chronic exposure to cadmium via drinking water for 3 months increased systolic blood pressure [46].Cadmium affects the heart and blood vessels causing cardiovascular disease such as hypertension and atherosclerosis[47].

Antidiabetic Effect of Herbal Medicine

There are many reports on the antidiabetic properties of plant compounds. Antidiabetic and antioxidant activity of some herbal medicinal plant *Swietenia mahagoni*, *Cynodon dactylon, Tectona grandis, Rumex patientia* were studied in Streptozotocin induced diabetic rats[49].Due to the enormous costs of modern treatment of diabetes in developing countries, the use of medicinal plants has substantially increased as an alternative for the control and prevention of diabetes complications.According to the World Health Organization (WHO) there are more than 1200 plant species used world wild in the treatment of diabetes mellitus and substantial number of plant showed effective hypoglycemic activity after laboratory testing[56].*Pterocarpus santalinus* showed a maximal blood glucose lowering effect in diabetic rats[59]. *Trigonella foenum-graecum* (Fenugreek) (Leguminosae) is employed as an herbal medicine for its antidiabetic effects[60].*Tinospora cordifolia* is widely used in Indian ayurvedic medicine for treating diabetes mellitus[60].Ethanolic extract prepared from the seed of *Vernonia anthelmintica* was evaluated for its antihyperglycemic activity in STZ induced diabetic rats[61].tested the antihyperglycemic and antioxidant effect of *Berberis aristata* in alloxan induced diabetic rats. Hypoglycemic medicinal plants (known and less known) have been selected for thorough studies from indigenous folk medicines, Ayurvedic, Unani and Siddha systems of medicines. In all the experiments with different herbal samples (vacuum dried 95% ethanolic extracts), definite blood glucose lowering effect within 2 weeks has been confirmed in alloxan diabetic albino rats. Blood glucose values are brought down close to normal fasting level using herbal samples at a dose of 250 mg/kg once, twice or thrice daily, as needed.

ANIMAL MODELS OF DIABETES MELLITUS

Diabetes can be induced by pharmacological, surgical or genetic manipulations in several animal species. Chemically induced models of diabetes are common in elucidating the possible role of environmental factors involved in the endocrine pancreatic destructive processes and subsequent development of diabetes. Rats are used for screening as well as for quantitative evaluation of blood glucose lowering agents[62]. Diabetes mellitus (DM) is a syndrome of impaired carbohydrate, fat, and, protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin[63]. Diabetogenesis in experimental animals is achieved by the chemical agents, who have been reported to exert an immediate toxic effect on the β -cells of the islets of Langerhans, which is followed by chronic not necessarily life-long diabetic state. These substances have also been referred to as β-cytotoxic substances or simply β-cytotoxins with the implication that the actions are restricted to the β -cells of the islets of Langerhans [64].

Streptozotocin Induced Diabetes

Experimental diabetes induced by streptozotocin has been used extensively to study the relationship between diabetes and autonomic cardiovascular dysfunction[65]. Streptozotocin (60 mg/kg) has been extensively used as diabetogenic drug. STZ destroys pancreatic β -cells resulting in a diabetic syndrome in animals similar to that seen in human type I diabetes characterized by hyperglycemia, hypoinsulinemia, glucosuria and loss in body weight[66]. Streptozotocin and Alloxan are toxic glucose analogues that preferentially accumulate in pancreatic β- cells via the GLUT2 glucose transporter and causes alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation, a process that is more important for the diabetogenicity of streptozotocin than DNA damage itself. Poly ADP-ribosylation leads to depletion of cellular NAD+ and ATP. Enhanced ATP dephosphorylation after streptozotocin treatment supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals. Consequently, hydrogen peroxide and hydroxyl radicals are also generated. Furthermore, streptozotocin liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage. As a result of the streptozotocin action, β-cells undergo the destruction by necrosis[68]. Streptozotocin, which was reported to be diabetogenic[69], appears to be comparable to alloxan with regard to islet β -cell specificity. Rakieten *et al*., (1963) reported the diabetogenic activity of the antibiotic streptozotocin. The compound turned out to be specifically cytotoxic to β -cells of the pancreas. Streptozotocin induces diabetes in the rat, dog, hamster, monkey, mouse, and Guinea pig. In the rat the

intravenous LD50 was estimated to be about 140 mg/kg. A single intravenous injection of 50 mg/kg was reported to yield 100% diabetes[69].Because of low stability of STZ the rapid intravenous injection appears to be the only dependable route of administration. The biological half-life of STZ was estimated to be about 5 min in mice. Streptozotocin diabetes in rat was described as a specific form of hyperglycemia with virtually no ketosis or elevations of plasma free fatty acids[70].The specificity of the streptozotocin with regard to the effect on the β -cell is striking and has been claimed to be greater than that of alloxan [71].

Alloxan Induced Diabetes

Alloxan monohydrate (150 mg/kg) has been extensively used as diabetogenic drug[68].Alloxan has two distinct pathological effects: it selectively inhibits glucose-induced insulin secretion through specific inhibition of glucokinase, the glucose sensor of the beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce ROS formation, resulting in the selective necrosis of β-cell. However alloxan diabetes has been produced after intravenous, intramuscular, intraperitoneal, subcutaneous, oral, enteral and intrapulmonary administration.In the normal nonfasted animals the blood glucose level fluctuates after a diabetogenic dose of alloxan in a characteristic way usually reported to be triphasic. The phases are: 1) an early, marked hyperglycemia of short duration (about 1 to 4 hr); 2) a more or less severe hypoglycemia lasting up to 48 hr and often resulting in convulsions and death, which may be prevented by treatment with glucose; 3) a chronic hyperglycemia of long, but not necessarily for life long duration, representing the alloxan diabetes. The triphasic pattern of blood glucose level fluctuations observed after diabetogenic doses of alloxan is also seen after Streptozotocin[71].The effect of STZ and alloxan has recently been compared under the same laboratory conditions in fed mice .It appeared that the initial hyperglycemia following STZ had a characteristic delay in onset of about 45-60 min. this delay was not observed in fasted mice but is also evident from experiments in rats [71]. Hypoglycemia was more severe with STZ than with alloxan, and accordingly fatal convulsions were more frequent in the former group of mice.

Fructose Induced Diabetes

Dietary fructose is a monosaccharide which can induce metabolic disorder including insulin resistance, hyperinsulinemia, hypertension and dyslipidemia which is of pathophysiological importance for the development of diabetes and atherosclerosis. Type 2 diabetic models by simply feeding high fat feed to nonobese; non diabetic mouse was initially developed in

Japan. It is characterized by marked obesity, hyperinsulinaemia, insulin resistance and glucose intolerance. These mice are demonstrated to develop peripheral leptin resistance. Fructose feeding was also found to cause insulin. resistance, hyperinsulinemia, and hypertriglyceridemia in normal rats. Cardiovascular dysfunction is associated with obesity and metabolic disorders which occur when animals are fed a high fructose or fat diet. A diet high in fructose may lead to insulin resistance, obesity hypertension and lipid abnormalities symptoms associated with type 2 diabetes [75].

CONCLUSION

The models discussed in this review are useful platforms on which basic science is translated into clinical medicine. One must remember that hypertension and diabetes may have the same phenotype in many patients, but their etiology and clinical course may differ significantly. Currently, the antihypertensive and antidiabetic drugs in use for long term therapy are found to be either decrease in responsiveness or associated with various toxicities owing to which the development process in drug discovery has shifted its focus to natural plant sources having minimal side effects Any of the animal models described apparently share similar characteristic features of diabetes and hypertension and have allowed experimentation that would be impossible in humans. In the screening programme of cardiovascular compounds, it is particularly important to note that some animal models are better suited to screen particular class of antihypertensive and antidiabetic compounds. Further, the selection of particular animal model is particularly depending on the investigator's choice whether to use inbred or outbreed, availability of particular strain, aim of scientific strategy, type of drug being sought, institutional financial and facility sources in the diabetic hypertension research and pharmaceutical drug discovery and development programme. Animal studies have focused on several mechanisms involved in hypertension/diabetes that remain to be translated into clinical medicine, including hypoxia, oxidative stress, and advanced glycation. Several target molecules have been identified that need to be incorporated into a treatment modality. The challenge continues to be the identification and interpretation of the clinical evidence from the animal models and their application to human treatment.

REFERENCES:

1. Guo X, Zou L, Zhang X, Zheng L, Sun Z. Prehypertension: A Metaanalysis of the epidemiology, risk factors, and predictors of progression. Tex Heart Inst J, 2011; 38(6): 643-52.

2. Bansal P, Paul P, Mudgal J, Nayak P, Pannakal ST, Priyadarsini KI. Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla in highfatdiet/streptozotocin induced diabetes in mice. Exp Toxicol Pathol, 2011.
3. Srinivasan K. Ramarao. P. Animal models in type 2 diabetes research: An overview Indian J Med Res 2007; 451-72.
4. Talma R., Younis F, and Alter A. Combating Combination of Hypertension and Diabetes in Different Rat Models. Pharmaceuticals 2010; 3: 916-.39.
5. Bankar GR, Nayak PG, Bansal P, Paul P, Pai KS, Singla R. Vasorelaxant and antihypertensive effect of Cocos nucifera Linn. endocarp on isolated rat thoracic aorta and DOCA salt-induced hypertensive rats. J Ethnopharmacol, 2011; 134: 50-4.
6. National Diabetes Data Group, Summary. In, National Diabetes Data group (ad), Diabetes in America, US Dept of Health and Human Services Publication 1985; 85: 1468l-86.
7. Rosen P, Nawroth PP, King G, Moller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a congress series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes Metab Res Rev 2001; 17: 189-212.
8. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2007; 30: 42-6.
9. American Diabetes Association. Diabetes Care in Specific Settings. Diabetes Care, 2011; 34 (1): 43
10. Chrysant SG, Chrysant GS. Current status of aggressive blood glucose and blood pressure control in diabetic hypertensive subjects. Am J Cardiol, 2011; 15:107(12): 1856-61.
11. Fuller J, Stevens LK, Chaturvedi N, Holloway JF. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes mellitus. Cochrane Database Syst Rev, 2007; 4: 2188-91.
12. Hudson BI, Hofmann MA, Bucciarelli L, Wendt T, Moser B, Lu Y. Glycation and diabetes: The RAGE connection. Curr Sci 2002; 83(12):1515-21.
13. Girard A, Madani S, Boukortt F, Cherkaoui M, Belleville J, Prost J. Fructose enriched diet modifies antioxidant status and lipid metabolism is spontaneously hypertensive rats. Nutrition 2006; 22:758-66.

14. National Diabetes Data Group, Summary. In, National Diabetes Data group (ad), Diabetes in America, US Dept of Health and Human Services Publication, 1985; 85: 1468l-86.
15. Hakim ZS, Goyal RK. Comparative evaluation of different rat models with coexisting diabetes mellitus and hypertension. Indian J Physiol Pharmacol 2000; 44: 125-35.
16. Van Zwieten PA. Diabetes and hypertension: experimental models for pharmacological studies. Clin Exp Hypertens 1999; 21(2): 1-16.
17. Rodrigues B, Goyal RK, McNeill JH. Efects of hydalzine on STZ induced diabeteic rats-prevention of hyperlipidemia and improvement in cardiac function. J Pharmac Expt Ther 1986; 237: 299-307.
18. Lakkad NB, Bangaru RA, Rao MV, Goyal RK. Studies on the chronic treatment with enalapril on diabetes induced cardiac depression and other complications. Pharmacol Rev Comm, 1996; 5: 11-5.
19. Hebden RA, Todd ME, tang C, Gowen B, McNeill JH. Association of DOCA hypertension with induction of atherosclerosis in rats with short term diabetes mellitus. Am J Physiol ,1990; 258: 1042-50.
20. Herck H, Baumans V, Van der NR, Hesp AP, Meijer GW, Van TG . Histological changes in the orbital region of rats after orbital puncture. Lab Anim,1992; 26: 53-8.
21. Ibarrola DA, Hellión-Ibarrola MC, Montalbetti Y, Heinichen O, Campuzano MA, Kennedy ML et al. Antihypertensive effect of nuatigenin-3-Ochacotriose from Solanum sisymbriifolium Lam. (Solanaceae) in experimentally hypertensive (ARH + DOCA) rats under chronic administration. Phytomedicine, 2011; 18: 634–40.
22. Bankar GR, Nayak PG, Bansal P, Paul P, Pai KS, Singla R. Vasorelaxant and antihypertensive effect of Cocos nucifera Linn. endocarp on isolated rat thoracic aorta and DOCA salt-induced hypertensive rats. J Ethnopharmacol ,2011; 134:50-4.
23. Mojiminiyi FB, Dikko M, Muhammad BY, Ojobor PD, Ajagbonna OP. Antihypertensive effect of an aqueous extract of the calyx of Hibiscus sabdariffa. Fitoterapia, 2007; 78(4): 292-97.
24. Jouad H, Lacaille-Dubois MA, Lyoussi B, Eddouks M. Effects of the flavonoids extracted from Spergularia purpurea Pers on arterial blood pressure and renal function in normal and hypertensive rats. J Ethnopharmacol, 2001; 76:159-63.
25. Guerrero MF, Carrona R, Martýna ML, San Romana L, Reguerob MT. Antihypertensive and vasorelaxant effects of aqueous extract from Croton schiedeanus schlecht in rats. J Ethnopharmacol, 2001; 75: 33-6.

26. Theophile D, Silvere V, Rakotonirina, Paul V, Tan, Jacqueline Azay, Etienne Dongo, Gerard Cros. Leaf methanol extract of Bidens pilosa prevents and attenuates the hypertension induced by high-fructose diet in wistar rats. J Ethnopharmacol, 2002; 83: 183-91.
27. RAO Man-Ren, Effects of tetrandrine on cardiac and vascular remodeling. Acta Pharmacol 2002; 23(12): 1075-85.
28. Balaraman R, Hingorani N, Rathod SP. Studies on the antihypertensive effect of abana in rats. Indian J Pharmacol, 1993; 25:209-14.
29. Vogel HG,Vogel WG, Scholkens BA, Sandow J, Muller G, Vogel WF. Drug Discovery and Evaluation-pharmacological assays. 2nd ed. Germany: Springer publication; 2002; 122-24.
30. Badyal DK, Lata H, Dadhich AP. Animal model of hypertension and effect of drugs. Indian J Pharmacol, 2003; 35: 349-62.
31. Dahl LK. Possible Role of Salt Inake in the Development of Essential Hypertension. In: Pork KD, Cottier PT, editors. Essential Hypertension-an international symposium. Berlin: Springer-Verlag; 1960; 53-65.
32. Seyle H, Bois P. The hormonal production of nephrosclerosis and periarteritis nodosa in the primate. Br Med J, 1957; 1:183-86.
33. Bopanna KN, Kannan J, Sushma G, Balaraman R, Rathod SP. Antidiabetic and antihyperlipidemic effect of neem seed, kernel powder on alloxan diabetic rabbits. Indian J Pharmacol, 1997; 29: 162-67.
34. Katholi RE, Naftilan AJ, Oparil S. Importance of renal sympathetic tone in the development of DOCA-salt hypertension in the rat. Hypertens, 1980; 2:266-73.
35. Rathod SP, Shah N, Balaraman R. Antihypertensive effect of dietary calcium and diltiazem chennel blocker on experimentally induced hypertensive rats. Indian J Pharmacol, 1997; 29: 141-46.
36. Girard A, Madani S, Boukortt F, Cherkaoui M, Belleville J, Prost J. Fructose enriched diet modifies antioxidant status and lipid metabolism in spontaneously hypertensive rats. Nutrition, 2006; 22: 758-66.
37. Verma S, Bhanot S, McNeill JH. Antihypertensive effects of metformin in fructose-fed hyperinsulinemic, hypertensive rats. J Pharmacol Exp Ther, 1994; 271(3): 1334-37.
38. Hall CE, Hall O. Comparative effectiveness of glucose and sucrose in enhancement of hyper alimentation and salt hypertension. Proc Soc Expe Biol Med, 1966; 123: 370-74.

39. eFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care, 1991; 14: 173-94.
40. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose induced insulin resistance and hypertension in rats. Hypertens, 1987; 10: 512-16.
41. Dimo T, Rakotonirina A, Tan PV, Dongo E, Dongmo AB, Kamtchouing P. Antihypertensive effects of Dorstenia psilurus extract in fructose-fed hyperinsulinemic, hypertensive rats. Phytomedicine ,2001; 8(2): 101-06.
42. Dai S, McNeill JH. Fructose-induced hypertension in rats is concentration and duration-dependent. J Pharmacol Tox Meth, 1995; 33: 101-07.
43. Bourgoin F, Bachelard H, Badeau M, Melancon S, Pitre M, Lariviere R, et al. Endothelial and vascular dysfunction and insulin resisitance in rats fed a high fat, high sucrose diet. Am J Physiol Heart Circ Physiol, 2008; 295 (3): H1044-55.
44. Bhanot S, McNeill JH, Bryer-Ash M. Vanadyl sulphate prevents fructose induced hyperinsulinemia and hypertension in rats. Hypertens, 1994; 23: 308-12.
45. Fang TC, Huang WC. Role of angiotensin II in hyperinsulinemia-induced hypertension in rats. J Hypertens, 1998; 16: 1767-74.
46. Verma S, Bhanot S, McNeill JH. Antihypertensive effects of metformin in fructose-fed hyperinsulinemic, hypertensive rats. J Pharmacol Exp Ther, 1994; 271(3): 1334-37.
47. Sompamit K, Kukongviriyapan U, Donpunha W, Nakmareong S, Kukongviriyapan V. Reversal of cadmium-induced vascular dysfunction and oxidative stress by meso-2, 3-dimercaptosuccinic acid in mice. Toxicol Lett, 2010; 198: 77-82.
48. Yoopan N, Wongsawatkul O, Watcharasit P, Piyachaturawat, P, Satayavivad J. Contribution of cholinergic muscarinic functions in cadmium induced hypertension in rats. Toxicol Lett, 2006; 164: S155.
49. Varoni MV, Palomba D, Gianorso S, Anania V. Cadmium as an environmental factor of hypertension in animals: new perspectives on mechanisms. Vet Res Commun, 2003, 27: 807-10.
50. Meijer GW, Beems RB, Janssen GB, Vaessen HA, Speijers GJ. Cadmium and atherosclerosis in the rabbit: reduced atherogenesis by superseding of iron. Food Chem Toxicol ,1996; 34: 611-21.
51. Panda SP, Haldar PK, Bera S, Adhikary S, Kandar CC. Antidiabetic and antioxidant activity of Swietenia mahagoni in streptozotocin-induced diabetic rats. Pharm Biol, 2010; 49(2) :974-79.

52. Singh SK, Kesari AN, Gupta RK, Jaiswal D, Watal G. Assessment of antidiabetic potential of Cynodon dactylon extract in streptozotocin diabetic rats. J Ethnopharmacol, 2007; 114(2) :174-79.
53. Storz G, Imlay JA. Oxidative stress. Curr Opin Microbiol, 1999; 2: 188-94.
54. Subramaniam R, Aiyalu R, Manisenthil KT. Antidiabetic, antihyperlipidemic and antioxidant potential of methanol extract of Tectona grandis flowers in streptozotocin induced diabetic rats. Asian Pac J Trop Med, 2011; 4(8): 624-31.
55. Sedaghat R, Roghani M, Ahmadi M, Ahmadi F. Antihyperglycemic and antihyperlipidemic effect of Rumex patientia seed preparation in Streptozotocin diabetic rats. Pathophysiology, 2011; 18: 111-15.
56. Grover JK, Yadav S, Vats V. Medicinal plants of India with antidiabetic potential. J. Ethnopharmacol, 2002; 81: 81-100.
57. Luo J, Fort DM, Carlson TJ, Noamesi BK, Nii-Amon-Kotei D, King SR. Cryptolepis sanguinolenta: an ethno botanical approach to drug discovery and the isolation of a potentially useful new antihyperglycaemic agent. Diabet Med, 1998; 15: 367-74.
58. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. Phytomedecine, 1995; 7-189.
59. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. Phytomedicine 1995; 2: 137–89.
60. Kameswara B, Giri MM, Kesavulu CH. Effect of oral administration of bark extracts of Pterocarpus santalinus L. on blood glucose level in experimental animals. J Ethnopharmacol, 2001; 74: 69-74.
61. Tayyaba Z, Nazrul Hasnain S, Hasan SK. Evaluation of the oral hypoglycaemic effect of Trigonella foenum-graecum L.(methi) in normal mice. J Ethnopharmacol, 2001; 75: 191-95.
62. Stanely P, Mainzen P, Venugopal P, Menon. Hypoglycaemic and other related actions of Tinospora cordifolia roots in alloxan-induced diabetic rats. J Ethnopharmacol,, 2000; 70: 9-15.
63. Fatima SS, Rajasekhar MD, Kumar KV, Kumar MT, Babu KR, Rao CA. Antidiabetic and antihyperlipidemic activity of ethyl acetate Isopropanol (1:1) fraction of Vernonia anthelmintica seeds in Streptozotocin induced diabetic rats. Food Chem Toxicol, 2010; 48: 495-501
64. Gill AM, Yen TT. Effects of ciglitazone on endogenous plasma islet amyloid polypeptide and insulin sensitivity in obese-diabetic viable yellow mice. Life Sci ,1991; 48: 703-10.

65. Guyton AC, Hall JE. Insulin, glucagon and diabetes mellitus In: Textbook of Medical Physiology. 11th ed. Philadelphia, Pennsylvania: Saunders and Imprint of Elsevier; 2006; 961-76.
66. Rerup C, Trading F. Streptozotocin and alloxan diabetes in mice. Eur J Pharmacol ,1969; 7: 89.
67. Angelis KD, Irigoyen MA, Morris M. Diabetes and cardiovascular autonomic dysfunction: application of animal models. Auton Neurosci, 2009; 145: 3-100.
68. Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin, Relationship of dose to metabolic syndrome. J Clin Invest,1969; 48(11): 2129-39.
69. Tomlinson KC. Gardiner SM, Hebden RA, Bennett T. Functional consequences of streptozotocin induced diabetes mellitus with particular reference to the cardiovascular system. Pharmacol Rev, 1992; 44: 103-79.
70. Szkudelski T. The mechanism of alloxan and streptozotocin action in β-cells of the rat pancreas. Physiol Res, 2001; 50: 536-46.
71. Rakieten N, Rakieten ML, Nadkarni MV. Studies on the diabetogenicaction of Streptozotocin (NSC-37917). Cancer Chemother, 1963; 29: 91-102.
72. Mansford KR, Opie L.Comparison of metabolic abnormalities in diabetes mellitus induced by streptozotocin or by alloxan. Lancet, 1968; 1: 670.
73. Junod A, Lambert AE, Orci L, Pictet R, Gonet AE, Renold AE. Studies of diabetogenic action of streptozotocin. Proc Soc Exp Biol Med, 1967; 126: 201-205.
74. Szkudelski T. The mechanism of alloxan and streptozotocin action in β-cells of the rat pancreas. Physiol Res, 2001; 50: 536-46.
75. Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin, Relationship of dose to metabolic syndrome. J Clin Invest, 1969; 48(11): 2129-39.
76. Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose fed rats. Metabolism of insulin resistance in fructose fed rats. Metabolism, 1982; 31: 608-12.
77. Basciano H, Federico L, Adeli K. Fructose, insulin resistance and metabolic dyslipidemia. Nutr Metab, 2005; 2: 5-20.