Review Article

Didymocarpus pedicellata: Bioactive Constituent, their Molecular Target in Diabetes Mellitus

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ABSTRACT

Didymocarpus pedicellata (Family: Gesneriaceae), is an herbal drug traditionally used in renal disorders mainly as antiurolithiatic and do not have much data on this plant, is selected for study and hereby reviewed. This review is based on compilation of data from the various researchers on their research work and other data including anti-diabetic activity of *Didymocarpus pedicellata* and antioxidant activity in relation with the type 2 diabetes mellitus and its cardiovascular complications. By using various scientific studies, the evidence has been demonstrated as to the antidiabetic effect of the various extract of *Didymocarpus pedicellata* as well as its chemical constituents including various flavonoid like chalcones which are major bioactive constituents chiefly present in *Didymocarpus pedicellata.* The chalcones present in these plants have various therapeutic targets for the management of type 2 diabetes like PPAR-g, DPP-4, a-glucosidase, PTP1B, aldose reductase, and stimulate insulin secretion and tissue sensitivity. The *Didymocarpus pedicellata* has also been reported to exhibit antispasmolytic, antimalarial activity and nephroprotective activity. On the basis of given evidence, it may be concluded that *Didymocarpus pedicellata* could be the potential target for the treatment of type 2 diabetes mellitus and can reduce the cardiovascular complication associated with diabetes mellitus.

Keywords: *Didymocarpus pedicellata*, Diabetes Mellitus, Bioactive Compound, Molecular target in diabetes.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder currently affecting 230 million peoples in the world [1] and by 2025 it is expected to reach 350 million peoples in worldwide[2] which causes damage to the various organ of the body due to the increase in the blood glucose level for the prolong period of time[3] Among the type 1 and type 2 diabetes mellitus, type 2 diabetes mellitus is very common affecting more than 90 per cent of all cases. [4]

In between 1980 and 2019 diabetes has become more common and major problem in both men and women. The rate of diabetes mellitus is significantly high in low and middle income countries which include China, India, Indonesia, Egypt and Mexico.

It is the chronic condition characterized by hyperglycaemia[6, 7] which is highly associated with the long term micro vascular complications affecting eye, kidney, nerves and increase the risk of various short term and long term cardiovascular complications which includes micro vascular disease like hypertension hyperlipemia, heart attack, coronary artery disease, strokes,[8] cerebral vascular disease and peripheral vascular disease[9] and micro vascular disease like retinopathy, nephropathy and neuropathy.[10-12] There are various synthetic medicines available for the treatment of diabetes mellitus but continuous and sustain use of synthetic drug causes toxicity to the diabetic patients which leads to further complications in the diabetic patients. Therefore, a revival of interest in the use of herbal medicines has been emerge worldwide as a conventional and complementary therapies.

Ethnomedicine

Didymocarpus pedicellata is highly valuable though a lesser-known medicinal plant because of not having much of data on this herbal drug. It is also known as stone flower. It is an annual and perennial plant which grows on rocky surface in shady and moist localities of temperate zone. [13, 14] it is commonly found in the temperate region of western Himalaya from Chamba Tokumaon and also subtropical Himalaya from Himachal Pradesh to Arunachal Pradesh. It is also known as Shilapushpa, Shantapushpi and sometimes Pashanbheda in Ayurveda. [15] In common language it is also called as black stone flower or stone flower (English), charela or patharphori (unani name), shilapushpa or shantapushpi (in Sanskrit).

In very comprehensive study the plat is used in the treatment of urinary calculi, polyuria, dysuria, fever, piles, dysentery and uterine disorders. [16]

The common names of this herb i.e. stone flower probably come from its believed efficacy in kidney stone. According to a hypothesis the plant is supposed to regulate calcium absorption in the body. The plant is known for its diuretic effect and in maintaining healthy urinary tract. [17, 18]

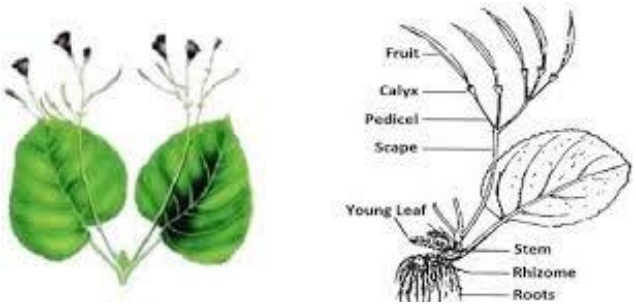

Figure 1: *Didymocarpus Pedicellata*

Figure 2: leaf and flower structure of *Didymocarpus pedicellata* in natural habitats

ANTIDIABETIC PROPERTIES OF *DIDYMOCARPUS PEDICELLATA*

Evaluation of antidiabetic properties of whole extract of *Didymocarpus pedicellata* on the basis of evidence obtained from different studies-

The whole plant of *Didymocarpus pedicellata* has been reported foe large number of bioactive molecules including alkaloids, terpenoids, steroids, phenols, glycoside, protein, carbohydrate, tannins, saponins and mainly flavonoids.

Flavonoids like chalcones present in the *Didymocarpus pedicellata* are the chief constituents which ate mainly required for antidiabetic activity. Because of lesser data available on this plant the antidiabetic activity not yet demonstreted hence the aim of present review is to focus on the antidiabetic potential of *Didymocarpus pedicellata*.

Various researchers has been reported for large number of bioactive constituents mainly flavones and chalcones namely pedicine, isopedicine, methyl pedicine, methyl pedicinine, pedicellin, pedicellic acid, 2,3,4,5,6–pentamethoxychalcone, 2’ - hydroxy -4’, 5’,6’ - trimethoxy chalcone, 4,5,7- trihydroxy - 6 – methoxybenzyl coumaranone, 2’- hydroxy – 4’, 5’, 6’- trimethoxychalcone, Isodidymocarpin, 5,6- dihydroxy-2, 3,4-trimethoxychalcone, 5-hydroxyl-2,3,4 trimethoxybenzyl coumaranone, methyl tridecylsuccinc acid, 8 – hydroxyl – 5, 6, 7 – trimethoxy flavanone, 8 – hydroxy – 5, 6, 7 – trimethoxy flavanone, 5, 6, 7, 8 - tetra methoxy flavanone.

POSSIBLE MOLECULAR TARGETS OF ANTI-DIABETIC CHALCONES

Chalcones as PTP 1B inhibitors

Insulin binds to Insulin receptor leads to the activation of insulin receptor kinase through the autophosphorylation of the receptor which causes the recruitment of insulin receptor substrate leading to activation of phosphatidylinositol 3-kinase (PIP3K) by binding to P85 subunit and activate catalytic P110 subunit. The activation of PIP3K induces downstream effectors like phosphatidylinositol dependent kinase 1 (PDK1) and protein kinase B (PKB). This causes the translocation of glucose transporter 4 (GLUT4) which increases the glucose uptake from the muscle by inactivating glucose synthase kinase 3.

So chalcone selectively inhibit the protein tyrosine phosphate 1B and prevents the translocation of glucose from GLUT4 and decrease the uptake of glucose by muscle and increase the blood glucose level.

Chalcones as a-glucosidase inhibitors

Alpha glucosidase enzyme presents in the brush border of small intestine which facilitate the absorption of carbohydrates like starch (maltose, maltotriose and dextrin) and sucrose.

While chalcones are the compound which play and important role in the inhibition of alpha glycosidase receptor.

Chalcone decreases the uptake of dietary carbohydrates that suppress postprandial hyperglycemia without increasing insulin level, which is useful to treat diabetic and/or obese patients.

Chalcones as aldose reductase (ALR) inhibitors

Aldose reductase is an enzyme which is normally present in the eye and many other part of the body. ALR initially catalyses the NADPH-dependent reduction of the aldehyde form of glucose to form sorbitol. Sorbitol dehydrogenase then utilizing NAD oxidizes the intermediate sorbitol to fructose. In absence of insulin as the alternative route for metabolism, high concentration of glucose in nerve, lens and retina gets metabolized into sorbitol in absence of insulin, leading to accumulation in tissues, which precipitates symptoms like osmotic swelling, changes in membrane permeability and oxidative stress causing tissue injury.

Chalcone act by inhibiting the aldose reductase enzyme have been evaluated against inhibition of aldose reductase (AR) and generation of advanced glycation end products (AGE).

Chalcones as peroxisome proliferator-activated receptor-ᵞ (PPAR-ᵞ) activators

PPAR-ᵞ is type 2 nuclear receptor which is encoded by PPARG gene in human and is also known as NR1C3 or glitazone receptor which has pivotal role in the homeostasis of glucose. The PPAR-ᵞreceptor is mainly expressed in adipose tissue and for optimum binding and transcriptional activity it is essential which is mainly required for heterodimerization with retinoid X receptor.

In diabetic patients the PPARg is responsible for the regulation of the insulin responsive gene and work by activating dietary fatty acids and stimulate the expression of GLUT4 receptor and its translocation which leads to reduction of blood glucose level, increase in lipid storage, suppression of gluconeogenesis in hepatic tissues, and entry of glucose in muscles.

So, the chalcone acts as an agonist of peroxisome proliferator-activated receptor-ᵞ and is responsible for increase insulin sensitizing action.[14]

CONCLUSION

From the above mentioned pharmacognostic and pharmacological studies, herbal drugs *Didymocarpus pedicellata* have antioxidant properties and can be also use for the treatment of diabetes mellitus. This plant has various possible targets for the treatment of diabetes through which it can show the effect. So, from overall study it can say that the plant not only have potential to act as antioxidant but also useful for the treatment of diabetes mellitus.

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