Review on Nelliyathi kasayam in the management of Diabetes Mellitus (Neerizhivu)

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Abstract- Globally diabetes is one of the major health challenges disease. This disease direct impact the socio economical level in person and country. Diabetes Mellitus is caused by lack of insulin activity. In type 2 diabetes there is resistance to the action of relative insulin it cause insulin deficiency. Ancient Siddha text Sarabenthira Vaithiya Muraigal has mentioned that Neerizhivu and their management under the Neerizhivu Sigitchai. "Neerizhivu can be correlated with the Diabetic mellitus. Nelliyathi kasayam is mentioned for the treatment of Neerizhivu (diabetic). Nelliyathi kasayam is a poly herbal formula which include the following herbs such as Phyllanthus emblica, Strychnos potatorum, Tereminalia bellirica, Cissampelos pareira, Cyperus rotundus. The objective of this study (review) was to assess the efficacy and safety of Nelliyathi kasayam management of diabetes. A review of research work had been done in web search (Pub med Google Scholar, Medline and Science Direct) journals and herbs related books. Each herb in the drug has anti-diabetic effect. Following are the common Mechanism of action when the herbs are do the anti-diabetic pharmacological action such as reduced insulin resistance in tissues, stimulates insulin secretion, regenerated β-cells, hypoglycemic effect inhibit the intestinal absorption inhibitory effects alpha-glucoesidase and alpha -amylase activities) and antioxidant action. For this pharmacological action the most of the ingredients of this drug contain the bioactive constituents of polyphenols, flavonoids alkaloids, terpenoids, saponins glycosides, and tannins. Therapeutic activity of this drug had been alterate the pathological changes of the diabetes mellitus and improvement of illness. This study had been give scientific explanation for ancient drug of Nelliyathi kasayam use of diabetic. It can be concluded that Nelliyathi kasayam can be used as a siddha drug in treatment of diabetes mellitus. Further scientific evidence base on clinical studies are recommended with appropriate study design, adequate sample size, and statistical evidence to prove its therapeutic action.

Index Terms- Diabetes Mellitus, Phyllanthus emblica, Strychnos potatorum, Tereminalia bellirica, Cissampelos pareira, Cyperus rotundus.

I. INTRODUCTION

Diabetes mellitus is one of the Non Communicable Disease. It is major public health problem in the present era. In the world wide day to day increase the prevalence and incidence rate of diabetic mellitus (1). WHO reports show About 422 million people worldwide have diabetes particularly in low and middle-income countries population who will be in the age 45-64 year. The following reasons are mention by ‘WHO’ such as ageing population growth, unhealthy diets, obesity and sedentary lifestyles (2).

Diabetes is a chronic metabolic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin and it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, which in turn damage many of the body's systems, in particular the blood vessels and nerves. In the management of diabetes involves diet, physical activity, and oral medication, but may also require insulin (2, 3, 4).

Siddha Medicine is one of the ancient (more than 10000 years ago) traditional Medicine (5). This system plays a prominent role in traditional health care system in the Northern and Eastern parts of Sri Lanka, especially in Jaffna. In particular, Siddha medicine had been established by the relationship of South India (6). Herbs are the main source of the siddha medicines and also used inorganic substance and animal products (5). Interest in traditional systems of medicine and, in particular, herbal medicines, has increased substantially in both developed and developing countries over the past two decades (7). In general, herbal secondary metabolites exhibit a wide array of biological and pharmacological properties (8). The people believe that the herbal remedies from natural origin are harmless and carry no risk. Eighty percentages (80 %) of the people in this world depend on traditional medicine for their primary health care needs (9).

Sarabenthira Vaithiya Muraigal is one of the Indian ancient Siddha book which is abstract of palm script, it is edited by Mr.Vasudevasasthiri and Dr.venkatramaiyer published by Saraswathamahal library in thanjavur. This book has mentioned that Neerizhivu and it is management under the Neerizhivu Sigitchai”.Neerizhivu can be correlated with the Diabetic mellitus (10). The disease Neerizhivu is called by different names in Siddha books such as Neeriliva, Mathumeham,Salarogam, Mihuneer, Vehumoththiram, Inippumeer, Mehaneer, Theanmeer(11).

Following are the common challenges, when the diabetic patients are facing their quality of life.
1. Diabetic patient can’t to control their blood sugar level.
2. Continuously treated with high dosage of Allopathi drugs therefore they suffer with lot of side effects.

Therefore, safety and efficacy of Siddha drugs are needed for them. WHO reports say that the herbal medicines, therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or

regulation of the physical and mental status of the body. However, scientific research is needed to provide additional evidence of its safety and efficacy (9).

*Nelliyathikasayam* is mentioned for the treatment of Neerizhivu (diabetic). *Nelliyathikasayam* is a poly herbal formula which includes the following herbs such as *Phyllanthus emblica, Strychnos potatorum, Tereminaliabellirica, Cissampelos pareira, and Cyperus rotundus*. All these herbs are easily available. Any institution can simply producing these drugs and increase the patient benefit with less expensive. To the best of our knowledge, there are no previous studies done in this drug and relevant information’s are also not available. In other way thus this review for evidence base study if this drug is found to be effective for Neerizhivu. The objective of this study was to assess the efficacy and safety of *Nelliyathikasayam* management of diabetes. Therefore, this study review will be scientific evident base of its safety and efficacy. This study will provide suggestions to the based on the results obtained.

II. METHODOLOGY

A review of research work had been done in web search (Pub med Google Scholar, Medline and Science Direct) journals and herbs related books. Following key words had been used in this study anti-diabetic effect of *Phyllanthus emblica, Strychnospotatorum, Tereminalia bellirica, Cissampelos pareira, and Cyperus rotundus*. A totally 50 scientific papers had been review for this study which were published from 2000 to 2019.

III. RESULT AND DISCUSSION

Majority of the articles were in review and animal studies. According this search all ingredients of *Nelliyathikasayam* herbs (*Phyllanthus emblica, Strychnos potatorum, Tereminalia bellirica, Cissampelos pareira, and Cyperus rotundus*) have anti-diabetic effect. These herbal secondary metabolites exhibit the anti-diabetic effect in through various multiple mechanisms of action. As show in the table (2.2) describe in the herbs detail, description, phytochemicals, and mechanism of action which ingredients of *Nelliyathi kasayam*.

Diabetes Mellitus is caused by lack of insulin activity. Commonly this is the result of diminished production of insulin. In type 2 diabetes there is resistance to the action of insulin i.e there is a relative insulin deficiency. Following are the main results when the lack of insulin such as Inability to control carbohydrate metabolism, increased fat catabolism, and increased catabolism of amino acids prevents proper protein synthesis (12). As show in diagram (2.1) accommodates etiology and pathology of the diabetes mellitus were correlate the pharmacological action of drugs. The treatment is in contrast to nature and temperament of the disease. Therefore the elimination of the root cause is the main treatment regime.

**The table (2.2) describe in the herbs which ingredients of Nelliyathi kasayam**
<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Phyllanthus emblica</th>
<th>Strychnos potatorum</th>
<th>Terminalia bellirica</th>
<th>Cissampelos pareira</th>
<th>Cyperus rotundus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Euphorbiaceae</td>
<td>Loganaceae</td>
<td>Combretaceae</td>
<td>Menispermaceae</td>
<td>Cyperaceae.</td>
</tr>
<tr>
<td>Name</td>
<td>Nelli</td>
<td>Tetta</td>
<td>Tanri</td>
<td>Ponmusueddi</td>
<td>Koori</td>
</tr>
<tr>
<td>Tamil:</td>
<td>Embile</td>
<td>Cleaning nut tree</td>
<td>Bellericmyrobala n</td>
<td>Velvet-leaf</td>
<td>Coco-grass</td>
</tr>
<tr>
<td>English:</td>
<td>myrobalan tree</td>
<td>Ingini</td>
<td>Bulu</td>
<td>Diyanmitta</td>
<td>Muisthka(17)</td>
</tr>
<tr>
<td>Sinhala:</td>
<td>Ambulla</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Tree about 10m in high spreading branches leaves single alternative very numerous&lt;sup&gt;(17)&lt;/sup&gt;</td>
<td>A small moderate sized tree with a blackish grey corky barks Leaves simple opposite 7.5-12.5 cm long Seeds:- black 1-2 cm diameter, circular bluntly</td>
<td>A large deciduous tree with straight buttressed trunk Leaves simple alternate without stipules placed at the ends of branches’ 10-20 cm long Fruit :- brownish-yellow tomentum stone large woody with a large seed cavity&lt;sup&gt;(17)&lt;/sup&gt;</td>
<td>perennial climber leaves simple alternative, ovate-orbicular Flowers small unisexual Rootstock woody, perennial&lt;sup&gt;(19)&lt;/sup&gt;</td>
<td>Perennial weed with slender, scaly creeping rhizomes, The tubers are externally blackish in colour and reddish white inside, The stems grow to about 25 cm tall and the leaves are linear, dark green&lt;sup&gt;(20)&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Distribution</td>
<td>India, malay China, Ceylon(very common)</td>
<td>Ceylon (North,central, province), India, Myanmar;</td>
<td>Ceylon (kurunegala, Galya). India, Barma, Malaya</td>
<td>Tropical and subtropical India, Ceylon, Singapore, Philippine</td>
<td>tropical, subtropical and temperate regions In Asia Ceylon(very common)</td>
</tr>
<tr>
<td>Part used</td>
<td>Fruit, seeds</td>
<td>Fruit, seeds</td>
<td>Leaves</td>
<td>Leaves</td>
<td>Rhizome</td>
</tr>
<tr>
<td>Phytochemicals</td>
<td>Carbohydrates, Vitamin C, amino acids, minerals, polyphenol (Ellagic acid)flavonoids,HydrolysableTannins, Alkaloids(Phyllantine, Phyllembein, Phyllantidine) &lt;sup&gt;(13,14)&lt;/sup&gt;</td>
<td>Alkaloids(diaboline), flavonoids, glycosides, lignins, phenols, saponin, sterols triterpenes, mannogalactans and tannins</td>
<td>polyphenolic (gallic acid, ellagic acid, and chebulagic acid) triterpinoids (arjunenin, bellericagenin and belleric acid</td>
<td>phenols, tannins, flavonoids, alkaloids, terpenoids, sterols, and reducing sugars. Potassium, calcium, and iron flavonoids, tannins, glycosides, furochromones, monoterpenes, sesquiterpenes, sitosterol, alkaloids saponins, terpenoids, essential oils, starch, carbohydrates, protein, separated amino acids</td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Inhibitory effects against both alpha-glucosidase and alpha-amylase activities&lt;sup&gt;(15)&lt;/sup&gt; inhibitory action of lipase&lt;sup&gt;(16)&lt;/sup&gt; antioxidant activity</td>
<td>Secretion of insulin by inhibiting the opening of the K+ ATP sensitive channel&lt;sup&gt;(32)&lt;/sup&gt;</td>
<td>Reduced insulin resistance, Antioxidant action, regeneration of β-cells,&lt;sup&gt;(22,23)&lt;/sup&gt;</td>
<td>It stimulates insulin secretion from the remnants of β-cells or from regenerated β-cells&lt;sup&gt;(26)&lt;/sup&gt;</td>
<td>Inhibitory effects against both alpha-glucosidase and alpha-amylase activities antioxidant activity&lt;sup&gt;(31)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
The diagram (2.1) accommodates the aetiology, and pathology of the diabetes mellitus were correlate the pharmacological action of drugs.

**Un healthy Diet**

Sedentary lifestyles → Obesity

Increased insulin resistance in tissues (particularly muscles and liver)

Genetic influence

Unhealthy Diet

Increased B cell activity → Blood insulin raised

Blood glucose normal → Pre-Diabetic phase

Gradual B cell inadequacy → Blood insulin low

Blood glucose raised → Diabetic state

B cell secrete islet amyloid protein along with insulin. Amyloid is deposited in in islets in Type 2 diabetes probably reflecting the prolonged B cell activity

Need Therapeutic effect drug

1. Reduced insulin resistance
2. It stimulates insulin secretion
3. Regenerated β-cells
4. Hypoglycemic effect
5. Reduce intestinal glucose absorption
6. Reduce lipid absorption

**Phyllanthus emblica**

Anti-diabetic effect is in the *Phyllanthus emblica*. Sultana.et.al (2014) confirmed that the ethanolic extracts of fruit of *Phyllanthus emblica* has significant anti-diabetic effect. It is endowed with reduction of sucrose absorption and partly related to inhibition of disaccharides activity in the gut. (21) Krishnaveni.et.al also reported ethanolic extracts of fruit of *Phyllanthus emblica* has anti-diabetic action. Bashir.et.al(2018) evaluated the Antioxidant and Antidiabetic activity of ethanolic extract of dry fruits of Phyllanthus emblica and the result indicated the presence of carbohydrates, tannins, phenols, alkaloids, flavonoids, saponins, glycosides, amino acids and proteins.
phenolic and flavonoid contents observed that Phyllanthus emblica is a potent antioxidant and antidiabetic agent\(^{(36)}\). Srinivasan.et.al (2018) was reported the methanolic extracts of Phyllanthus emblica has major constituent Antidiabetic properties of quercetin. quercetin is a potential drug with anti-diabetic and anti hyperglycemic action mediated by changes in the levels of glucose, cholesterol, and triglycerides as indicated by in silico and in vivo studies\(^{(37)}\). Fatima.et.al (2017) reported the Phyllanthus emblica can act as potent Anti-diabetic agent as it has active constituent, ellagic acid. Ellagic acid in Phyllanthus emblica exerts anti-diabetic activity through the action on β-cells of pancreas that stimulates insulin secretion and decreases glucose intolerance\(^{(38)}\).

**Terminalia belerica**

Ellagic and gallic acid are major ingredients of *Terminalia belerica*. It has antioxidant activity it may be possible that these extracts may reduce the effect of inflammatory cytokine release during diabetes which may be one of the causative agents for the tissue distruction and insulin resistance\(^{(22)}\). The hot water extract of *Terminalia belerica* fruit active ingredients has gallic acid. It is the responsible for the inhibition of pancreatic lipase activity and suppression of the absorption of meal \(^{(23)}\).

Latha.et.al was carried out the animal and laboratory study. The compound was identified as gallic acid. Gallic acid was administered to streptozotocin (STZ)-induced diabetic male wistar rats at different doses for 28 days. Plasma glucose level was significantly (p < 0.05) reduced in a dose-dependent manner. Histopathological examination of the pancreatic sections showed regeneration of β-cells in addition, significantly decreased serum total cholesterol, triglyceride, LDL-cholesterol, urea, uric acid, and creatinine at the same time markedly increased plasma insulin of diabetic rats. \(^{(24)}\)

Another study with alloxan – induced rats given ethanolic extract of *Terminalia belerica* suspended in water has shown significant decrease of the blood glucose (from 6th day of administration), as well as Oxidative stress produced by alloxan\(^{(25)}\).

**Cissampelos pareira**

Basumata.et.al (2012) conducted an animal study to evaluate the anti-diabetic potential of *Cissampelos pareira* leaf extract. Fructose-aloxan-induced diabetic rats have shown the anti-diabetic effect. It stimulates insulin secretion from the remnants of β-cells or from regenerated β-cells. Light microscopic studies using Aldehyde-fuchsinstaining technique showed significant higher islet volume and β-cells granulation scores in the *Cissampelospareira* treated diabetic rats compared to diabetic control rats \(^{(26)}\).

Shanker.et.al (2013) was carry out animal study to the assessment of anti-diabetic effect of *Cissampelospareira* leaf extract and results support the medicinal uses of *Cissampelospareira* leaf in the treatment of diabetic\(^{(27)}\). Other in vivo studies done by Piero.et.al (2015).The result show that the hypoglycemic activities and safety of *Cissampeolspareira*\(^{(28)}\)

**Cyperusrotundus**

Another study with streptozotocin-induced mice given, ethanolic extract of *Cyperusrotundus* rhizomes has shown significant anti-diabetic activity, improvement in body weight, and reduction in elevated biochemical parameters such as SGPT, SGOT, cholesterol, and triglyceride levels \(^{(29)}\).

Raut.et.al evaluate the Anti-diabetic activity of hydroethanolic extract of rhizomes of *Cyperusrotundus* and the result conform the Anti-diabetic activity of *Cyperusrotundus*. This anti hyperglycemic activity can be attributed to its antioxidant activity as it showed the strong 11-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging action \(^{(30)}\).

Tran.et.al was conducted a laboratory study to Identification of Phytochemical from methanol extract compounds of *Cyperus. rotundus* rhizomes responsible for the inhibition of Alpha glucosidase and alpha-amylase. A new (2RS,3SR)-3,4,5,6,7,8-hexahydroxyflavane , together with three known stilbene dimers, cassigarol E, scirpusin A and B were isolated. Compound cassigarol E inhibited both Alpha -glucosidase and Alpha -amylase activities while the flavane 1 only showed effect on alpha-amylase, and compounds scirpusin A and scirpusinB were active on alpha-glucosidase. All four compounds showed significant 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity\(^{(31)}\).

*Cyperus. rotundus* has 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging Antioxidant action. *Cyperusrotundus* to suppress age formation and protein oxidation in a model of fructose-mediated protein glycoxidation. Scientists concluded that, since non-enzymatic glycation has been shown to correlate with severity of diabetes and its complications\(^{(32)}\).

**Strychnos potatorum**

*Strychnos potatorum* has anti-diabetic action. It causes an enhanced secretion of insulin on the pancreatic Beta-cells in as much as they block the ATP sensitive K+ channel which initiates the membrane depolarization process. This leads to the activation of the voltage operated calcium channels. The latter event elevates the free intracellular Ca++ concentrations which function as a coupling signal for the exocytosis of insulin that resides in the beta cells of pancreas. Potential to control post prandial hyperglycemia. Blood glucose lowering effect and significant increase in serum AST and ALT of ethanol extract of *Strychnos potatorum* was observed in alloxan diabetic rats as well as in fasted normal rats, this effect could, possibly be due to increased peripheral glucose utilization. Inhibition of the proximal tubular reabsorption mechanism for glucose in the kidney\(^{(32)}\).

Biswas.et.al was carry out the animal study to evaluate the anti-diabetic effect of *Strychnos potatorum on streptozotocin* induced male diabetic rats.in this study result conformed the *strychnos potatorum* has anti-diabetic action as it significantly reduce the blood sugar level\(^{(33)}\). Biswas.et.al was carry out the another animal study to compared with glipizide and conformed the *Strychnos potatorum* has effective hypoglycemic compound. Mishra.et.al (2013) reported that the ethanolic extract of Strychnospotatorum showed significant anti-diabetic action and antioxidant.

**IV. CONCLUSION**

This study had been given scientific explanation for ancient drug of Nelliayathi kasayam use of diabetic. That the Nelliayathi kasayam can be used as a siddha drug in treatment of diabetes mellitus. Further scientific evidence base on clinical studies are...
recommended with appropriate study design, adequate sample size, and statistical evidence to prove its therapeutic action.

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