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INVESTIGATIONS ON SOME PLANTS FOR THE MANAGEMENT OF TYPE 2 DIABETES AND DIABETIC WOUND HEALING ACTIVITY

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ABSTRACT

Medicinal plants are sources of health-promoting substances, including phytochemicals and phytoalexins that comprise polyphenols, flavonoids, carotenoids, vitamins A, C, E and several other constituents. Due to the present fast life of the humans a drastic increase in chronic disease conditions mainly diabetes has been determined. Most of these patients tend to face a tremendous problem when they get an infected wound. Plants and their extracts have a tremendous potential in the management and treatment of wounds. The phyto-medicines for wound healing are not only cheap and cost-effective but also reportedly safe as compared to allopathic drugs in context of hypersensitive reactions. The presence of various life sustaining constituents in the plants has also urged scientist to examine these plants with a view to determine their potentiating wound healing properties. The work includes a list of traditionally claimed plants used for type 2 diabetes and diabetic wound healing which are scientifically proved as well as scientifically not proved. Considering the importance of medicinal plants in terms of their beneficial health effects, some of the medicinally important plants used for the management of type 2 diabetes and diabetic wound healing are covered in this review with respect to their pharmacological and phytochemical profile.

Keywords: Type 2 diabetes, Diabetic wound healing, Medicinal plants, *Corchorus olitorius*

INTRODUCTION

Diabetes mellitus is a major endocrine disorder, affecting approximately 5% of the world's population. WHO estimates that almost 3 million deaths occurring annually are as a result of diabetes and that there will be 366 million cases of diabetes by the year 2030.[1] Diabetes is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolisms, which not only lead to hyperglycaemia but also cause many complications such as hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis.[2,3] Wound is an injury, especially one in which the skin or another external surface is torn, pierced, cut or otherwise broken with disruption of normal continuity of structures. [4] Wounds are the unavoidable events of life. It may be produced by physical, chemical, thermal, microbial or immunological insult to the tissue.[5] They result in the loss of continuity of epithelium with or without the loss of underlying connective tissue.

Diabetes mellitus is one of the major contributors to chronic wound healing problems. When diabetic patients develop an ulcer, they become at high risk for major complications, including infection and amputation. The pathophysiological relationship between diabetes and impaired healing is complex. Vascular, neuropathic, immune function and biochemical abnormalities each contribute to the altered tissue repair. Despite treatment of these chronic wounds, which involves tight glucose control and meticulous wound care, the prognosis for their healing is quite poor. [6] Wound healing is impaired in diabetic patients with infection or hyperglycemia.[7] The prevalence of chronic wounds in the community was reported as 4.5 per 1000 population, whereas that of acute wounds was nearly double, at 10.5 per 1,000 populations.[8]

Efforts are being made worldwide to discover newer drugs that can promote diabetic wound healing with minimal side effects and to reduce the cost of hospitalization and management of complications. Medicinal plants are known to induce wound healing and regeneration of injured tissues by multiple mechanisms, one of such is *Corchorus olitorius* however there is not much scientific information regarding its diabetic wound healing activity. There is the need for scientific investigation and safety evaluation of plant medicines used in folklore before they could be recommended for use.[9] *Corchorus olitorius* (Tiliaceae) is an annual herb whose leaves and roots are used as herbal medicine and eaten as vegetable by local people in East Malaysia, India, Egypt, and Philippines. [10] Traditionally, its leaves are used in the treatment of pain, fever, chronic cystitis and tumors.[11] The leaves of *Corchorus olitorius* were reported to exhibit antioxidant,[12] antitumor,[13] gastroprotective,[14] antibacterial and antifungal,[15] anti-inflammatory and analgesic [16] activities. In addition, the leaves are used as demulcent and febrifuge.[17] Therefore in the larger perspective of usefulness and nutritional values of indigenous leafy vegetable like jute (*Corchorus olitorius*) is required to be rediscovered and establish on scientific ground.

Since, pharmaceutical products used for the management of diabetes are expensive for rural populations and may induce serious side effects, medicinal plants are used predominately to treat this disease. Plant products are potential agents for wound healing and largely preferred because of their widespread availability and effectiveness as crude preparations.

Medicinal plants used for the management of type 2 diabetes

The chloroform extracts of *Acacia arabica* (Leguminosae) bark in diabetic rats at 250 and 500 mg/kg, p.o. for two weeks, significantly decreased the serum glucose level and restored total cholestrol (TC), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) level. Moreover chloroform extract of *Benincasa hispida* fruit, *Tinispora cordifolia* stem, *Ocimum sanctum* (O. sanctum) areal parts and *Jatropha curcus* leaves were shown the similar effect in the diabetic rats.[18]

The aqueous and ethanolic extracts of *Achyranthes rubrofusca* (Amaranthaceae) leaves in diabetic rats were investigated for anti -diabetic activity. It decreased the blood glucose level significantly, pancreatic enzyme such as superoxide dismutase (SOD), catalase (CAT) and glutathione level were significantly increased in the treated group compared to control group. Further aqueous extract showed better result compared to the ethanolic extract.[19]

The oral administration of ethanol extract of *Andrographis paniculata* (Acanthaceae) in diabetic rats at a dose of 100 and 200 mg/kg, p.o. for 30 days treatment, significantly decreased the blood glucose level. Further it restored TG, TC, phospholipids, glycosylated hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), acid phosphatase (ACP) and alkaline phosphatase (ALP) level which indicates its anti-diabetic activity. [20]

The anti- diabetic activities of ethanol extract of leaves of *Argyriea cuneata* (Convolvulaceae) in diabetic rats were investigated and found to have significant anti-diabetic as well as lipid lowering potential. [21]

Alcoholic extracts of leaf and root of *Barleria prionitis* (Acanthaceae) in diabetic rats at 200 mg/kg, p.o. for 14 days treatment, significantly decreased blood glucose and glycosylated hemoglobin level. Moreover, serum insulin and liver glycogen level were significantly increased.[22]

The aqueous and ethanolic extract of *Capparis decidua* (Capparaceae) stem in diabetic rats at 250 and 500 mg/kg, p.o. for 21 days treatment significantly decreased the blood glucose level which signified its anti-diabetic potential. [23]

The aqueous and ethanolic extracts of *Cassia grandis* (Leguminosae) in diabetic rats at the dose level of 150 mg/ kg, p.o. for ten days treatment, significantly decreased the blood glucose, TC, and TG level proving its anti-diabetic potential. [24]

The anti-diabetic activity of ethanolic extract of the leaves of *Ceriops decandra* (Rhizophoraceae) in diabetic rats at 30, 60, 120 mg/kg, p.o. for 30 days treatment were investigated. Extract treated group modulated all the parameters such as blood glucose, hemoglobin, liver glycogen and some carbohydrate metabolic enzymes. Further 120 mg/kg, p.o. dose level was found to be more significant compared to other tested dose level. [25]

Ethanol extract of *Colocasia esculenta* (Araceae) in diabetic rats at at 400 mg/kg, p.o. for 14 day, significantly decreased the blood glucose level and prevented loss of body weight. It indicates its anti-diabetic potential. [26]

Ethanolic extracts of leaves of *Costus igneus* (Costaceae) extracts in diabetic albino rats showed significant reduction of blood glucose level and prevented body weight loss indicating its anti-diabetic potential. [27]

Aqueous extract of *Eucalyptus citriodora* (Myrtaceae) leaf in diabetic rats at 250 and 500 mg/kg, p.o. for 21 days treatment, significantly reduced the blood glucose level which confirms its anti-diabetic potential. [28]

The aqueous extract of *Ficus bengalensis* (F. bengalensis) (Moraceae) bark in both insulin dependent diabetes mellitus (IDDM) and N on-insulin dependent diabetes mellitus (NIDDM) rats at 1.25 g/kg, p.o. for 4 weeks, significantly decreased the plasma glucose and serum lipids level. It shows anti-diabetic potential of F. bengalensis. [29]

The ethanolic leaf extract of *Heinsia crinata* (Rubiaceae) in diabetic rats for 2 weeks, significantly reduced the fasting blood glucose levels. It indicates its anti-diabetic potential. [30]

The ethanolic and aqueous extracts of stem of *Ipomoea reniformis* (I. reniformis) (Convolvulus) in diabetic rats at 300 and 600 mg/kg, p.o. for 12 days treatment, significantly decreased the blood glucose and lipid level. From the obtained data it was found that *I. reniformis* have significant anti-diabetic antihyperlipidaemic potential. [31]

Anti- diabetic effects of methanolic extract of *Juglans regia* (J. regia) (Juglandaceae) leaves was estimated in diabetic male wistar rats at 250 mg/kg and 500 mg/kg, p.o. for three weeks. *J. regia* significantly decreased the blood glucose, TG and TC level. Further it increased GPX, SOD and cell antibody level significantly and therefore signified its anti-diabetic potential.[32]

The anti-diabetic effect of ethanolic extract of the dried mature roots of *Lantana aculeata* (verbenaceae) in diabetic rats at 25, 50 and 100 mg/kg, p.o. for 30 days treatment, was assessed. The plant significantly reduced the blood glucose level. Further it decreased TC and TG level and increased insulin and glycogen concentration in a dose-dependent manner, justifying its anti-diabetic potential. [33]

Methanolic extract of *Limonia acidissima* (R utaceae) in diabetic rats at 200 and 400 mg/kg, p.o. for 21 days treatment, significantly decreased the blood glucose and malondialdehyde (MDA) level. Further the activity of antioxidant enzymes such as SOD, CAT was found to be higher in treated group compared to the control group which shows the anti-diabetic and antioxidant potential of the plant. [34]

The alcoholic and aqueous extracts of *Luffa aegyptiaca* (Cucurbitaceae) in diabetic rats at 100 mg/kg, p.o. for 15 days treatment, significantly decrease the blood glucose of hyperglycemic rats which signifies its anti- diabetic potential. [35]

Anti- hyperglycemic and anti-oxidative potential of aqueous extracts of *Momordic charantia* (*M. charantia*) (Cucurbitaceae) pulp in diabetic rats for 30 days treatment were investigated. *M. charantia* extract significantly decreased the blood glucose levels. Moreover all other parameter was significantly restored in the treated group compared to control group. Further similar activity was found with the *T. foenum graecum* extract treatment. [36]

The methenolic root extract of *Mukia maderaspatana* (Cucurbitaceae) in diabetic rats at a dose of 500 mg/kg, p.o. for 21 days treatment, significantly decreased the blood glucose, TC, TG, LDL, phospholipids and very-low density lipoprotein (VLDL) level. Further it decreased serum glutamate oxaloacetate transaminases (SGOT), serum glutamate pyruvate transamineses (SGPT), alkaline phosphateses (ALP) and increased total protein (TP) content significantly at tested dose level. [37]

The ethanolic extract of *Nymphaea pubescens* (Nymphaeaceae) in diabetic rats at 200 and 400 mg/kg, p.o. after 14 days treatment significantly reduced the blood glucose level. Further histopathological examination of pancreas revealed its regenerative potential corroborating its anti-diabetic potential. [38]

The methanolic extracts of *Ocimum gratissimum* (Lamiaceae) in diabetic Wister rats at 500 mg/kg, p.o. showed significant reduction of blood glucose level. Moreover methanolic extracts of *Ocimum americanum, O. sanctum* and *Ocimum basilicum* also showed similar effect in the diabetic rats, with maximum potential in case of O. sanctum compared to the other tested extracts. [39]

Aqueous and ethanolic extracts of *Paspalum scrobiculatum* (Poaceae) in diabetic rats at 250 and 500 mg/kg, p.o. for 15 days treatment, significantly reduced the blood glucose level and lipid parameters. Further extract treated group showed a significant increase in the liver glycogen contents and a significant decrease in glycated haemoglobin level. Moreover 500 mg/kg, p.o. dose level showed more significant anti-diabetic activity compared to the 250 mg/kg, p.o. dose level. [40]

The *Phoenix dactylifera* (*P. dactylifera*) (Arecaceae) leaf extract in diabetes Wistar rats at 100, 200, and 400 mg/kg, p.o. and its fractions at 50, 100 and 200 mg/kg, p.o. for 14 days treatment, significantly reduced blood glucose, TC, TG level and water intake but increased plasma insulin level significantly compare to control group. The data obtained from experiment showed that *P. dactylifera* have anti-diabetic potential. [41]

The methanol extract of aerial parts of *Phyllanthus niruri* (Euphorbiaceae) in diabetic rats significantly reduced the blood glucose, TC and TG in a dose -related manner. Moreover, histological studies showed that extract had imparted cell regenerative power in drug treated group which boosted its anti-diabetic potential.[42]

Various fractions of *Phyllanthus simplex* (Euphorbiaceae) such as petroleum ether (200 and 400 mg/kg), ethyl acetate (100 and 200 mg/kg), methanol (125 and 250 mg/kg), water fraction (150 and 300 mg/kg) were investigated for their anti-diabetic potential. Methanol (125 and 250 mg/kg) and aqueous fractions (150 and 300 mg/kg) showed significant antihyperglycemic effect. The active fractions also restored the antioxidant enzymes levels in liver and kidney. [43]

The standardized ethanolic extract of *Pongamia pinnata* (*P. pinnata*) (Fabaceae) in diabetic rats was tested for its anti-diabetic potential. After 21-day treatment it was found that *P. pinnata* posseses significant anti-diabetic activity. [44]

Antihyperglycemic and hypolipidemic effects of aqueous leaf extracts of *Solanum nigrum* (*S. nigrum*) (Solanaceae) in diabetic rats at 200, 400 mg/kg b.w. for 21 days treatment was investigated. Extracts of *S. nigrum* significantly reduced the blood glucose and other lipid parameter. Similar effect was also found with Musa extract. These findings show the anti-diabetic potential of these two plants. [45]

The methanolic extract of seeds of *Sphenostylis stenocarpa* (Leguminosae) in diabetic rats at the doses of 200, 400 and 600 mg/kg, p.o., significantly reduced the blood glucose level. Moreover, 600 mg/kg, p.o. was found to be more significant compared to other tested dose level. [46]

Ethanolic extract of leaves of *Tephrosia villosa* (Fabaceae) in diabetic rats at two different doses, showed significant reduction in the blood glucose level. Moreover, histopathological examination of pancreas showed regenerative power and therefore signified its anti-diabetic potential. [47]

The anti-diabetic activity of ethanol extract of *Trigonella foenum-graecum* (Fabaceae) seeds in diabetic rats at 2 g/ kg, 1 g/kg, 0.5 g/kg and 0.1 g/kg, p.o. was investigated and it was found to have significant blood glucose lowering capacity. Further among all the tested dose level, 1 g/kg, p.o. was found to be more significant comparing to other dose levels. [48]

Treatment with ethanolic extract of *Triumfetta rhomboidea* (T. rhomboidea) (Malvaceae) in diabetes rats at doses of 100, 200, and 400 mg/kg, p.o., significantly decreased the blood glucose level in dose dependent manner. From the data it was found that *T. rhomboidea* has significant anti-diabetic potential.[49]

The anti-diabetic activity of the various combinations of metformin (50 mg/kg) and aqueous extracts of the leaves of *Vernonia amygdalina* (Asteraceae) (100 mg/kg) in diabetic rats were investigated. Extract and metformin at the ratios of 1:1 and 2:1 were given to both normoglycemic and diabetic. From the data it was found that, blood glucose level was decreased more significantly by the drug combination compared to the single treatment of the drug in the diabetic rats. [50]

The petroleum ether and aqueous extract of *Zizyphus mauritiana* (Rhamnaceae) at 200 and 400 mg/kg, p.o. doses, significantly restored the elevated biochemical parameters such as glucose, urea, creatinine, TC, TG, HDL, LDL, hemoglobin, and glycosylated hemoglobin. From the obtained data it was found that this plant had significant anti-diabetic potential. [51]

Medicinal plants used for the management of diabetic wounds

Romero-Cerecero et al. (2014) aimed to investigate the wound healing and possible genotoxic effects of the standardized aqueous and hexane-ethylacetate extracts of A. *pichinchensis* by using a diabetic foot ulcer rat model. A. pichinchensis accelerated wound healing in diabetic rats without inducing genotoxicity. [52]

The diethyl ether extract of *Malva sylvestris* and *Punica granatum* flowers were used to evaluate the wound healing activity at 200 mg/kg/day dose in alloxan-induced diabetic rats.

Extracts of *Argyreia nervosa* (Convolvulaceae) showed significant wound healing effect in normal (topically treated) and diabetic (both topically and orally treated) rats. In diabetic rats, the topically treated group showed more significant effect than the orally treated groups. [53]

Murthy S. *et al,* (2013), wound healing effects of 50% ethanol extract of dried whole plant of *Bacopa monniera* (BME) was studied on wound models in rats. BME (25 mg/kg) was administered orally, once daily for 10 days (incision and dead space wound models) or for 21 days or more (excision wound model) in rats.[54]

A 10% methanolic extract of the root of *Onosma hispidum* was prepared as an ointment, which exhibited significant increase in mean percentage wound contraction and tensile strength in excision and incision wound models, respectively, in both normal and diabetic rats. [55]

An overview and future scope

Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes. *Galega officinalis* is rich in guanidine, the hypoglycemic component.

Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available.

Traditional medicine (herbal) is used for treatment of diabetes in developing countries where the cost of conventional medicines is a burden to the population. India is the largest producer of medicinal herbs and is called the botanical garden of the world. [56-60] Ethnobotanical information reports about 800 plants which possess anti-diabetic potential. [61] Plant products are known to be rich in phenolic compounds, flavonoids, terpenoids, coumarins and other constituents which reduce blood glucose levels. In the current review most of the plants have the flavonoid, and terpenoids may be the reason for reducing the blood glucose level in animals.

Plant based drugs have been known to be safe and cheaper and the plant play the major role to manage the diabetes mellitus. World health organisation (WHO) has recommended the evaluation of traditional plant treatments for diabetes as they are effective, non-toxic, which less or no side effects and are considered to be a valuable source for the investigation of hypoglycaemic agents. Several reviews on the plants used in the management of diabetes have been reported in the past.

Use of medicinal plants is expected to rise globally, due to increasing trend towards self-medication, reduction in costs of subsidized health care, various international and national organizations improving the status of herbal medicine industry and renewed interest of companies in isolating useful compounds from the plants. It implies increasing pressure on wild plant resources and therefore, the need for serious conservation efforts including development of cultivation techniques has never been greater. Serious over-exploitation of many medicinal plants such as Rauwolfia, Dioscorea, *Swertia chirata*, Valeriana, Orchis and *Harpagophytum procumbens* has already occurred.

Despite of so much potential and scope of future development of plant drugs, a mere two per cent of the flora provided by nature is being used beneficially. The major pitfalls in plant drug research include a lack of standardization, confusion in nomenclature, controversial botanical identification, danger of extinction of some plants due to extensive exploitation, lack of proper dosage formulation and bitter experiences of searching for a single active principle. Modern instrumentation and biological assay methods provide the possibility of developing suitable quality control criteria for herbal drugs. The structural determination of novel plant constituents can be performed with minimal delay by using a combination of sophisticated spectroscopic and X-ray crystallographic techniques. High-throughput automated bioassays are widely available, so that a detailed biological profile can be obtained easily on just a few milligrams of a natural product. With the support of novel advances in techniques, there is

every indication that the direct utility and promise of plants for the improvement of human health will continue well into the 21st century.

Prevalence of diabetes is increasing 3% annually. This increase in the disease burden is believed to be caused by the number of factors such as gene defect and the environment. Therefore, as the disease is progressing unabated, there is an urgent need of identifying indigenous natural resources such as *Corchorus olitorius,* in order to procure them, and study in detail, their potential on different newly identified targets in order to develop them as new therapeutics. The current review showed that plants possessed antidiabetic property as well as diabetic wound healing potential and may of the study not properly mention the precise mechanism of the plant and the active compound responsible for the antidiabetic effect.

Conclusion

Although modern medicine is well developed in most of the world, large sections of the population in developing countries still rely on traditional practitioners, medicinal plants and herbal medicines for their primary care. Despite the great strides that have been made in understanding and management in this disease, serious problems like diabetic retinopathy, diabetic nephropathy and lower extremity amputation continue to confront patients and physicians. It is important therefore, that herbal medicines and preparations should be taken with the consideration of their holistic therapeutic approach. The multiple activities of plant-based medicinal preparations meant for diabetes offer enormous scope for combating the threat of the diabetic epidemic. A sound basic and rigorous clinical investigation to confirm and advocate the excellence over the existing therapies of traditional medicinal plants, preparation(s) mechanism(s) of action and therapeutic effects is absolutely required. This article presents an overview of medicinal plants and discusses the present status and future prospects for the management of type 2 diabetes and diabetic wound healing activity.

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