



Table of Contents

No.	Title	Page No.
Chapter 1 Introduction		1-87
1.1	Diabetes Mellitus	1
1.2.	Classification	1
1.3.	Diagnostic criteria for diabetes mellitus	3
1.3.1	Prognostic criteria	4
1.4.	Diabetes mellitus – consequence of insulin deficiency/resistance	4
1.5.	Prevalence of diabetes	5
1.6.	Evolution of the diabetes epidemic in India	5
1.6.1	Undiagnosed diabetes - the hidden danger	8
1.7.	Urban-rural differences in diabetes prevalence	9
1.8.	Burden of diabetes related complications in India	9
1.9.	The pathobiology of diabetic complications	11
1.10.	Increased flux through the polyol pathway.	13
1.11.	Intracellular production of AGE precursors.	14
1.12.	PKC activation	14
1.13.	Increased hexosamine pathway activity.	16
1.14.	A unified mechanism	17
1.15.	Hyperglycemia-induced mitochondrial superoxide production activates the four damaging pathways by inhibiting GAPDH.	20
1.16.	Hyperglycemia-induced mitochondrial superoxide production inhibits GAPDH by activating poly (ADP-ribose)	22

polymerase.		
1.17.	How does the unifying mechanism explain diabetic macrovascular disease?	23
1.18.	Therapies for diabetes mellitus	25
1.18.1	Sulfonylureas	25
1.18.2	Meglitinides	26
1.18.3	Biguanides	26
1.18.4	Thiazolidinediones	27
1.18.5	Alpha-glucosidase inhibitors	28
1.18.6	Insulin	28
1.18.7	Gene and Islet therapy	28
1.18.8	Exercise	29
1.18.9	Vitamin E	29
1.18.10	α -Lipoic acid	29
1.18.11	Chromium species	31
1.18.12	Magnesium	31
1.18.13	Vanadium	32
1.19.	Hypolipidemic drugs	32
1.19.1.	Statins (HMG-CoA reductase inhibitors)	33
1.19.2.	Bile acid sequestrants (resins)	33
1.19.3.	Nicotinic acid (Niacin)	34
1.19.4.	Fibrates	34
1.19.5.	MTP inhibitor	35
1.19.6.	Dietary and biliary cholesterol absorption inhibitor	35
1.19.7.	ACAT inhibitor	35
1.20.	Combination Therapy	35

1.21.	Herbal Therapy	37
1.21.1	<i>Ginseng</i>	37
1.21.2	<i>Momordica charantia</i> (<i>bitter melon</i>)	43
1.21.3	<i>Coptis chinensis</i> (<i>Huanglian</i>)	45
1.22.	<i>Chinese herbal preparations for diabetes</i>	46
1.22.1	<i>ADHF</i> (<i>anti-diabetes herbal formulation</i>)	46
1.22.2	<i>BN</i> (<i>Byakko-ka-ninjin-to</i>)	46
1.23.	Antidiabetic Indian medicinal plants	47
1.23.1	<i>Murraya koenigii</i> (<i>curry leaves</i>)	47
1.23.2	<i>Mangifera indica</i> : mango	48
1.23.3	<i>Syzygium cumini</i> (<i>Eugenia jambolana</i>): black berry	49
1.23.4	<i>Trigonella foenum graecum</i> (<i>fenugreek</i>)	51
1.22.6	<i>Azadirachta indica</i> (<i>Neem</i>)	53
1.22.6	<i>Allium sativum</i> (<i>Lahasun</i>)	54
1.22.7	<i>Enicostemma littorale</i> Blume	54
	Aims and objectives	58
	References	60
Chapter 2 Materials and Methods		88-143
Chapter 3	Evaluation of efficacy of <i>E. littorale</i> aqueous extract in diet induced insulin resistance rat model.	139-165
3.1	Review of literature	139
3.1.1	Diet and insulin resistance	140
3.1.2.	How fructose induces insulin resistance?	141
3.2.	Experimental design	144
3.2.1.	Fructose enriched diet (FRU)	145

3.3.	Results	146
3.3.1.	Changes in Body weight, fasting glucose, fasting insulin and Fasting insulin resistance index.	146
3.3.2.	Oral Glucose Tolerance Test	147
3.3.3.	Lipid profile	148
3.3.4.	Serum CK-MB, LDH, SGOT and SGPT activity	148
3.3.5.	Platelet aggregation, Platelet count and Blood clotting time (PT & APTT)	150
3.3.6.	Systolic blood pressure and vascular reactivity	150
3.3.7.	Serum Testosterone and 3β -HSD and 17β -HSD activity	150
3.3.8.	LPO, GSH and Antioxidant enzymes activity in blood	152
3.4.	Discussion	153
3.5.	Summary	158
3.6.	References	159
Chapter 4	Evaluation of protective effect of <i>E. littorale</i> methanolic extract against H_2O_2 induced apoptosis of islets of langerhans.	166-184
4.1	Review of literature	166
4.2.	Experimental Design	170
4.3.	Results	172
4.3.1.	Effect of EL on H_2O_2 -induced loss of islets viability	172
4.3.2	Effect of EL on H_2O_2 -induced apoptosis in isolated islets	173
4.3.3.	Comet Assay	173
4.3.4.	Caspase-3 Activity	173
4.3.5	Effect of EL on H_2O_2 -induced reactive oxygen species in	173

	islets	
4.3.6.	Effect of EL on the antioxidant enzyme activities in islets	173
4.4	Discussion	173
4.5	Summary	178
4.6	References	179
Chapter 5	Evaluation of efficacy of <i>E. littorale</i> methanolic extract in nephropathic condition in rat models.	185-188
5A.1	Introduction	185
5A.1.1.	Acute interstitial nephritis (AIN)	186
5A.1.2.	Acute tubular necrosis (ATN)	186
Chapter 5a	Evaluation of efficacy of EL extract in Gentamicin-induced nephrotoxicity in rat model	189-198
5a.1.	Review of literature	189
5a.2.	Experimental design	190
5a.2.1.	Animals and treatment	190
5a.3.	Results	192
5a.3.1.	Body weight and urinary volume	192
5a.3.2.	Serum creatinine and urea levels	192
5a.3.3	Lipid peroxidation, reduced glutathione and antioxidant enzymes activities in mitochondrial and post-mitochondrial fractions of kidney tissue.	193
5a.3.4	Histopathological analysis	194
5a.4.	Discussion	194
5b.	Evaluation of efficacy of EL extract in diabetic nephropathy in rat model	199-226

5b.1.	Review of literature	199
5b.1.1	Management of diabetic nephropathy	201
5b.2.	Experimental design	207
5b.2.1	Extract preparation	207
5b.2.2	Animals and treatment	208
5b.2.2.1	Surgical procedure for unilateral nephrectomy	207
5b.2.2.2	Induction of diabetes	207
5b.3	Results	209
5b.3.1.	Body weight, Relative organ weight and urinary volume	209
5b.3.2.	Blood glucose and glycosylated hemoglobin levels	209
5b.3.3.	Serum creatinine and urea (BUN)	209
5b.3.4.	Hypolipidemic parameters	210
5b.3.5.	Platelet aggregation and blood clotting time (PT & APTT)	210
5b.3.6.	Systolic and <i>diastolic</i> blood pressure	210
5b.3.7.	Aldose reductase and Na ⁺ -K ATPase activity in kidney tissue	211
5b.3.8.	LPO, GSH and Antioxidant activity in mitochondrial and post-mitochondrial fraction of kidney	211
5b.4.	Discussion	213
5b.5	Summary of the chapter	224
5b.6	References	227
Chapter 6	Evaluation of efficacy of <i>E. littorale</i> methanolic extract in diabetic complications in alloxan induced rat model.	248-322
6A.1	Introduction	248

6A.1.1	Microvascular and Macrovascular Complications of Diabetes	248
6A.2.	Pathophysiology	248
6A.2.1.	Retinopathy	250
6A.2.3.	Nephropathy	250
6A.2.4.	Neuropathy	251
6A.3.	Macrovascular Complications of Diabetes	251
6A.4.	Preventive strategies	252
6A.5.	Experimental Design	252
6A.5.1.	Induction of diabetes	253
Chapter 6a	Evaluation of efficacy of EL extract in diabetic neuropathy in rat model	255-277
6a.1.	Review of Literature	255
6a.2.	Experimental Design	256
6a.3.	Results	256
6a.3.1.	Blood glucose Level	256
6a.3.2.	Nociceptive threshold	259
6a.3.3.	Aldose Reductase and Na-K ATPase activity from sciatic nerve	259
6a.3.4.	Antioxidant parameters	259
6a.4.	Discussion	259
6b.1.	Review of literature	265
6b.2.	Experimental design	266
6b.3.	Results	268

6b.3.1.	Blood glucose level	268
6b3.2.	Relative organ body weight and body weight	268
6b.3.3.	Testicular $\Delta 53\beta$ -HSD and 17 β -HSD	268
6b.3.4.	Plasma testosterone level	269
6b.3.5.	Sperm count, viability, morphology and motility of sperms	269
6b.3.6	Epididymal LDH activity and prostatic ACP activity	270
6b.3.7.	Aldose reductase activity in testis, epididymis, seminal vesicle and prostate	270
6b.3.8.	Fructose content in seminal vesicle and prostate	271
6b.3.9.	Prostate and epididymis vitamin C content	271
6b.3.10.	LPO levels in Testes and epididymis	271
6b.3.11.	GSH levels in testis and epididymis	271
6b.4.	Discussion	273
Chapter 6c	Evaluation of efficacy of EL extract in diabetic cardiovascular complications in rats	278
6c.1.	Review of literature	278
6c.2.	Experimental design	280
6c.3.	Results	281
6.2.2	Heart and Body weight	281
6c. 3.2.	Blood glucose and glycosylated hemoglobin levels	281
6c. 3.3.	Lipid profile	282
6c. 3.4.	Serum CK-MB, LDH and SGOT activity	282
6c. 3.5.	Platelet aggregation, platelet count and blood clotting	286

	time (PT & APTT)	
6c. 3.6.	Systolic blood pressure and heart rate	286
6c. 3.7.	Ca ²⁺ -ATPase and Na ⁺ -K ⁺ -ATPase activity in heart tissue	286
6c. 3.9	LPO, GSH and antioxidant enzyme activities in mitochondrial and post-mitochondrial fractions of heart tissue	287
6c.4	Discussion	287
6c.5.	Summary of the chapter	295
	References	298
Chapter 7	Summary of the Thesis	323
	Conclusion	329
	Publications and Presentations	330