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Management of type 2 diabetes mellitus through a Sri Lankan indigenous medicinal formulation

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Abstract
The indigenous medical system of Sri Lanka possesses remarkable inherited resources for diagnosis and management of various diseases like Type 2 diabetes mellitus (Type 2 DM) is associated with improper utilization of insulin in target cells that are characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. The current study based on a pharmacological review on a specific formula referred from an indigenous ola leaf manuscript written on 1895 AC consisting with dried fruits of Aralu (*Terminalia chebula*), Bulu (*Terminalia bellerica)*, Nelli (*Phyllanthus emblica*), dried rhizome of Kalanduru (*Cyperus rotundus*), and dried bark of Devadāra (*Cedrus deodara*). The scientific studies conducted in both *in-vitro* and *in-vivo* elaborated that phytochemical compounds contained in aforementioned ingredients likely flavonoids, tannins and essential oils are highly beneficial in antidiabetic and antihyperlipidemic purposes.

Keywords: diabetes mellitus, indigenous medicine, herbal, phytochemicals

Introduction

The indigenous system of medicine in Sri Lanka is a good resource for herbal formulation which could be used to manage Type 2 diabetes mellitus (Type 2 DM) effectively and efficiently. Most of the traditional herbal formulations are found in ola leaves manuscripts. Therefore, a scientific exploration for herbal formulations in Sri Lankan ola leaves manuscripts provides useful evidence in the research and development of new strategies for effective management of Type 2 DM. This study focuses on a herbal drug formulation derived from Sri Lankan ola leaves manuscript and the aim is to review the effect and efficacy of the selected herbal formulation which could be used as an effective medicine in the management of Type 2 DM patients. As patients of Type 2 DM are experiencing difficulty in taking conventional hypoglycemic medicine, this study will be very important for finding more effective herbal formulation for economically burden and burning diseases like Type 2 DM.

Medicinal plants are used for the treatment of diabetes and many drugs have been derived from medicinal plants. One of the great advantages of medicinal plants is that these are readily available and have very low side effects. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly [1]. Considering metformin, that is an oral anti-glycemic formulation prepared using *Galega officinalis* which is rich in hypoglycemic agents called guanidine. Guanidine is toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced and metformin is developed with guanidine and biguanides [2]. Similarly, hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of Type 2 DM. The World Health Organization (WHO) Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated because of lack of scientific and clinical data proving their efficacy and safety. Hence conducting clinical research in herbal drugs, for safety evaluation is an utmost necessity in current era

The current study is based on a medicinal review on an indigenous Sri Lankan herbal formulation mentioned in traditional ola leaf manuscript on the management of Type 2 DM. The Selected ola leaves manuscript also has been secured for a long time (123 years). Podi Marakkala Gurunnanselage Isthegu Prera is the owner of this manuscript and written on 20th of May in 1895. It is 24cm long and 5cm wide and consists of 157 pages written in Sinhala.

The following treatments are given in that ola leaves manuscript. *Kalāduru ala thripal devadāra samawa gena kakārā pataka helā perā gena powanu siyalu diyawadiyā nasā.* According to the formula, which composed with dried rhizome of Kalāduru ala (*Cyperus rotundus*), dried fruits of Aralu (*Terminalia chebula*), Bulu (*Terminalia bellerica)*, Nelli (*Phyllanthus emblica*), and dried bark of Devadāra (*Cedrus deodara*).

Review on pharmacological activity of selected formula

Terminalia chebula

Pharmacological activity

T. chebula is widely using for antibacterial, antifungal, antiviral, antimutagenic, adaptogenic and anti-anaphylacatic, hypolipidemic or hypocholesterolemic, gastrointestinal motility improving and anti-ulcerogenic, hepato protective, cardio protective, radio protective, antidiabetic and retinoprotective, antispasmodic, wound healing, purgative, immunomodulatory and chemopreventive purposes in pharmacologically. It facilitates the receptor power of sensory organs and reduces adverse effects from fat enriched food. Hence, useful as a supplement to normalize serum cholesterol [3]. As well, it is used as an antioxidant, neuroprotective drug and treatment

for heart diseases, inflammations, and brain dysfunctions. For the rejuvenation purpose, use as an anti-aging agent and positively facilitate the cognitive functions of the mental faculties such as recovering stress through the adrenergic function [4]. In the Unani medicine, the pulp of the fruit is given in piles, chronic diarrhea, dysentery, costiveness, flatulence, asthma, urinary disorder, vomiting, hiccup, intestinal worms, ascites and enlarged spleen and liver considering the blood purifying effect [5].

Chemical constituents

The fruit of *T. chebula* is rich in tannins (about 32%-34%) in pyrogallol (hydrolysable) type. 14 components of hydrolysable tannins (gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl- β-D-glucose, 1,6-di-o-galloyl-D-glucose, casuarinin, 3,4,6-tri-o-glloyl-D-glucose, terchebulin) are available in *T. chebula* fruits [6]. Some of phytochemical analysis of *T. chebula* has been elaborated the availability of gallic acid, ellagic acid, tannic acid, ethyl gallate, chebulic acid, chebulagic acid, corilagin, mannitol, ascorbic acid (vitamin C) [7].

Antidiabetic activities

Gupta, 2012 mentioned that the oral administration of 75% methanolic extract of *T. chebula* (100 mg/kg body weight) has reduced the serum glucose level in normal and alloxan diabetic rats significantly within 4 hours, though the continued daily administration of the drug has produced a sustained effect. The chloroform extract of *T. chebula* seeds (100, 200 and 300 mg/kg body weight) produced dose-dependent reduction in blood glucose of diabetic rats in both short term and long term study (300 mg/kg body weight for 8 weeks). Similarly, remarkable renoprotective activity has also been observed in rats treated with *T. chebula*. Oral administration of ethanolic extract of fruits of *T. chebula* (200 mg/kg body weight for 30 days) has been reduced the levels of serum glucose and glycosylated hemoglobin in streptozotocin (STZ)-induced experimental diabetic rats. As well, aqueous extract of *T. chebula* (200 mg/kg body weight for two months) has been reduced the elevated serum glucose and increase in glycosylated hemoglobin, as well marked improvement in controlling the elevated serum lipids as well as decreased serum insulin levels were depicted. The *in vitro* studies with pancreatic islets have elaborated that the release of insulin was nearly two times more than that in untreated diabetic animals with evidence of no effect on liver and kidney function tests.[8] Phenolic compounds in the fruit are effective scavengers of free radicals, the aptitude of the extract to deactivate the free radicals such as 1, 1- diphenyl-2-picrylhydrazyl (DPPH) radicals [5]. As metabolites of gallic acid, 3-O-methylgallic acid, 3, 4-O- dimethylgallic acid and pyrogallol (both the conjugated and unconjugated forms) have been reported as well and which facilitate antioxidative, antimutagenic, anticarcinogenic, anti-inflammatory, and hepatoprotective activities. Gallic acid and its metabolites is also a glucocorticoids receptor agonist, which on binding with these receptors shows potent anti-inflammatory activity [5]. Another study revealed that the n-hexane and ethyl acetate extract of *Terminalia chebula* showed significant antimicrobial and antioxidant activities compared to the standard drugs.[9] *T. chebula* possessed hypocholesterolemic activity against hypercholesterolemia [6].

Terminalia bellerica

Pharmacological activity

Terminalia bellerica is possessed with multifarious pharmacological properties such as analgesic activity, antibiofilm activity, anticancer activity, antidepressant activity, antidiabetic activity, antidiarrhoeal activity, anti-ulcer activity, immunomodulatory activity, antispasmodic and bronchodilator activity, antifertility activity, antihypertensive activity, antifungal, antimicrobial activity, anti-inflammatory activity, antioxidant activity [10].

The fruit extract stimulates the secretion of insulin and enhances its action by inhibiting digestion of starch which is beneficial to develop antidiabetic drugs. The phytosterols, triterpenoids, glycosides, tannins and phenolic compounds contained in the fruit account for anti-inflammatory, analgesic, antimicrobial, antioxidant and antitumor properties [11]. Oxidative stress produced by alloxan has been found to be significantly reduced by the administration of *T. belerica* extract with evident from a significant reduction in thiobarbituric acid reactive substances, conjugated dienes and hydroperoxides in serum and liver respectively [10].

In vitro assessment of the antioxidant activity of ethanolic fractions revealed that the semi pure compounds present in the fractions as a useful potential source of antioxidants that are beneficial in the management of cancer, coronary heart disease, ageing and any other disease related to oxidative stress [12].

Chemical Constituents

The plant include alkaloid, coumarin, flavones, steroids (β-Sitosterol), lignans (termilignan, thannilignan), tannins (gallic acid, ellagic acid), glycosides (fructose, sucrose, galactose), terpenoid (belleric acid and chebulagic acid), saponin (bellericoside and bellericanin) [10].

Antidiabetic Activity

Hexane, Ethyl Acetate and Methanolic extracts of the fruit has been significantly (p<0.05) increased the plasma insulin, C-peptide and glucose tolerance levels, body weight, serum protein at the doses of 200, 300 and 400 mg/kg, p.o for 60 days to Streptozotocin induced diabetic rats. As well, the extracts significantly reduced the serum cholesterol, triglycerides, low density lipoprotein, cholesterol, urea, uric acid and creatinine in diabetic rats [10].

Phyllanthus emblica

Pharmacological activities

P. emblica is one of the richest sources of vitamin-C and low molecular weight hydrolysable tannins which possess antioxidant effects. The tannins of amla like emblicanin-A (37%), emblicanin-B (33%), punigluconin and pedunculagin are reported to provide protection against oxygen radical induced haemolysis in peripheral blood erythrocytes of rats that facilitates conversion of the polyphenol into medium and high molecular weight tannins. Ellagic acid in the fruit inhibits mutations in genes and repairs the chromosomal abnormalities. Similarly, effects in inhibition of growth and spread of various cancers in breast, uterus, pancreas, stomach and liver. As well, prevent and/or reduce the side effects of chemotherapy and radiotherapy [13]. A study on Cu^{2+} induced LDL oxidation and cholesterol fed rats concluded that the fruit is effective in hypercholesterolemia and prevents atherosclerosis. Flavonoids in *Emblica officinalis* reduced the levels of lipid in serum and tissues of

hyperlipidemic rats causing the degradation and elimination of cholesterol [14].

Chemical constituents

Alkaloid, coumarin, flavones, steroids (β-Sitosterol), lignans (termilignan, thannilignan), tannins (gallic acid, ellagic acid), glycosides (fructose, sucrose, galactose), terpenoid (belleric acid and chebulagic acid), saponin (bellericoside and bellericanin) are contained in the fruit [10]. Gallic acid facilitates hydrolysis. Additionally, phyllemblin, corilagin, furosin and flavonoids like quercetin, alkaloids like phyllantine and phyllantidinegeraniin are contained [13]. The fruit is reported to contain nearly 20 times as much vitamin C as orange juice. In ash studies, the plant contains minerals such as chromium, Zinc and copper which are adaptogenic that improves immunity [15].

Cyperus rotundus

Pharmacological Activities

Cyperus rotundus rhizomes extract was evaluated in a series of in vitro assay which exhibited scavenging effect in concentration dependent manner on superoxide anion radicals, hydroxyl radicals, nitric oxide radical, hydrogen peroxide, in addition to property of metal chelating and reducing power. The lipid peroxidation effect of the extract has been also studied by thiobarbituric acid–reactive substances using young and aged rat brain mitochondria [16]

Chemical constituents

The major compounds isolated from essential oil and the extracts of *C. rotundus* rhizome are Alpha-cyperone, Alpha-rotunol, Beta-cyperone, Beta-pinene, Beta-rotunol, Beta-selinene, Calcium, Camphene, Copaene, Cyperene, Cyperenone, Cyperol, Cyperolone Cyperotundone D-copadiene, D-epoxyguaiene, D-fructose, D-glucose, Flavonoids, Gamma-cymene, Isocyperol, Isokobusone, Kobusone, Limonene, Linoleic-acid, Linolenic-acid, Magnesium, Manganese, C. rotunduskone, Myristic-acid, Oleanolic-acid, Oleanolic-acid-3-o-neohesperidoside, Oleic-acid, P-cymol, Patchoulenone, Pectin, Polyphenols, Rotundene, Rotundenol, Rotundone, Selinatriene, Sitosterol, Stearic-acid, Sugeonol, Sugetriol [17]. Essential oils of the plant provide characteristic odour and taste of the herb, comprising mostly sesquiterpene hydrocarbons, epoxides, ketones, monoterpenes and aliphatic alcohols. Sesquiterpenes include selinene, isocurcumenol, nootkatone, aristolone, isorotundene, cypera-2, 4(15)-diene, and norrotundene, as well the sesquiterpene alkaloids rotundines A-C. Other constituents include the ketone cyperadione, and the monoterpenes cineole, camphene and limonene. *C. rotundus* also contains miscellaneous triterpenes including oleanolic acid and sitosterol, as well as flavonoids, sugars and minerals [17].

Antidiabetic activity

Cyperus rotundus revealed a significant decrease of fasting serum glucose level in alloxan induced diabetic and normoglycemic rabbits. The preventive role of ethanolic extract of *Cyperus rotundus* rhizomes was investigated on age associated changes in glucose in young and aged rats and observed that age associated increase in serum glucose in aged rats compared to young rats and prevented the age associated changes in glucose level [16].

Hypolipidemic activity of *Cyperus rotundus* rhizomes was evaluated in a high fat diet induced hyperlipidaemic rats that elaborated a statically significant reduction in serum total cholesterol, LDL, TG levels. Similarly, the preventive role of ethanolic extract of *Cyperus rotundus* rhizomes was investigated on age associated changes in lipids in young and aged rats. The biological efficacy of *Cyperus rotundus* was studied on weight control in obese Zucker rats and found a significant reduction in weight gain without affecting food consumption or inducing toxicity. *In vitro*, 250 micrograms/ml of this extract was able to stimulate lipolysis in 3T3-F442 adipocytes suggesting that this medicinal plant contained activators of beta-adrenoreceptors [16]. In another study, observed that bioactive compounds present in *Cyperus rotundus* rhizome effects in hypolipidemic potentials [18]. The anti-obesity potential of the of the *Cyperus rotundus* L. in high fat cafeteria diet fed obese rats revealed that significant weight reduction activity [19].

Cedrus deodara

Pharmacological Activity

The plant possess with anti-inflammatory, analgesic, immunomodulatory, antispasmodic, anti-hyperglycemic, anti-cancer, molluscicidal, insecticidal, anti-apoptotic, anti-bacterial, anti sarcoptic, anxiolytic and anticonvulsant activities [20]. The chloroform extract of *C. deodara* elaborated strong antioxidant activity on 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical [21].

Chemical constituents

Wikstromal, matairesinol, dibenzylbutyrolactol, 1, 4 diaryl butane, benzofuranoid neo lingam, cedrin (6-methyldihydromyricetin), taxifolin, cedeodarin (6-methyltaxifolin), dihydromyricetin, cedrinoside, deodardione, diosphenol, limonenecarboxylic acid,(–)-matairesinol, (–)-nortrachelogenin, and a dibenzylbutyrolactollignan (4, 4', 9-trihydroxy-3, 3'-dimethoxy-9, 9'-epoxylignan) are the key chemical compounds available in *Cedrus deodara*. A new dihydroflavonol named deodarin (3, 4, 5, 6-tetrahydroxy-8-methyl dihydroflavonol) was isolated from the stem bark. As the essential oils, sesquiterpenes-L II: isohemacholone and sesquiterpenes L III: deodarone, atlantone, α-himacholone, β-himacholone, ά-pinene, β-pinene, myrcene, himachalene, cis-atlantone, ά-atlantone were reported [20].

Anti-diabetic activity

In phytochemical screening *Cedrus deodara* woods reported that contain of glycosides, tannins, fixed oils, flavonoids, and triterpenoids which effects in the management of serum glucose levels and serum cholesterol levels [21, 22].

Conclusion

Indigenous systems of medicine in Sri Lanka possess remarkable resources to facilitate diagnosis and management of diseases in cost effective, health protective and eco-friendly manner. The indigenous medicinal formula extracted from an ancient ola leaf manuscript consists with five herbs likely dried fruits of Aralu (*Terminalia chebula*), Bulu (*Terminalia bellerica)*, Nelli (*Phyllanthus emblica*), dried rhizome of Kalanduru *(Cyperus rotundus*), and dried bark of Devadāra (*Cedrus deodara*) which consist with antidiabetic effect through enriched phytochemistry.

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