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Antidiabetic Activity of Polyherbal Formulation in Streptozotocin – Nicotinamide Induced Diabetic Wistar Rats

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ABSTRACT

Glycosmis pentaphylla, *Tridax procumbens*, and *Mangifera indica* are well-known plants available throughout India and they are commonly used for the treatment of various diseases including diabetes mellitus. The antidiabetic activity of the individual plant parts is well known, but the synergistic or combined effects are unclear. The concept of polyherbalism has been highlighted in *Sharangdhar Samhita*, an Ayurvedic literature dating back to 1300 AD. Polyherbal formulations enhance the therapeutic action and reduce the concentrations of single herbs, thereby reducing adverse events. The aim of the present study is to formulate a polyherbal formulation and evaluate its antidiabetic potential in animals. The polyherbal formulation was formulated using the ethanol extracts of the stem bark of *G. pentaphylla*, whole plant of *T. procumbens*, and leaves of *M. indica*. The polyherbal formulation contains the ethanol extracts of *G. pentaphylla*, *T. procumbens*, and *M. indica* in the ratio of 2:2:1. The quality of the finished product was evaluated as per the World Health Organization's guidelines for the quality control of herbal materials. The quality testing parameters of the polyherbal formulation were within the limits. Fingerprint analysis of the polyherbal formulation showed effective separation at 366 nm, and it revealed that the active compound present in the polyherbal formulation and the active compounds present in all the three extracts were the same. The acute toxicity studies of the polyherbal formulation did not show any toxic symptoms in doses up to 2000 mg/kg over 14 days. The oral antidiabetic activity of the polyherbal formulation (250 and 500 mg/kg) was screened against streptozotocin (50 mg/kg; i.p.) + nicotinamide (120 mg/kg; i.p.) induced diabetes mellitus in rats. The investigational drug was administered for 21 consecutive days, and the effect of the polyherbal formulation on blood glucose levels was studied at regular intervals. At the end of the study, the blood samples were collected from all the animals for biochemical estimation, and the animals were sacrificed and the liver and pancreatic tissues were collected for histopathologic analysis. Polyherbal formulation showed significant antidiabetic activity at 250 and 500 mg/kg, respectively, and this effect was comparable with that of glibenclamide. The antidiabetic activity of polyherbal formulation is supported by biochemical and histopathologic analysis.

Key words: *Glycosmis pentaphylla*, High Performance Thin Layer Chromatography fingerprint analysis, *Mangifera indica*, Polyherbal formulation, *Tridax procumbens*

INTRODUCTION

Plants are very useful to mankind. Many of them are used exclusively for medicinal purposes. According to the World Health Organization (WHO), "a medicinal plant is a plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi-synthesis." Such plants are in great demand by pharmaceutical companies for their active ingredients.[1,2]

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Diabetes mellitus is one of the most common disorders affecting almost 6% of the world population and the dynamics of the diabetes are changing rapidly in low- to middle-income countries.[3] According to International Diabetes Federation's (IDF) estimates, 80% of the world diabetic population will be from low- and middle-income countries in 2030. As per IDF 2011 report, China, India, and the United States of America have a diabetic population of 90.0, 61.3, and 23.7 million, which may be increased up to 129.7, 101.2, and 29.3 million, respectively, in 2030.[4] Globally, diabetes is one of the six major causes of death and also causing various systemic complications. Diabetes mellitus is treated by hormone therapy (insulin) or by administering glucose-lowering agents such as alpha-glucosidase inhibitors, sulfonylureas, biguanides, and thiazolidinediones. Development of an adverse event is one of the complications in the treatment of any systemic disorder; hence, many of the research institutes and pharmaceutical companies are involved in drug development to find the molecules with good therapeutic potential and less adverse events.[5] In the USA, 10-25% of patients experience an adverse drug reaction and these adverse drug reactions are responsible for 3.4-7.0% of hospital admissions.[6]

In traditional systems of medicine, many plants have been documented to be useful for the treatment of various systemic disorders. Many of the traditional/indigenous systems of medicine are effective than the modern system of medicine, but they suffer from lack of complete standardization which is one of the important challenges faced by the traditional system of medicine. The concept of polyhedral formulation is well documented in the ancient literature. Compared to the single herb, the polyherbal formulation has better and extended therapeutic potential. Hence, the present study was planned to formulate and standardize a polyherbal formulation using a plant having known antidiabetic activity and evaluate its therapeutic effects in rodents.

MATERIALS AND METHODS

Collection of the plant

Taxonomically identified stem bark of *Glycosmis pentaphylla* (Rutaceae), whole plant of *Tridax procumbens* (Asteraceae), and leaves of *Mangifera indica* (Anacardiaceae) were collected from the Alagar kovil region, Madurai district. The collected plants were authenticated at the Department of Botany, American college, Madurai, Tamil Nadu. The voucher specimen of the plant was deposited in the Department of Pharmacology, Ultra College of Pharmacy, Madurai, India for further reference.

Animals

Adult Wistar rats (180 ± 10 g) of either sex were obtained from Sainath Enterprises, Hyderabad, India. The animals were housed in large, spacious polyacrylic cages at an ambient room temperature with 12-h light/12-h dark cycle. Rats had free access to water and rodent pellets diet (Hindustan Lever Ltd, Bangalore, India). The study was approved by the Institute Animal Ethics Committee of the Ultra College of Pharmacy and all the animal experiments were carried out according to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines, Ministry of Environment and Forests, Government of India.

Preparation of ethanolic extract of *G. pentaphylla, T. procumbens*, and *M. indica* plants

The shadow-, air-dried stem bark of *G. pentaphylla*, whole plant of *T. procumbens*, and leaves of *M. indica* were powdered and extracted with 80% absolute ethanol using Soxhlet apparatus for 6 h. The extracts were evaporated to dryness (resinous material) under reduced pressure at 60°C and stored at 4°C until use.

Phytochemical analysis

One gram of each of the ethanolic extracts of *G. pentaphylla*, *T. procumbens* and *M. indica* was dissolved in 100 ml of its own mother solvent to obtain a stock of concentration 1% w/v and tested for the presence of carbohydrates, proteins, sterols, alkaloids, tannins, glycosides, flavonoids, phenolic compounds, and saponins.[7]

Preparation of polyherbal formulation

The polyherbal formulation (capsules) contained the ethanolic extracts of *G. pentaphylla, T. procumbens*, and *M. indica* in the ratio of 2:2:1. The quality of the polyherbal formulation was tested as per the WHO guidelines for the quality control of herbal materials.[8] As per the guidelines, specific tests such as sampling, ash content, extractable matter, foaming index, loss on drying, tannin content, foreign matters, and specific powder characteristic tests such as angle of repose and bulk density were undertaken and significant results were recorded.

Preparation of formulation by wet granulation method

The formulation preparation began with trials by adding a different ratio of binders and selecting the quantity of lubricants and preservatives, and finally the procedure was optimized. *G. pentaphylla, T. procumbens*, and *M. indica* extracts were finely powdered (sieve 40), and mixed in the ratio of 2:2:1 and taken for the preparation of capsules by wet granulation technique using 20% lactose solution as a binder. The wet mass was passed through sieve number 22 to obtain granules. The granules were dried at 45°C in a tray dryer. The granules were lubricated with 1% magnesium stearate. Diluents and preservatives were added. The optimized formulation showed very good flow properties. After this, the granules from the optimized batch (20% lactose) were filled in capsules colored yellow-red of size "0" in a capsule filling machine. The capsules were then deducted and transferred into poly bags, labeled, and the samples were evaluated as per the testing requirements. Each 750 mg of herbal capsule contained the extracts of *G. pentaphylla* (100 mg), *T. procumbens* (100 mg), *M. indica* (50 mg), and lactose and excipients– quantity sufficient (q.s.).

Preformulation studies

Preformulation parameters such as bulk density, tap density, Carr's index, Hausner's ratio, and angle of repose were determined for the laboratory granules.[9,10]

Standardization of formulation

Physicochemical parameters of raw materials were determined as per the guidelines of the WHO, which includes moisture content,