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ABSTRACT

Manipur is a state in northeastern states of India with the city of Imphal, rich in flora and fauna including aromatic and medicinal plants of bioactive compounds. Thousands of plant species are estimated to have exist and has been in used since then as food, in prevention and treatment of different diseases in different ethnic traditional way. In today’s world Diabetes has been in transition, having long lasting effect in the economic growth of a nation. Inhabitants of Manipur takes different plant species as in form of raw leaves, stem, fruit, root, whole plant, and tender stalks etc. that are mostly associated with health benefits. More than 100 wild plants have been identified in the region. These plants are used traditionally to treat diseases like diabetes, asthma, arthritis, skin diseases, cough and fever. The review outlines the medicinal plants found in Manipur which has been used by the locals in preventing, curing and treatment of diabetes.

KEYWORD: Manipur, Traditional, Diabetes, medicinal plants, treatment.

INTRODUCTION

Medicinal plants, a natural source of bioactive compounds has been in use since thousands of years.\textsuperscript{[1]} The beginning of the medicinal plants use were instinctive, as in the case with animals.\textsuperscript{[2]} Healing with medicinal plants is as old as mankind itself. Contemporary science has knowledge in their active action and has included in modern pharmacotherapy, a range of drugs of plant origin.\textsuperscript{[3]} From 250 – 500 thousand plant species are estimated to exist, only 1-10 per cent are used as foods by humans and animals.\textsuperscript{[4]} Plants have been used
for flavor and conserve food, treat health disorder and to prevent diseases with its active compounds produced during metabolism which are responsible for various treatment of diseases and biological functions.\textsuperscript{[5]}

India leads the world and has been termed as diabetes capital of the world. The number of diabetes published in diabetes atlas 2006 by international diabetes federation, in India is 40.9 million people with diabetes currently which is expected to rise to 60.9 million by 2025.\textsuperscript{[6]} The epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary pattern and decreased physical activity with the trends of shifting age of onset of diabetes to younger age can have adverse long lasting effects on nation’s health and economy.\textsuperscript{[7]} The national study reported on overall prevalence of 2.1 per cent in urban areas and 1.5 per cent in rural areas. Environmental and lifestyle changes resulting from industrialization and migration to urban environment may be the reason responsible for epidemic of type 2 diabetes in India.\textsuperscript{[8]}

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The symptoms of mark hyperglycemia include polyuria, polydipsia, weight loss, polyphagia and sometimes blurred vision.\textsuperscript{[9]} Type I diabetes results from insulin deficiency following destruction of insulin producing pancreatic cells. It is most commonly present in childhood.\textsuperscript{[10]} The incidence of childhood diabetes is rising worldwide with 2-5 per cent in Europe, Middle East, Australia, \textsuperscript{[11]} <14 year ranging from 0.1/100,000 per year in china to 37/100,000 per year in Finland.\textsuperscript{[12]} Type II diabetes is characterized by disorder of insulin action and insulin secretion. The risk increases with age, obesity and physical inactivity.\textsuperscript{[10]}

\textbf{Plants that has anti-diabetic activity:} Manipur is a state in northeastern states of India with the city of Imphal as its capital. It is bounded by Nagaland-north, Mizoram to south, Assam to west and Burma lies to its east. The state covers an area of 22,327 sq.km.\textsuperscript{[13]} It is rich in flora and fauna including aromatic and medicinal plants of bioactive compounds.

People of Manipur use medicinal plants for treatment of diabetes giving its first preferences to herbal medicines.\textsuperscript{[14]} The inhabitants of Manipur states have the habit of eating raw leaves, young inflorescence, tender stalks and other plant parts.\textsuperscript{[15]} Medicinal plants are associated with folk traditions depending on the medicinal plants for treatment of diseases. About 1200 plants are used by practitioner in traditional home remedies.\textsuperscript{[16]} 100 wild plants belonging to
41 families had been collected in which 63 plants are aromatic and 37 plants are non-aromatic. 20 per cent of medicinal plants were used for treatment of diabetes, blood pressure, piles, 21 per cent for rheumatism, gout, 9 per cent for asthma, 6 per cent for stone case and 12 per cent for cancer. Medicinal plants like Adiantum Capillur, Aegle Marmelos, Ardisia Crenata, Lantana Camara Linn, Mangifera Indica Linn, Sesbania Sesban, Clerodendrum Viscosum Vvent, Fagopyrum Esculantium, Portulaca Oleracea are found in the hill stations of Manipur which are used as traditional herbs for diabetes.\cite{17}

Leishangthem et al (2014) revealed 50 medicinal plants, belonging to 26 families which are used for various treatment of diseases like asthma, arthritis, cough, fever, diabetes, gastric, skin diseases etc. which are found in Imphal east district of Manipur.\cite{64} Survey of anti-diabetic plant was conducted by Premila devi (2011) revealing 51 plant species which were commonly used by the Meitei community of Manipur for treatment of diabetes in their own traditional way of which plants parts like leaf, fruit, bark, seed, root, whole plant, flower, twig, rhizome, stem, bulb, root and bean are used.\cite{65}

**Aegle Marmelos**: Aegle Marmelos (A.Marmelos) also commonly known as wood apple plant belong to rutaceae family is used in the treatment of diarrhea and dysentery. Leaves of this plant used to cause infertility or abortion in women.\cite{18} The phytochemical screening of the crude extract of A.Marmelos revealed the presence of Reducing Sugars, Saponins, Tannis, Flavonoids and Phenols.\cite{19} The GC-MS analysis revealed the presence of many bioactive compounds such as flavonoids, alcohols, aldehydes, aromatic compounds, fatty acid methyl esters, terpenoids, phenolics, and steroids that can be postulated for antibacterial activity.\cite{20}

An ethanolic extract of A.Marmelos 2ml/day for 20 days reduces blood sugar in alloxan induced diabetic rats.\cite{21} A varying dose of A.Marmelos leaf extract on hyperalgesia in alloxan induced diabetic rats provides protection against diabetic neuropath in rats.\cite{22} Aqueous extract of A.Marmelos seed on a dose of 100,250,500mg/kg reduces fasting blood glucose by 60.84%, urine sugar 75 per cent, 33.43 per cent increased in HDL, decreased LDL and Triglyceride by 53.97 and 45.77 per cent indicating its anti-diabetic and hypolipidemic effects in diabetic rats.\cite{23} Oral administration of water extract of A.Marmelos 125 and 250mg/kg twice a day for 4 weeks in streptozotocin induced diabetic rats reduces blood glucose, plasma thiobarbituric reactive substances, hydroperoxides with significant elevation in plasma reduced glutathione and Vit.C.\cite{24}
Adiantrum Capillus – veneri: Adiantrum Capillus– veneri contains flavonoids, terpenoids, aoleananes, phenylpropanoids, carbohydrates, carotenoids and alicyclics.\(^{[25]}\) Plant leaves and stem were found to contain higher amount of fats, flavonoids, triterpenoids, phenols, tannins, saponins and fats.

Aqueous extracts at dose of (100, 200 and 400 mg/kg, orally) and methanol extracts at dose of (200 and 400 mg/kg, orally) in distilled water were administered daily for 21 days to streptozotocin induced diabetic rats, indicating a very good antidiabetic potential with very low side effects.\(^{[26]}\)

Total extract of the plant was prepared by boiling the dried material with water. The extract was given to mice (25 mg/kg) orally and found to reduce glucose-induced hyperglycemia.\(^{[27]}\)

Lantana Camara: Lantana camara have therapeutic potential due to the presence of natural agents like flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins, isocatechins, alkaloids, tannin, saponins and triterpenoids.\(^{[28]}\) Lantana camara is well known to cure several diseases and used in various folk medicinal preparations.\(^{[29]}\)

Administration of the methanol extract of L. camara (400 mg/kg body weight) leaves orally to induced diabetic rats resulted in decrease in blood glucose level to 121.94 mg/dl.\(^{[30]}\) Carbohydrates, cardiac glycosides, flavonoids, polyphenols, sterols, saponins, tannins and triterpenoids were present in the extract and fractions. Triterpenes were isolated from the aqueous and n-butanol fractions via oral administration for 28 days to observe induced alloxan diabetic rats showed hypoglycaemic activity and hypolipidaemic effect.\(^{[31]}\) 200 and 400mg/kg body weight of oral administration of methanol extract of Lantana Camara in alloxan induced diabetic rats reduces blood glucose. Treatment with extract of 400mg/kg body weight reduces blood glucose level to 121.94mg/dl, also effective against hyperlipidemias.\(^{[32]}\)

Sesbania sesban: Preliminary Phytochemical screening revealed the presence of several chemical compounds such as alkaloids, phytosterol, phenol, flavonoids, fixed oil and gum, triterpenoids, carbohydrates, vitamins, amino acids, proteins, tannins, Saponins, glycosides and steroids. Flowers contain cyanidin and delphinidin glucosides. Pollen and pollen tubes contain alpha-ketoglutaric, oxaloacetic and pyruvic acids.\(^{[38, 39]}\)
The aqueous leaves extract of *Sesbania sesban* (L) Merr. (Family: Fabaceae) was administered to normal and STZ-induced diabetic rats at the doses of 250 and 500 mg/kg body weight (b.w.) per day for 30 days and indicated significant increase in the body weight, liver glycogen, serum insulin and HDL levels and decrease in blood glucose, glycosylated hemoglobin, total cholesterol and serum triglycerides.\[^{40}\] *Sesbania sesban* was administered orally at different doses (250, 500 and 1000mg/kg) to normal and streptozotocin (STZ) induced type-2 diabetic mice. It decreased the cholesterol, triglyceride (TG), urea, creatinine level and increased the insulin, HDL cholesterol, and total protein level. Decrease in body weight and glycogen level induced by STZ was restored.\[^{41}\]

*Clerodendrum Viscosum Vent*: Phytochemical analysis displayed that the plant extract contains carbohydrates, glycosides, tannins, saponins, flavonoids, alkaloids, carbohydrates and steroids types of compounds.\[^{42, 43}\] *Clerodendrum viscosum* (Vent.) methanolic leaves extract dose of 500mg/kg significantly reduces the blood glucose level at 1\(^{st}\) hour to 3\(^{rd}\) hour 130 to 36 mg/dL in *in-vivo* induced alloxan diabetic mice model.\[^{44}\] Administration of methanol extract of leaves at doses of 200 and 400 mg per kg body weight in glucose-loaded mice reduced blood glucose levels by 25.2 and 33.3\%, respectively.\[^{45}\]

*Portulaca oleracea*: *Portulaca oleracea*, has active compounds such as flavonoids, alkaloids, polysaccharides, fatty acids, terpenoids, sterols, proteins vitamins and minerals. *Portulaca oleracea* possesses a wide spectrum of pharmacological properties such as neuroprotective, antimicrobial, antidiabetic, antioxidant, anti-inflammatory, anti-ulcerogenic, and anticancer activities.\[^{46}\] The effect of hydroalcoholic combined plant extract containing seeds of *Portulaca oleracea* and whole plant of *Caralluma attenuata* extract at doses of 100 and 200 mg/kg body weight for 28 days in Streptozotocin induced diabetic rats showed a an improve alterations in blood glucose levels, serum triglyceride, serum cholesterol, liver glycogen, glycosylated hemoglobin and body weight.\[^{47}\]

Polysaccharide from *Portulaca oleracea* L. (POP) treatment (200, 400 mg/ kg body weight) for 28 days resulted in a significant decrease in the concentration of fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG) in diabetes mellitus mice and increased the concentration of high-density lipoprotein cholesterol (HDL-C) and serum insulin level.\[^{48}\] Oral administration of the *Portulaca oleracea* extract (PE) 75mg/kg alone and plus gliclazide (GI), to diabetic rats for 15 and 30 days resulted in a significant decrease in the level of blood glucose, with a concomitant increase in serum insulin level as compared to untreated diabetic
rats.\textsuperscript{[49]} 30 subjects with type-2 diabetes receive 5 g of \textit{Portulaca Oleracea} (PO) seeds twice daily showed a significant decrease in serum levels of triglycerides (TGs), total cholesterol (TC), low density lipoprotein cholesterol (LDLC), liver alanine-, aspartate- and gamma glutamyl transaminase (ALT, AST, and GGT), total and direct bilirubin, fasting and post-prandial blood glucose, insulin, body weight and BMI while a significant increase in high density lipoprotein cholesterol (HDLC) and albumin but nonsignificant change of alkaline phosphatase (ALP).\textsuperscript{[50]}

\textit{Cassia Alata}: The presence of varying quantities of saponins, flavonoids, tannins, oxalate and alkaloids. 500mg/kg body weight of ethanolic leaf extract of cassia alata via orogastric tube for 28 days on streptozotocin induced diabetic rats, showed reduced Blood sugar level and histology revealed regeneration of destroyed pancreatic islet cells inferring that \textit{Cassia Alata} potentiates the regeneration of beta cells in the pancreas of diabetic rats and has hypoglycaemic effect.\textsuperscript{[51]} The \(\alpha\)-glucosidase inhibitory effect of the crude extract has the possible antidiabetic mechanisms of action by inhibiting carbohydrate digestion.\textsuperscript{[52]}

\textit{Sesbania grandiflora}: One of the medicinal plants used for antioxidant activities. It contains several kinds of alkaloids, flavonoids, saponins, tannin, diterpenes, triterpenoids, glycosides, phenols, carbohydrates, chlorogenic acid and anthocyanin.\textsuperscript{[53,54]} The methanolic extract of \textit{Sesbania Grandifola} leaves at dose level of 100,200 and 400 mg/kg in glucose overloaded hyperglycemic rats exhibiting a significant antihyperglycemic activity, reduced serum lipid profile like total cholesterol, triglycerides, LDL, VLDL and increasing HDL.\textsuperscript{[55]}

Antidiabetic activity was screened in alloxan induced diabetic rats at dose of 250 mg/kg and 500 mg/kg of the 70\% alcoholic extract of \textit{Sesbania grandiflora} flower for 28 days per orally showed anti-diabetic ctivity and reduces serum total cholesterol, triglycerides, SGOT, SGPT and BUN in diabetic rats.\textsuperscript{[56]} Sangeetha et al.\textsuperscript{[57]} studied the 300 mg/kg S. grandiflora leaves using streptozotocin induced diabetic rats for 30 days. The results showed the effects of this plant also restored all the biochemical parameters such as glucose, glycosylated hemoglobin, blood urea nitrogen, uric acid, creatinine, aspartate and alanine transaminase, alkaline phosphatase, glycogen content.

\textit{Stevia rebaudiana}: Phytoco\textit{chemical screening of aqueous (AE), ether (EE) and methanolic (ME) extracts of S. rebaudiana indicates the presence of alkaloids, steroidal compounds, phenols, flavonoids, saponins and tannins. 50 and 100 mg/kg daily dose administration of}
aqueous, ether and methanol extract of *Stevia rebaudiana* on alloxan induced diabetic rats for 28 days. The blood glucose levels were 220.16 ± 8.63, 220.00 ± 11.20 mg/dl in AE-, 209.66 ± 4.15, 220.83 ±09.24 mg/dl in EE-, 218.66 ±4.93, 232.00 ± 11.81 mg/dl in ME-treated rats on day 0. The blood glucose level was significantly reduced after 28 days of administration with greater effect at the dose of 100mg/kg. [58]

The antidiabetic effect might be due to steviosides counteracting the glucotoxicity in β-cells or also by suppressing the glucagon secretion by α-cell of pancreas.[59, 60] Stevioside, a glycoside of *Stevia rebaudiana* was able to regulate blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats; the latter was due to decreased PEPCK gene expression in rat liver by stevioside's action of slowing down gluconeogenesis. [61] Stevia leaves and its extracted polyphenols and fiber was fed on streptozotocin induced diabetic rats for one month. Stevia leaves extract has the potential of reducing blood glucose, ALT and AST, and increment of insulin level. [62] Leaf extract (0.5g and 1g) of Stevia leaf powder was given three times a day with tea to 15 diabetic patient between the age group of 35-60 years for 15 days and their glucose level were measured. There was a significant decrease in the fasting blood sugar, FBS (195.7) and post prandial blood sugar, PPBS (271.3) while consuming Stevia leaf powder. [63]

*Alocasia Indica:* The ethanolic extract of *Alocasia indica* tuber was found to be rich in carbohydrate, marginal protein content. Moderate amount of dietary crude fiber, very low fat content and sufficient source of ascorbic acid and alpha-tocopherol. The tuber was also found to contain all the essential micro and macro mineral elements. It especially served as a good source of potassium and calcium while moderate source of iron, zinc and magnesium. [66]

Preliminary Phytochemical screening indicated the presence of phenolic compounds (flavonoids) & steroids. Alcoholic extract of *Alocasia indica* leaves at dose of 200 & 400 mg kg-1 b.w. for 21 days to streptozotocin induced diabetic rats was orally administered. At the end of experiment blood glucose level was 131.98±0.98 & 105.26±0.87 mg/dl at the doses of 200 & 400 mg kg-1 of alcoholic extract of *Alocasia indica* leaves respectively indicating significant reduction in blood glucose levels and reducing serum cholesterol and triglycerides level thereby increasing HDL-cholesterol. [67] Ethanolic extract of *Alocasia indica* (EEAI) rhizomes 100 and 200 mg/kg b.w. was administered to diabetic rats for 28 days in HFD/STZ-induced Type 2 diabetic rats and for 15 days in STZ/nicotinamide-induced Type 2 diabetic rats resulting in a significant decrease in blood glucose level and significant increase in body
weight in the HFD/STZ and STZ/nicotinamide-induced Type 2 diabetic rats, also showed antihyperlipidemic activity.[68]

**Andrographis paniculata**: 20 patients with type 2 diabetes mellitus were given powdered *A. paniculata* starting with 600 mg daily, gradually increasing to a maximum of 1.8 gm daily for a period of 12 weeks significantly lowered HbA1c and fasting serum insulin in patients with type 2 diabetes. These results suggest that the mechanism of action of *Andrographis* is by increasing peripheral utilization of glucose, probably by potentiating insulin action and not by a direct insulin releasing action on islet cells in pancreas.[69] Oral administration of the crude ethanolic extract of *Andrographis paniculata* in normal and streptozotocin (STZ)- at different doses (0.1, 0.2, and 0.4 g/body weight) were administered to induced diabetic rats for 15 days significantly reduced the fasting serum glucose level.[70]

Oral administration of 1000 mg/kg extract to streptozotocin-diabetic rats for 30 days was able to cause a significant (p<0.05) reduction of elevated glucose-insulin index, signifying a potential insulin sensitizing effect. The ethanolic extract of *Andrographis paniculata* may have an insulin sensitizing effect, by attenuating the impairment of insulin stimulated glucose disposal in insulin resistant rats. This probably indicates that the extract may increase the activity of endogenous insulin to improve insulin resistance condition.[71] Hyperglycemia in rats was induced by high-fructose-fat diet containing 36% fructose, 15% lard, and 5% egg yolks in 0.36 g/200 g b.wt. 55 days of dose 434.6 mg/kg BW and 1303.8 mg/kg orally, twice daily. At doses of 434.6 and 1303.8 mg/kg b.wt twice daily the extract decreased the pre-prandial blood glucose level by 41.12 ± 7.50% and 45.76 ± 9.89%, postprandial blood glucose level by 53.55 ± 13.75% and 60.14 ± 12.39% respectively.[72]

**Passiflora edulis**: On supplementation of 30g/day of *passiflora edulis flavicarpa* fruit peel flour for 60 days among type II diabetic patient , blood glucose (T0 = 162.55 ± 52.09, T60= 120.83 ± 36.72), glycated hemoglobin (T0 = 6.58 ± 3.04, T60= 5.71 ± 1.82) was significantly reduced. The presence of fibers, pectin which forms viscous mixture can change the gastric emptying time, increases satiety and delay the absorption of simple carbohydrates, also ability to form complexes with bile salts increases the cholesterol excretion.[73] Passion fruit has a significant content of iron, potassium, zinc and manganese. The diet contain 5% flour of passion fruit peel reduces blood glucose by 59% in diabetic rats reaching the normal glycemic amount (112.6mg/dl). The mechanism is due to the presence of fiber, tannins and
phenolic compounds\textsuperscript{1} which reduces the digestion and absorption of carbohydrates, increased the sensitivity of muscle and adipose tissue to insulin.\textsuperscript{74, 75}

\textbf{Bombax ceiba} Linn

Oral doses of 200, 400, 600 mg/kg/day was administered to streptozotocin-induced diabetic rats for 21 days. The results showed that a dose of 600 mg/kg of B. ceiba extract is the most effective to cause significant (p<0.001) hypoglycemic and/or hypolipidemic effects on streptozotocin-induced diabetic rats. Phytochemical and GC-MS studies confirmed the presence of the triterpenoid compounds in the extract, which may account for its significant hypoglycemic activity.\textsuperscript{76}

\textbf{Brucea javanica} Linn

Bioactivity-guided fractionation of bruceines E (1) and D (2) from \textit{Brucea javanica} Linn was isolated, administered 1mg/kg to normoglycemic mice and streptozotocin induced diabetic rats reduces blood glucose concentrations significantly of 40.07+/−11.45\% and 48.82+/−13.34\%, and blood glucose concentration reduction of 73.57+/−13.64\% and 87.99+/−2.91\%, respectively.\textsuperscript{77} Antidiabetic activity was evaluated both in vitro and in vivo using a glycogen phosphorylase α (GPα) inhibition assay and oral glucose tolerance test (OGTT) in nondiabetic rats. The ethyl acetate fraction (EAF), rich in tannin, exhibited the strongest antioxidant activities to DPPH, FRAP, and NORSA, except for FCA. The EAF also exerted a dose-dependent inhibition of GPα (IC\textsubscript{50} = 0.75mg/ml). Further evaluation of hypoglycemic effect on OGGT indicated that rats treated with EAF (125mg/kg bw) showed a 39.91\% decrease (\textit{P} < 0.05) in blood glucose levels at 30 min, and continuous fall (\textit{P} < 0.05) of 28.89\% and 20.29\% was observed in the following hours (60 and 90 min) compared to the normal control during OGTT.\textsuperscript{78}
CONCLUSION
Considering the health benefits of different plant species found in Manipur, with its rich bioactive compounds, can be used in prevention and treatment of diabetes. Traditional
knowledge about using herbs by the forefathers in alleviating has been acquired through traditional medicine practioners known as maibi / maiba. Younger generations should focus on this traditional plants and do extensive research in treating diseases. An urgent need is to explore ethnobotanical potential of the area extensively, to identify plants of pharmaceutical value which will bridge the gap in research in treatment and development of pharmaceutical drug.

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