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ANTIDIABETIC COMPOUNDS FROM MEDICINAL PLANTS USED IN THE INDIGENOUS SYSTEM OF MEDICINE (*'DESHIYA CHIKITSA'*) IN SRI LANKA

Malitha Aravinda Siriwardhene

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We certified that the candidate has incorporated all corrections, amendments and additions recommended by the examiners.

Dr. A. K. E. Goonetilleke ..... Date 15/06/2015

Dr. G. A. Sirimal Premakumara ..... Date 15/06/2015

DECLARATION

"The work described in this thesis was carried out by me under the supervision of Dr. A. K. E. Goonetilleke, Senior Lecturer, Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda and Dr. G. A. Sirimal Premakumara, Research fellow and former Director, Industrial Technology Institute, Colombo 7 and a report on this has not been submitted in whole or in part to any university or any other institution for anther Degree/Diploma".

15/06/2015 .....

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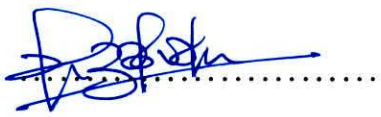

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15/06/2015

Date

Dr. A. K. E. Goonetilleke

Senior Lecturer.

Dept. of Pharmacology,

Faculty of Medical Sciences,

University of Sri Jayewardenepura,

Nugegoda.

"I certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation".

15/06/2015
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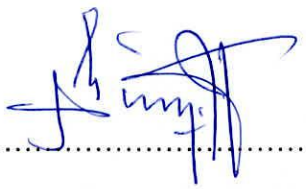
Date



Dr. G. A. Sirimal Premakumara

(Research Fellow)

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LIST OF ABBREVIATIONS

80%ME:	80% methanol extract
AAI:	Anti-Atherogenic index
AE:	Aqueous extract
AF:	Remaining aqueous fraction
ALX:	Alloxan monohydrate
BCG:	Bromo cresol green solution
BGL:	Blood glucose level
BF:	*n*-butanol fraction
CF:	Chloroform fraction
CP:	Corpulent rats
DM:	Diabetes mellitus
DMSO:	Dimethyl sulfoxide
DPPH:	di (phenyl)-(2, 4, 6-trinitrophenyl) iminoazanium
EF:	Ethyl acetate fraction
ELISA:	Enzyme-linked immunosorbent assay
FBG:	Fasting blood glucose concentration
GAE:	Gallic acid equivalent
GK:	Goto-Kakizaki rats
HbA_{1c}:	Serum glycosylated hemoglobin
HDL-C:	Serum high density lipoprotein cholesterol
HF:	*n*-hexane fraction
IDDM:	Insulin-dependent diabetes mellitus
IDF:	International Diabetes Federation

KK:	Mice of the KK strain develop diabetes of polygenic origin
LDL-C:	Serum low density lipoprotein cholesterol
ME:	Methanol extract
NIDDM:	Non-insulin-dependent diabetes mellitus
OD_{500}:	Optical density at 500 nm
PPAR:	Peroxisome proliferator activated receptor
RC:	Ratio of control
RT:	Ratio of test
SEM:	Standard error mean
STZ:	Streptozotocin
TC:	Serum total cholesterol
TH_b:	Serum total hemoglobin fraction
TZDs:	Thiazolidinedione
VLDL-C:	Serum very low density lipoprotein cholesterol
WHO:	World health organization
ZFR:	Zucker fatty rats

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Malitha Aravinda Siriwardhene

ABSTRACT

The present study investigated the anti-diabetic effects of *Costus speciosus, Passiflora foetida* and *Osbeckia octandra* used in the treatment of DM in Sri Lanka. Eighty percent methanol extract (80ME) of *C. speciosus, P. foetida* and *O. octandra* leaf were evaluated for their hypoglycemic activity. Thereafter, the 80% ME extracts of plants were partitioned with organic solvents *n*-hexane, chloroform, ethyl acetate and *n*-butanol to obtain *n*-hexane (HF), chloroform (CF), ethyl acetate (EF) and *n*-butanol (BF) soluble fractions. The dose response study of the plant extracts showed, at dose of 20 mg/kg was the most effective dose. Hence, the effects of partitioned fractions of 80ME on correction of hyperglycemia were tested at a dose of 20 mg/kg in three different rat models of diabetes viz., hypoglycemic, anti-hyperglycemic and ALX-diabetic (representing the type 2 diabetic model-NIDDM) using Swiss albino Wistar rats. The effects of extracts and fractions were compared with the effect of standard drugs metformin (100 mg/kg) and glipizide (10 mg/kg).

The fractions of EF and BF of *C. speciosus* and EF of both *P. foetida* and *O. octandra* produced significant ($p<0.05$) improvement in glucose tolerance activity compared to control rats. In the long-term study, once a day administration of EF and BF of both *P. foetida* and *O. octandra* (20 mg/kg) in both normal and ALX-diabetic rats produced significant ($p<0.05$) antidiabetic activity. However the effect produced by *P. foetida* and

O. octandra fractions were lower than that of BF of *C. speciosus*. The study of serum biochemical parameters at a dose of 20 mg/kg showed that the 80% ME fractions of *P. foetida* and *O. octandra* have potent hypolipidemic and anti-atherogenic activities. It also improved in liver enzyme activities on both normal and ALX diabetic rats. It was observed that both *C. speciosus* and *O. octandra* fractions increased serum insulin level and lowered lipid profile significantly ($p<0.05$) in both normal and ALX-diabetic rats. It finally concluded that the most active partitioned fractions of these plants are BF of *C. speciosus,* EFs of *P. foetida* and *O. octandra*. The DPPH scavenging *in-vitro* anti-oxidant activities of *C. speciosus* (BF), *O.octandra* (EF) and *P. foetida* (EF) fractions were compared against ascorbic acid showed similar anti-oxidant activities with that of ascorbic acid. The improved renal functions along with increased in Glomerular Filtration Rate (GFR), the effect of body weight and reduced serum creatinine indicates the renal safety in chronic use of these plant fractions in the treatment of DM. The phytochemical investigation revealed that the activity profile could be due to the synergistic interaction of small molecular weight compounds present in 80% methanol extracts which may be belongs to the plant secondary metabolites viz., phenolics, alkaloids or glycoside compounds. It also proven the ethno medicinal value of *C. speciosus*, *O.octandra* and *P. foetida*. Further detail characterization of chemical compounds which are responsible for hypoglycemic activity of these plants may provide a pathway to discover new chemical entities in the treatment of DM.

Key words: *Costus speciosus, Passiflora foetida, Osbechea octandra*, hypoglycemia and renal function