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R E S E A E C H A R T I C L E

Pharmacological Screening of PremnaLatifolia against High Fructose Diet Induced Insulin Resistance, Hyperlipidemia and Obesity in Male Wistar Rats

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A B S T R A C T

Insulin is a natural hormone made by the pancreas that controls the level of the sugar glucose in the blood. Insulin permits cells to use glucose for energy. Cells cannot utilize glucose without insulin. Insulin stops the use of fat as an energy source by inhibiting the release of glucagon. With the exception of the metabolic disorder diabetes mellitus and Metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When control of insulin levels fails, diabetes mellitus will result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type 2 diabetes are often insulin resistant and, because of such resistance, may suffer from a "relative" insulin deficiency. These findings investigated that the insulin resistance has been increased in the diabetic control group when compared to the control groups, as insulin resistance index is high in diabetic control group, in all other groups the insulin resistance index is decreased when compared with diabetic control so insulin resistance is decreased. The lipid profile was significantly increased in diabetic control group when compared to the control group and in all others groups the levels were decreased. but the HDL level was decreased in diabetic control group and increased in all others groups. The body weight of the animals was increased in the diabetic control group and the increase was very high. when compared to all other groups.

Keywords: Diabetic control, Insulin, Diabetes mellitus, Metabolic syndrome

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C O N T E N T S

1. Introduction

Insulin: Insulin is a natural hormone made by the pancreas that controls the level of the sugar glucose in the blood. Insulin permits cells to use glucose for energy. Cells cannot utilize glucose without insulin. Insulin is a hormone central, to regulate carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. Insulin stops the use of fat as an energy source by inhibiting the release of glucagon. With the exception of the metabolic disorder diabetes mellitus and Metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level, the body begins to use fat as an energy source through glycogenolysis, for example, by transfer of lipids from adipose tissue to the liver for mobilization as an energy source. As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body. When control of insulin levels fails, diabetes mellitus will result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type 2 diabetes are often insulin resistant and, because of such resistance, may suffer from a "relative" insulin deficiency. Some patients with type 2 diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately. Over 40% of those with Type 2 diabetes require insulin as part of their diabetes management plan.

Insulin resistance

Insulin resistance is a metabolic disorder whose prevalence is increasing alarmingly in populations worldwide. It is a condition wherein the body tissues become resistant to insulin, resulting in a marked decrease of glucose metabolism in response to insulin. Recent studies suggest that insulin resistance results from complex interactions between genetic and environmental factors and is associated with common diseases such as type 2 diabetes, hypertension, obesity, and coronary heart disease (Grundy, 2007).Insulin resistance in muscle and fat cells reduces glucose uptake (and also local storage of glucose as glycogen and triglycerides, respectively), whereas insulin resistance in liver cells results in reduced glycogen synthesis and storage and a failure to suppress glucose production and release into the blood.

Insulin resistance normally refers to reduced glucose-lowering effects of insulin. However, other functions of insulin can also be affected. For example, insulin resistance in fat cells reduces the normal effects of insulin on lipids and results in reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Elevated blood fatty-acid concentrations (associated with insulin resistance and diabetes mellitus Type 2), reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose levels. High plasma levels of insulin and glucose due to insulin resistance are a major component of the metabolic syndrome. If insulin resistance exists, more insulin needs to be secreted by the pancreas. If this compensatory increase does not occur, blood glucose concentrations increase and type 2 diabetes occurs. Insulin resistance is a major metabolic feature of obesity and is a key factor in the etiology of a number of diseases, including type 2 diabetes. In this review, we discuss potential mechanisms by which brief nutrient excess and obesity lead to insulin resistance and propose that these mechanisms of action are different but interrelated. We discuss how pathways that “sense” nutrients within skeletal muscle are readily able to regulate insulin action. We then discus show obesity leads to insulin resistance via a complex interplay among systemic fatty acid excess, micro hypoxia in adipose tissue, ER stress, and inflammation. In particular, we focus on the hypothesis that the macrophage is an important cell type in the propagation of inflammation and induction of insulin resistance in obesity. Overall, we provide our integrative perspective regarding how nutrients and obesity interact to regulate insulin sensitivity.

Inflammation: a link between obesity and insulin resistance

Many lines of evidence have shown that chronic activation of proinflammatory pathways within insulin target cells can lead to obesity-related insulin resistance. Consistent with this, elevated levels of the proinflammatory cytokines TNF-α, IL-6, and C-reactive protein (CRP) have been shown in individuals with insulin resistance and diabetes. Furthermore, TNF-α levels are elevated in adipose tissue and blood from obese rodents, and neutralization of TNF-α improves insulin sensitivity in these animals (Hotamisligil et al.,2000). As discussed below, fatty acids, microhypoxia in adipose tissue, ER stress, and certain cytokines can all initiate proinflammatory responses by activating the JNK/activator protein 1 (AP1) and IKK/NF-κB signaling pathways. JNK (Hirosumi et al., 2002, Bandyopadhyay 2000) and IKK (Yuan et al., 2001, Cai et al., 2005) signaling are upregulated and activated in insulin-resistant human and rodent skeletal muscle. This is important, as these serine kinases phosphorylate the transcription factor targets AP1 (c-Jun/Fos) and NF-κB, which then transcriptionally activate an overlapping set of inflammatory pathway genes (Karin et al., 2001), ultimately leading to decreased insulin sensitivity. Accordingly, KO or inhibition of JNK1 or IKKβ prevents insulin resistance in cell and mouse models (Hirosumi et al., 2002, Yuan et al., 2001, Arkan et al., 2005, Cai et al., 2005, Solinas et al., 2007) as well as human models (Hundal et al., 2002) of insulin resistance.

An important initiator of this inflammatory response is adipose tissue, which is not only a storage depot for excess calories but also actively secretes fatty acids and a variety of polypeptides. These peptides include hormones, cytokines, and chemokines that can function in both an

endocrine or paracrine fashion. The adipose tissue itself consists of a variety of cell types including adipocytes, immune cells (macrophages and lymphocytes), preadipocytes, and endothelial cells, etc. Several cytokines and chemokines, such as CCL2, IL-6, IL-1β, macrophage migration inhibitory factor (MIF), and TNF-α, can be released by adipocytes and macrophages. Adipocytes are the unique source of secreted adipokines such as leptin and adiponectin, which can promote insulin sensitivity, as well as resistin and retinol-binding protein 4 (RBP4), which can impair insulin sensitivity. Thus, the mixture of adipokines secreted by adipose tissue in a given pathophysiologic state can have important effects on systemic insulin sensitivity. However, a detailed description of these various adipokines and their actions is beyond the constraints of this review, and the reader is directed to other recent reviews on this subject. The events that potentially link obesity to the initiation and propagation of inflammation and that subsequently link inflammation to the induction of tissue and systemic insulin resistance are detailed below and are illustrated in Figure 1.

2. Results and Discussions

Results

The present study results shows the increased level of blood glucose, in diabetic control group when compared to control ,all other groups treated with P.latifolia and Pioglitazone reduced the blood glucose level when compare with diabetic control as shown in fig 2 and tab 1 .

Insulin resistance index was increased in diabetic control group when compared to control ,all other groups treated with P.latifolia and Pioglitazone reduced the Insulin resistance index when compare with diabetic control as shown in and tab 2 .

Lipid profile was increased in diabetic control group when compared to control, all other groups treated with P.latifolia and Pioglitazone reduced the Lipid profile when compare with diabetic control as shown in and tab 3 .

The body weight was also increased in all the groups when compared with the initial weight, but the increase is very high in the diabetic control group when compared to all other groups as shown in tab 5.

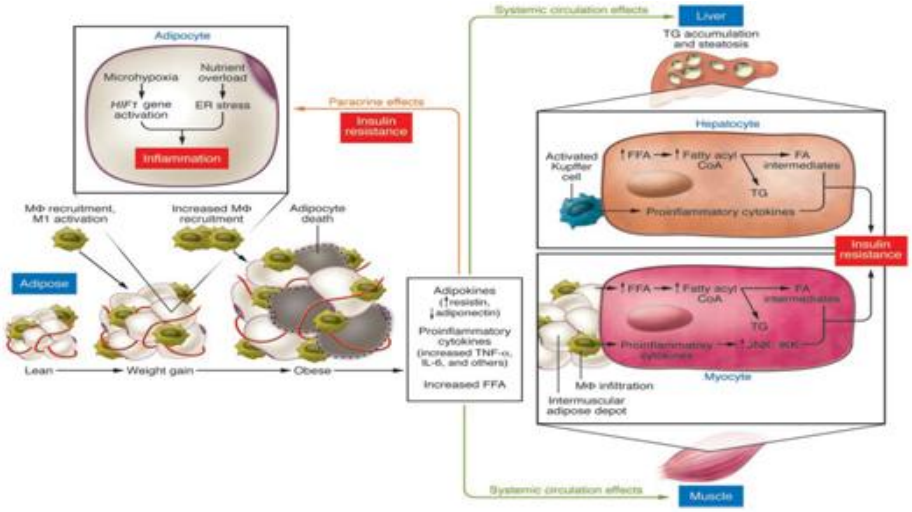

Fig 1: Obesity, tissue inflammation, and insulin resistance

Table 1: Blood glucose level in control, diabetic and *premna latifolia* treated groups

Groups	0th day	24th day	44th day	82th day	MEAN±SD
Control	83	83.16	85.5	87	85±1.9
Diabetic control	85	136.66	157.66	179	140±40*
Treatment I	84	141.66	134.66	113	118±26^{ns}
Treatment II	83	134.16	118.16	101	109±22^{ns}
Standard	82	136	110.5	89	104±24^{ns}

Table 2: Insulin levels and insulin index in control, diabetic and premna latifolia treated groups

Parameter	Control	Diabetic control	Treatment I	Treatment II	Standard
Insulin	21 ± 3.9	65 ± 12	49 ± 10	28 ± 4.8	30 ± 7.6
Insulin index	4.38	22.24	14.14	7.46	7.6

Table 3:lipid profiles of control, diabetic and premna latifolia treated groups

Parameters	Control	Diabetic control	Treatment I	Treatment II	Standard
Cholesterol	44±14	70±16**	53±8.6^{ns}	48±12^{ns}	46±4.3^{ns}
HDL	12±1.8	14±6.9^{ns}	15±6.2^{ns}	17±4.8^{ns}	14±7.6^{ns}

LDL	11±2.8	27±13***	21±1.4*	18±3.9^{ns}	16±5.4^{ns}
Triglycerides	50±6.5	129±16***	100±32***	70±19^{ns}	60±7.9^{ns}

All treatment groups were compared with diabetic control group, data was expressed Mean±SD (n=6). The significance between two groups was determined by one way ANOVA , followed by Dunnett multiple comparision, *p<0.05, **p<0.01, ***p<0.001.

Table 4: SGPT and SGOT values of control, diabetic and premna latifolia treated groups

Parameters	Control	Diabetic control	Treatment I	Treatment II	Standard
SGPT	46±3.9	90±19***	65±3.2*	61±6^{ns}	56±7.8^{ns}
SGOT	43±5.3	87±4.3***	75±6.5***	66±6.1***	55±4.3**

Table 5: Body weight of control, diabetic and premna latifolia treated groups

Body weight	control	Diabetic control	Treatment I	Treatment II	Standard
Initial	219±10	202±31	205±14	210±7.5	190±18
Final	220±16	288±40	240±18	232±15	223±14

Discussion

Premna latifolia significantly decreases glucose level in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test *p<0.05(vs. DC).

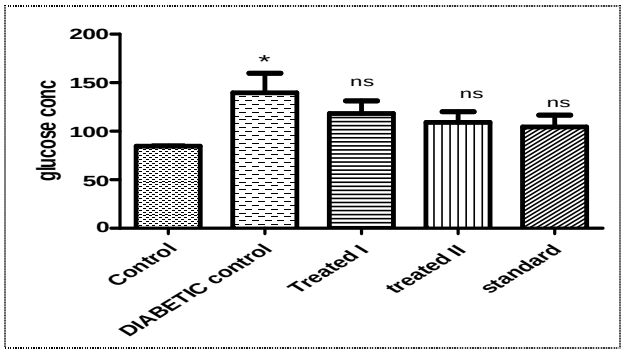

Fig 2: Blood glucose level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly decreases cholesterol level in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test **p<0.01(vs. DC).

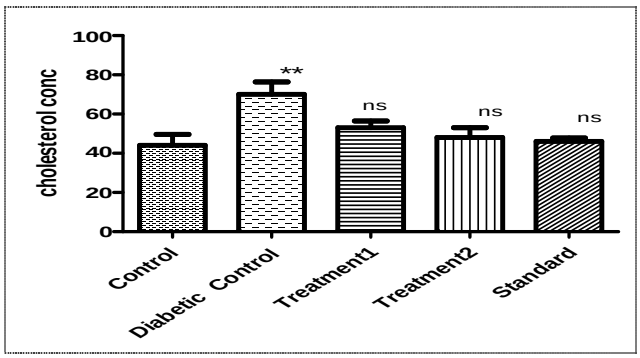

Fig 3: Cholesterol level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly increases HDL level in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test.

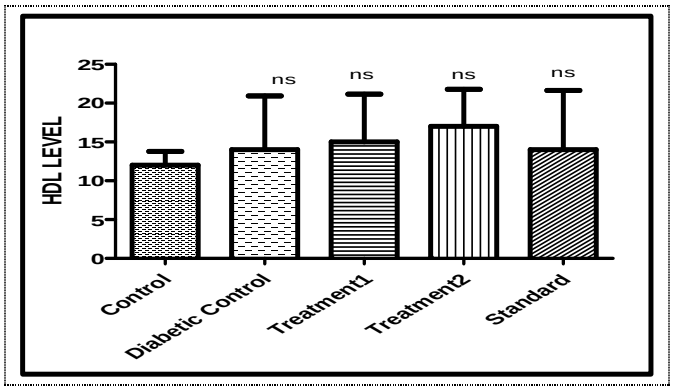

Fig 4: HDL level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly decreases Triglyceride level in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test ***P<0.001(vs.DC), ***P<0.001(vs.T1).

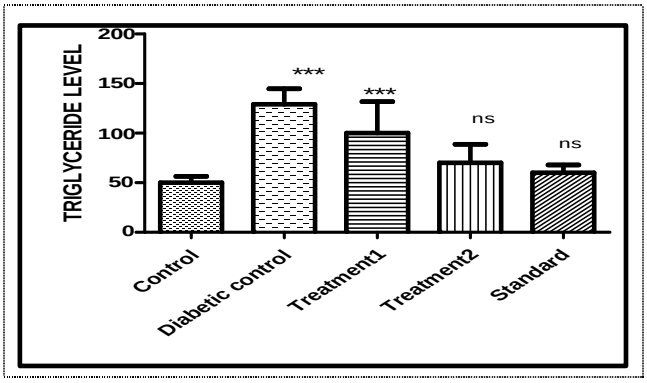

Fig 5: Triglyceride level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly decreases LDL level in treated groups when compare to diabetic control group. The

data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test ***P<0.001(vs.DC), *P<0.05(vs.T1).

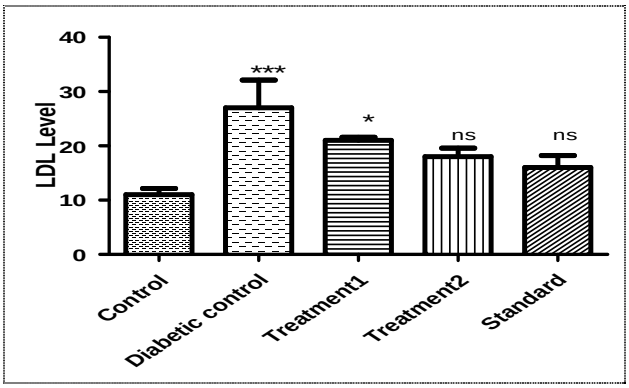

Fig 6: LDL level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly decreases SGOT Value in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test***P<0.001(vs.DC), ***P<0.001(vs.T1) ***P<0.001(vs.T2), **P<0.01(vs.S).

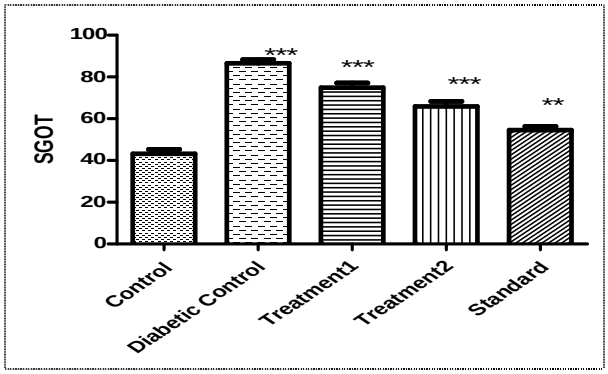

Fig 7: SGOT level in control, diabetic and premna latifolia treated groups

Premna latifolia significantly decreases SGPT Value in treated groups when compare to diabetic control group. The data was expressed as mean ± SD, (n=6) and evaluated by ANOVA followed by Dunnett test ***P<0.001(VS.DC), *P<0.05(VS.T1).

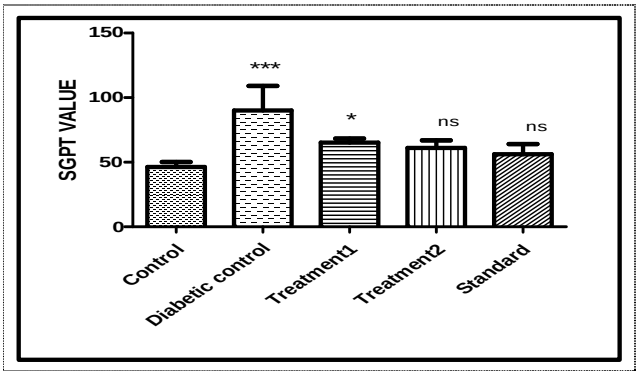

Fig 8:SGPT level in control, diabetic and premna latifolia treated groups

DPPH Assay:

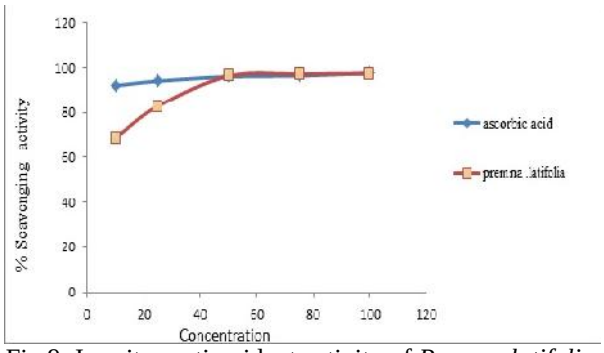

Fig 9: In- vitro anti oxidant activity of *Premna latifolia* compared with ascorbic acid

Tabel 6: % scavengering activity of ascorbic acid and premna latifolia

Concentration	% scavenging activity	
	Ascorbic acid	Premna latifolia
10	92.12	68.79
25	94.09	82.88
50	96.06	96.34
75	96.45	97.2
100	97.63	97.4
IC_{50}	75.5	77.14

3. Conclusion

These findings investigated that the insulin resistance has been increased in the diabetic control group when compared to the control groups, as insulin resistance index is high in diabetic control group, in all other groups the insulin resistance index is decreased when compared with diabetic control so insulin resistance is decreased. The lipid profile was significantly increased in diabetic control group when compared to the control group and in all others groups the levels were decreased. but the HDL level was decreased in diabetic control group and increased in all others groups. The body weight of the animals was increased in the diabetic control group and the increase was very high. when compared to all other groups. The above study as per literature review and preliminary phytochemical screening we conclude levels were significantly increased in diabetic control group and in the treated groups they were decreased due to the presence of flavonoids, pohyphenols, and alkaloids. So further investigation is needed for which chemical constituents were responsible for this activity.

4. References

[1] Wound Healing Activity Of Premna Latifolia Roxb- Garima Pandey- British Journal Of Pharmaceutical Research, Sciencedomain International4(8): 929-942, 2014.

[2] Ahmed saber Abu zaiton, Anti diabetic activity of Ferula assafoetida Extract in normal and alloxan – induced diabetic rats, Pakisthan journal of biological sciences, 2010;13(2): 97- 100.

[3] Amitai Elkayam, David Mirelman, The Effects of Allicin and Enalapril in Fructose-Induced

Hyperinsulinemic Hyperlipidemic Hypertensive Rats, AJH–April ,2001 ;14(4): 1.

[4] Aniagu et al., Toxicity studies in rats fed nature cure bitters, African Journal of Biotechnology, 2005;4 (1): 72-78.

[5] Bakoma B. et al Preventive Effects of Bridelia ferruginea against High–fructose diet induced glucose intolerance, oxidative stress and hyperlipidemia in male wistar rats. Journal of pharmacology and toxicology,2005; 6(3): 249 – 257.

[6] Bin Li et al, The butyrylcholinesterase knockout mouse is obese on a high fat diet. Chemico biological interactions, (2008);175: 88 – 91.

[7] Bolkent S. et al, Protective role of Melissa officinalis L.extract on liver of hyperlipidmic rats: A morphological and biochemical study. Journal of Ethnopharmacology ,(2005);99: 391 – 398.

[8] Chen Li, et al. , Effects of Persimmon Leaf Total Flavonoid on Enzyme of Lipoprotein Metabolism and Antioxidation in Hyperlipidemia Rats, Chinese Journal of Natural Medicines, 2011; 9(1): 74−77.

[9] Chidambaram, J. A. Carani Venkatraman, Cissus quadrangularis stem alleviates insulin resistance, oxidative injury and fatty liver disease in rats fed high fat plus fructose diet, Food and Chemical Toxicology ,2010;48:2021–2029.

[10] Feng L.-J et al. , Hypolipidemic and antioxidant effects of total flavonoids of Perilla Frutescens leaves in hyperlipidemia rats induced by high-fat diet, Food Research International ,2011; 44: 404–409.

[11] Guang Yi Liu et al, Evalution of sphingolpid metabolism in renal cortex of rats with streptozotocin induced diabetes and the effects of rapamycin. Nephrol dial transplant,2010;1 : 10.

[12] Hussein, M.A. S.M. Abdel-Gawad , Protective effect of Jasonia montana against ethinylestradiol-induced cholestasis in rats, Saudi Pharmaceutical Journal,2010; 18: 27–33.

[13] Hyeng sik lee et al, Hypolipemic effect of water extracts of picrorrhiza kurroa in high fat diet treated mouse. Fitoterapia , 2011;77(2006): 579 – 584.

[14] Jin X. et al. , Ameliorative effect of Eucommia ulmoides Oliv. Leaves extract (ELE) on insulin resistance and abnormal perivascular innervation in fructose-drinking rats, J. of Ethnopharmacology, (2010); 128 : 672–678.

[15] Khanna A.K. et al, Lipid lowering activity of phyllanthus niruri in hyperlipemic rats. Journal of ethnopharmacology, (2002); 82:19 – 22.

[16] Laxmi verma et al anti diabetic activity of cassia occidentalis(linn) in normal and alloxan – induced diabetic rats. Indian journal of pharmacology, an official publication of the Indian pharmacological society , 2010;42(4): 224 – 228.

[17] Leeetal. Y.-S., Effects ofa Citrus depressaHayata (shiikuwavsa) extract on obesity in high-fat diet-induced obesemice , Phytomedicine ,2010.

[18] lemhadri A.et al, Anti hyperglycaemic and anti obesity effects of capparis spinosa and chamaemelum nobile Aqueous extracts in HFD Mice. American journal of pharmacology and toxicology ,2007; 2(3): 106 – 110.

[19] Liu I.-M. et al. , Myricetin, a naturally occurring flavonol, ameliorates insulin resistance induced by a high-fructose diet in rats Life Sciences, 2007;81: 1479–1488.

[20] Mbaka G.O. et al, Anti – diabetic activity of the seed extract of sphenocentrum jollyanum and morphological changes on pancreatic beta cells in alloxan induced diabetic rabbits. Journal of medicine and medical science,2010;1(11): 550 556.

[21] Mohamed Fazil Ahamed et al, Anti Diabetic activity of Vinca rosea extracts in alloxan – induced diabetic rats. International journal of endocrinology, hindawi Publishing Corporation, 2010, article ID 841090, 6.

[22] Olatunji, L.A. A.O. Soladoye , Increased magnesium intake prevents hyperlipidemia and insulin resistance and reduces lipid peroxidation in fructose-fed rats Pathophysiology , 2007; 14:11–15.

[23] Patrick McCue Ms et al, Anti diabetic and anti Hypertensive potential of sprouted and solid – state bioprocessed soybean. Asia pac J Clin Nutr ,2005;14(2): 145 – 152.

[24] Qin Liao et al, antiproliferation of cardamonin is invoved in mTOP on aortic smooth muscle cells in high fructose – induced insulin resistance rats. European journal of pharmacology ,2010;641: 179 – 186.

[25] Rathee S. et al, Antidiabetic activity of capparis deciduas forsk edgew. Jounal of pharmacy Reasearch ,2010;3(2):231 – 234.

[26] Razien Jalal et al, Hypoglycemic effects of aqueous shallot and garlic etracts in rats with fructose – induced insulin résistance. J.clin. Biochem Nutr, 2007;41:218 – 223.

[27] Reddy S.S. et al. , Preventive effect of Tinospora cordifolia against high-fructose diet-induced insulin resistance and oxidative stress in male Wistar rats, Food and Chemical Toxicology ,2009;47 : 2224–2229.

[28] Ribas V. et al. , Paradoxical exacerbation of combined hyperlipidemia in human apolipoprotein A-II transgenic mice treated with fenofibrate Biochimica et Biophysica Acta 1 ,2005; 737: 130–137.

[29] Sabu M.C. et al, Anti diabetic activity of aegel marmelos and its relationship with its antioxid properties. Indian J physiol Pharmacol, 2004; 48(1): 81 – 88.

[30] Seifollah bahramika et al Effects of hydroalcoholic extracts of nasturtium officinale leaves on lipid

profile in high – fat diet, journal of Ethnopharmacology ,2008; 115: 116 – 121.

[31] Sharda Bisht et al, Anti hyperglycemic and antidyslipdemic potential of azadirachta indica leaf extract in STZ – induced diabetes mellitus. Sharda bisht et al /j pharm. Sci &res, 2010;2(10): 622 – 627.

[32] Suwannaphet W. et al. , Preventive effect of grape seed extract against high-fructose diet-induced insulin resistance and oxidative stress in rats, Food and Chemical Toxicology, 2010;48: 1853–1857.

[33] Wei Y. et al. Fructose-mediated stress signaling in the liver: implications for hepatic insulin resistance Journal of Nutritional Biochemistry ,2007; 18:1–9.

[34] Xing Wei – Wei et al, Effects of polydatin from polygonum cuspidatum on lipid profile in hyperlipidemic rabbits. Biomedicine & pharmacotherapy, 2009;63: 457 – 462.

[35] Zhang H. et al, Hypolipidemic effects of chitosan nanoparticles in hyperlipidemia rats induced by high fat diet , International Immunopharmacology ,2011.