Chapter 2

LITERATURE SURVEY
# CHAPTER 2

**Chapter-2: Literature Survey**

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Chapter 2

LITERATURE SURVEY

Chapter two makes a study of literature survey of polyherbal formulation which is composed of 19 medicinal plants to be tested for protective effect of polyherbal formulation against streptozotocin induced diabetic nephropathy.

Based on literature survey it can be said that no research has been published against polyherbal formulation in the prevention of diabetic nephropathy.

2.1. Animal models in experimental diabetes mellitus

For the selection of antihyperglycemic agents, DM can be created in animals like mouse, rat, guinea pig, cat, dog, hamster, rhesus monkey etc.

Animal models are classified as below

- Insulin Dependent Diabetes Mellitus (IDDM) analogous animal models.

- Non-insulin Dependent Diabetes Mellitus (NIDDM) analogous animal models.

2.1.1. IDDM like animal models

Destruction of β-cells of langerhns of islets produces the IDDM. This type of diabetes induced by viral infection, injection of diabetogens or by introduction of transgenes. Streptozotocin and alloxan were found to be more selective in β-cells devastation than other diabetogenic agents.
2.1.2. NIDDM like animal models

NIDDM animal models can be primed by injecting streptozotocin intravenously at a dose of 100mg/kg to neonatal wistar rats on the day of birth, through sapheneous vein which is easy to get to by transcutaneous puncture.

Another model of NIDDM is by injecting streptozotocin (90mg/kg, I.P) to two days old Sprague dawley rats resulting in temporary hyperglycemia followed by resurgence post prandial hyperglycemia, as well oral glucose intolerance, in the diabetic range is noticeable at 4-6 weeks of age.

NIDDM along with hypertension can be produced by injecting streptozotocin to neonates of the spontaneous hypertensive rats.

2.2. Rodent models for Diabetic Nephropathy\textsuperscript{38}

Trustworthy animal models for diabetic nephropathy are a precious tool to understand the molecular mechanisms answerable for this disease and for the preclinical improvement of new therapeutic strategies. Newly a number of genetically modified (knock out and transgenic) mouse strains have been used to afford vital insights in to the roles of oxidative stress, advanced glycation end products, inflammation and profibrotic mechanisms in the progress of diabetic nephropathy. It is dependent on various factors including

i) A steadfast technique for establishing a unfailing level of diabetes.  
ii) It should be able to maintain a firm level of diabetes throughout the period of the experiment.
iii) Considerate the disease distinctiveness and progression of injury in the rodent strain

iv) The attainment of a pathology condition will have clinical significance.

2.2.1. **Low-dose mouse model of STZ-induced Diabetic Nephropathy:**

- **Mice:** male
- **Age:** 6-7 weeks
- **B.W:** 20-25g
- **Dose of STZ:** 10mg/kg I.P

Mouse strain susceptibility to diabetes induced by several low doses of STZ are arranged in the following sequence

DBA/2<C57BL/6>MRL/MP<129/SVEV<BALB/C<90% of STZ –treated C57BL/6 mice obtained adequate diabetes to be used in animal model studies of diabetic nephropathy.

2.2.2. **Moderate and high-dose mouse models of STZ – induced Diabetic Nephropathy**

Some studies investigating the diabetic nephropathy in mouse strains which are challenging to STZ-induced pancreatic damage have used either a single high dosage of STZ (>or)=200mg/kg) or a two dose schedule of STZ (2×100-125mg/kg) given on consecutive days.

The following procedure describes a two –dose procedure (2×125mg/kg per day STZ) for establishing diabetes in C5TBL/6 mice with lack of genetics which facilitate mild resistant to STZ.
Using this procedure, roughly 90% of wild type C57BCL/6 mice will develop evident diabetes within 2 weeks, with a lower frequency expected for more resistant genotypes.

2.3. Rat models of STZ-induced Diabetic Nephropathy:

Models of STZ-induced diabetic nephropathy are normally performed in Sprague–dawley (SD), wistar–Kyoto (wky) or spontaneously hypertensive (SHR) rats

Sex: Male
Age: 8week
Weight: 200-250 g
Dose of STZ: SD=55 mg/kg, Wky =60mg/kg SHR=45mg/kg
Route: I.V.

STZ has also been administered intraperitoneally to rats

2.3.1. Uninephrectomized Rat Model of STZ induced Diabetic Nephropathy:

Uninephrectomy is performed in different rat strains (SD, wistar, SHR) which is considered to speed up the evolution of renal damage. Uninephrectomy leads to the swelling of the remaining kidney, which is more enlarged by the development of diabetes. Uninephrectomy causes the increase in glomerular capillary pressure in SHR rats. However, understanding of this model is multifaceted, it is difficult to dissect the virtual assistance of STZ-induced hyperglycemia and uninephrectomy induced changes in glomerular haemodynamics in the development of renal injury
Table 2.1: Representative animal models for diabetic nephropathy and their characteristic features (+: very week, +: weak, ++: moderate, and +++: strong)\textsuperscript{39}

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Diabetic type</th>
<th>Hyperglycemia</th>
<th>Albuminuria</th>
<th>Renal failure</th>
<th>Histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozotocin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose (mice)</td>
<td>1</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Low dose (mice)</td>
<td>1</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Insulin-2 Akita (mice)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Females</td>
<td>1</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NOD mice</td>
<td>1</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>db/db mice</td>
<td>2</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>KK mice</td>
<td>2</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>NZO mice</td>
<td>2</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>GK rats</td>
<td>2</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Zucker rats</td>
<td>2</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>
### 2.4. Polyherbal Formulation Profile

#### Table 2.2: Composition of Polyherbal formulation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Botanical name</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Eugenia jambolona</td>
<td>20%</td>
</tr>
<tr>
<td>02</td>
<td>Tinospora cardifolia</td>
<td>10%</td>
</tr>
<tr>
<td>03</td>
<td>Gymnema sylvestre</td>
<td>10%</td>
</tr>
<tr>
<td>04</td>
<td>Cressa cretica</td>
<td>5%</td>
</tr>
<tr>
<td>05</td>
<td>Casearia esculenta</td>
<td>5%</td>
</tr>
<tr>
<td>06</td>
<td>Curcuma longa</td>
<td>5%</td>
</tr>
<tr>
<td>07</td>
<td>Swertia chirata</td>
<td>5%</td>
</tr>
<tr>
<td>08</td>
<td>Centratherum anthelminticum</td>
<td>5%</td>
</tr>
<tr>
<td>09</td>
<td>Picrorhiza kurroa</td>
<td>5%</td>
</tr>
<tr>
<td>10</td>
<td>Trigonella foenum graecum</td>
<td>5%</td>
</tr>
<tr>
<td>11</td>
<td>Terminalia chebula</td>
<td>5%</td>
</tr>
<tr>
<td>12</td>
<td>Holarrhena antidysenterica</td>
<td>2.5%</td>
</tr>
<tr>
<td>13</td>
<td>Pterocarpus marsupium</td>
<td>2.5%</td>
</tr>
<tr>
<td>14</td>
<td>Glycyrrhiza glabra</td>
<td>2.5%</td>
</tr>
<tr>
<td>15</td>
<td>Mineral pitch</td>
<td>2.5%</td>
</tr>
<tr>
<td>16</td>
<td>Tribulus terrestris</td>
<td>2.5%</td>
</tr>
<tr>
<td>17</td>
<td>Withania somnifera</td>
<td>2.5%</td>
</tr>
<tr>
<td>18</td>
<td>NordoStachys jatamansi</td>
<td>2.5%</td>
</tr>
<tr>
<td>19</td>
<td>Bacopa monniera</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
2.5. Earlier works on composition of Polyherbal Formulation

1. *Eugenia jambolona*

The work entitled “Study of hypoglycemic and hypolipidemic activity of *Eugenia jambolana* pulp and seed extract in streptozotocin induced diabetic albino rats” carried out by Bhavana Srivastava.et. al. Published in Asian Journal of Pharmacy and Life science, 2012, vol. 2, issue 1 summarized that seed and pulp extract of *Eugenia jambolana* has antidiabetic, antihyperlipidemic activity and lowers blood urea in diabetic rats. It also increases body weight of diabetic rats\(^{40}\).

The research article entitled “Attenuation of renal dysfunction by antihyperglycemic compound isolated from fruit pulp of *Eugenia jambolona* in streptozotocin induced diabetic rats” by Tanwar et.al. Published in Indian Journal of Biochemistry and Biophysics, 2010, vol. 47 demonstrated significant protective effects of that partially purified compound FIIC on the consequences of hyperglycemia and early stages of experimentally induced diabetic nephropathy.\(^{41}\)

2. *Tinospora cardifolia*

The research article entitled “Magnoflorine from *Tinospora cordifolia* stem inhibits $\alpha$-glucosidase and is antiglycemic in rats” by Mayurkumar et. al. published in Journal of Functional Foods, 2012, vol. 4 concluded that embarrassment of intestinal $\alpha$-glucosidase enzyme by Magnoflorine offers this plant species as a choice for the treatment of diabetes mellitus

and for prevention and control of diabetes. \(^{42}\)
The research article entitled “Nephroprotector activity of hydroalcoholic extract of Tinospora cardifolia roots on cisplatin induced nephrotoxicity in rats” by Spandana et al. Published in Drug Invention Today, 2013, vol. 5. The present investigation suggests that the hydro alcoholic extract of roots of Tinospora cardifolia has protective effect against cisplatin induced nephrotoxicity.43

The research article entitled “Prevention and Management of diabetic retinopathy in STZ diabetic rats by Tinospora cardifolia and its molecular mechanisms” by Shyam et al. Published in Food and Chemical Toxicology, 2012, vol.50 demonstrated that Tinospora cardifolia plays a pivotal role in prevention and management of diabetic retinopathy due to its antihyperglycemic, antiangiogenic, anti-inflammatory and antioxidant properties.44

The work entitled “Hypoglycemic and other interrelated actions of Tinospora cardifolia roots in alloxan induced diabetic rats” by P. Stanley. Et al. published in Journal of Ethnopharmacology, 2000, vol.70 states that aqueous root extract of T. Cardifolia in alloxan induced diabetic rats caused a considerable reduction in blood glucose and brain lipids.45

3. Gymnema sylvestre

The research article entitled “Hypoglycemic effect of Gymnema Sylvestre R.Br leaf in normal and alloxan induced diabetic rats” by Sathya et al. Published in Ansent Science of Life, 2008, vol. 28. This study provided experimental evidence for the herbal plant Gymnema
sylvestre in the prevention and curing of alloxan induced diabetic rats without any side effects.\textsuperscript{46}

4. **Cressa cretica**

The research article entitled “Evaluation of Antidiabetic activity of *Cressa cretica* Linn in alloxan induced diabetes in rats” by Chaudhary et.al. Published in pharmacologyonline, 2010, vol. 3. Ethanolic extract of Cressa cretica showed significant hypoglycemic effect in Alloxan induced diabetic rat. It also reduced serum cholesterol and increased HDL-cholesterol.\textsuperscript{47}

5. **Casearia esculenta**

The research article entitled “phytochemical and hypoglycemic investigation *Casearia esculenta*” by Chodhury et.al. Published in Journal of Pharmaceutical Sciences, 2006 concluded that different fractions of both isolated and alcoholic and aqueous extracts of esculenta significantly decreased the blood glucose level.\textsuperscript{48}

6. **Curcuma longa**

The research article entitled that “Potential therapeutic effect of *Curcuma longa* on streptozotocin induced diabetic rats” carried out by Azza A.et.al. Published in Global advanced research Journal of Medicine and Medical sciences, 2012, vol. 1, issue 4 concluded that curcumin consist of antioxidant effect that may supply to its protective action beside lipid peroxidation and enhancing effect on cellular antioxidant defense. This activity contributes to the protection against oxidative damage in STZ induced diabetes.\textsuperscript{49}
The review article entitled “Renoprotective effect of the antioxidant curcumin: Recent findings” by Joyce Trujillo et.al. Published in redox biology, 2013, vol. 1 identified that curcumin as a promising renoprotective molecule against renal injury.50

7. *Swertia chirata*

The research article entitled “Potential hypoglycemic effect of *Swertia chirata* an Indian subcontinent herb with important medicinal value” by Alam et.al. Published in pharmacologyonline, 2011, vol. 2. This study confirmed the use of Swertia chirata in ethnomedical application for diabetes management.51

8. *Centratherum anthelminticum*

The research article entitled “Antidiabetic activity of *Centratherum Anthelminticum Kuntze* on alloxan induced diabetic rats” carried out by Bhatia et.al. Published in pharmacologyonline, 2008, vol. 3 summarized that aqueous extract of Centratherum anthelminticum showed dose dependent percentage of blood glucose reduction in diabetic rats.52

9. *Picrorrhiza kurroa*

The research article entitled “Antidiabetic activity of standardized extract of *Picrorrhiza kurroa* in rat model of NIDDM” carried out by Gulam Mohammed hussain et. al. published in Drug Discov Ther. 2009, vol. 3, issue 3 concluded that extract of Picrorrhiza kurroa has an antihyperglycemic effect. Therefore it may be potentially beneficial in type 2-diabetes and related dyslipidaemia.53
10. *Trigonella foenum graecum*

The research article entitled “Antioxidant activity of *Trigonella foenum graecum* using various in vitro and exvivo models” by N.Subhashini et.al. Published in International Journal of Pharmacy and Pharmaceutical Sciences, 2011, vol. 3, issue 2 indicated that ethanol extract of T. foenum graecum is effective against free radical mediated disease.\(^{54}\)

The work entitled “Antidiabetic activity of *Trigonella foenum graecum* L. Seeds extract (IND01) in neonatal streptozotocin-induced (N-STZ) Rats” by Chetan P.Kulkarni.et.al. Published in Diabetologica Croatica, 2012, vol. 41, issue 1 concluded that IND01 (100mg/kg, oral) and glyburide (10mg/kg, oral) showed considerable exchange in-STZ-induced changes (rise in SG, turn down in body weight and rise in HBA1C). Histology sections of pancreas from the rats treated with IND01 (but not glyburide) showed augment in number and size of pancreatic islet β-cells. IND01 showed a probable improvement in symptoms of DM during progressive worsening and better glycemic functions in n-STZ induced diabetic rats.\(^{55}\)

11. *Terminalia chebula*

The research article entitled “Antidiabetic and renoprotective effects of the chloroform extract of *Terminalia chebula* Retz. Seeds in streptozotocin-induced diabetic rats” by Nalamolu Koteswara Rao.et.al. Published in BMC Complementary and Alternative Medicine, 2006, vol. 6, issue 17 concluded that chloroform extract of seeds of T. chebula formed dose-dependent reduction in blood glucose and
analogous with that of drug, glibenclamide in short term study & long term study. Considerable nephroprotective activity is observed in T. chebula treated rats.\textsuperscript{56}

12. \textit{Holarrhena antidysenterica}

The research article entitled “Efficacy of aqueous extract of seed of \textit{Holarrhena antidysenterica} for the management of diabetes in experimental model rat: A correlative study with antihyperlipidemic activity” by Ali et.al. Published in International Journal of Applied Research in Natural Products, 2009, vol. 2 issue 2. The results of this study enlightened that the aqueous extract of seeds have antidiabetic and antihyperlipidemic activities.\textsuperscript{57}

13. \textit{Pterocarpus marsupium}

The research article entitled “Antidiabetic activity of heart wood of \textit{Pterocarpus marsupium} Roxb. and analysis of phytoconstituents” carried out by Akansha Mishra.et.al. Published in Indian Journal of Experimental Biology, 2013, vol. 51 concluded that results of this study demonstrate the usefulness of heart wood of P. marsupium for civilizing on the whole glycemic control and thereby sinking the risk of diabetic complications.\textsuperscript{58}

14. \textit{Glycyrrhiza glabra}

The research article entitled “Antidyslipidaemic activity of \textit{Glycyrrhiza glabra} in high fructose diet induced dyslipidemic Syrian golden hamsters” by Santosh kumar Maurya. et.al. Published in Indian Journal of Clinical Biochemistry, 2009, vol. 24, issue 4 indicated that 95% ethanolic extract of root of Glycyrrhiza glabra and
its fractions like water soluble, ethyl acetate soluble and hexane soluble showed decrease serum cholesterol. In the other way ethanolic extract, ethyl acetate soluble, water soluble and hexane soluble portion showed increase serum HDL-C. Ethanolic extract, ethyl acetate fraction, aqueous fraction, hexane part showed decreased triglyceride level. Ethanolic extract, ethyl acetate soluble portion and water soluble fraction showed reduction in LDL-cholesterol.\textsuperscript{59}

**15. Mineral pitch**

The research article entitled “Effect of shilajit on blood glucose and lipid profile in alloxan induced diabetic rats” by Trivedi et.al. Published in Indian Journal of Pharmacology, 2004, vol. 36, issue 6 concluded that due to its complex action Shilajit can offer a new and hopeful approach in the long time management of diabetes mellitus\textsuperscript{60}

**16. Tribulus terrestris**

The research article entitled that “Hypoglycemic effect of saponin from Tribulus terrestris” by Li M et.al. Published in Journal of Chinese Medicinal Materials 2002 vol 25 issue 6 concluded that saponin from Tribulus terrestris could significantly decrease the level of serum glucose.\textsuperscript{61}

**17. Withania somnifera**

The research article entitled “Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (Withania somnifera, Dunal) root by Andallu et.al. Published in Indian Journal of Experimental Biology, 2000, vol. 38. This study suggested that its being source of hypoglycemic, diuretic and hypocholesterolemic
agents the root of the Withania somnifera had a definite potential therapeutic value without detrimental side effects in humans.\(^{62}\)

**18. *NordoStachys jatamansi***

The research article entitled “Stress modulating antioxidant effect *Nardostachys jatamansi*” by Nazmun Lyle et.al. Published in Indian Journal of Biochemistry & Biophysics, 2009, vol. 46 summarized that ethanolic extract of *Nardostachys jatamansi* attenuated stress-induced elevation of biochemical changes such as membrane LPO, elevated NO production in brain as well as stomach and increase in antioxidant enzyme like Catalase, which are consistent with its anti-stress properties. In vitro study showed that it has potent free radical scavenging action.\(^{63}\)

**19. *Bacopa monniera***

The research article entitled “Antihyperglycemic activity of Bacosine, a triterpene from *Bacopa Monniera*, in alloxan induced diabetic rats” by Thritha Ghosh et.al. Published in Planta Medica, 2011, vol. 77, issue 88 concluded that Bacosine showed significant decrease in blood glucose and attenuated the antioxidants.\(^{64}\)