

A study of the chemistry of
***Artocarpus heterophyllus* Lam. leaves**
and identification of active antioxidant
and hypoglycemic fractions/ compounds

BY

KURUKULASOORIYA SAWALAKKARAGE

SHIVANTHI PALIKA FERNANDO

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leaves and identification of active antioxidant and
hypoglycemic fractions/ compounds**

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**KURUKULASOORIYA SAWALAKKARAGE SHIVANTHI
PALIKA FERNANDO**

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for the award of the Degree of the Master of Philosophy in
Chemistry on
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DECLARATION

“The work described in this thesis was carried out by me under the supervision of Prof. A. M. Abeysekera (Senior professor, Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda), Prof. (Mrs.) U.G. Chandrika (Professor, Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda), Dr. (Mrs.) C. Padumadasa (Senior lecturer, Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda), Dr. A.K.E. Gunathilake (Senior lecturer, Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda) and a report on this has not been submitted in whole or in part to any university or any other institution for another Degree/Diploma.”

14.06.2017

Date

Prando

Signature

We 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.

14/06/2017

Date

A. M. Abeysekera

Prof. A. M. Abeysekera

Department of Chemistry

University of Sri Jayewardenepura

14/06/2017

Date

U. G. Chandrika

Prof. U. G. Chandrika

Department of Biochemistry

University of Sri Jayewardenepura

16/06/17

Date

Chayan L Pad

Dr. (Mrs.) C. Padumadasa

Senior Lecturer

Department of Chemistry

University of Sri Jayewardenepura

14.6.17

Date

A. K. E. Goonathilake

Dr. A. K. E. Goonathilake

Faculty of Medical Sciences

University of Sri Jayewardenepura

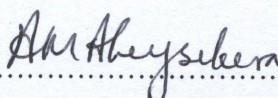
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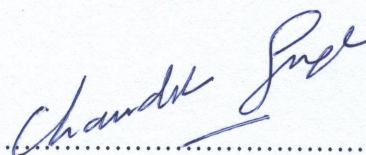


Prof. A. M. Abeysekera

Department of Chemistry

14/06/2017

Date

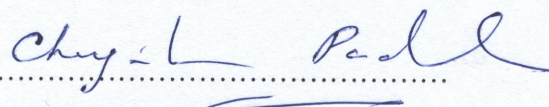


Prof. U. G. Chandrika

Department of Biochemistry

16-6-17

Date

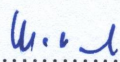


Dr. (Mrs.) C. Padumadasa

Department of Chemistry

14.6.17

Date



Dr. A. K. E. Goonathilake

Faculty of Medical Sciences

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ABBREVIATIONS

^{13}C NMR	Carbon-13 nuclear magnetic resonance
^1H NMR	Proton nuclear magnetic resonance
<i>A. heterophyllus</i>	<i>Artocarpus heterophyllus</i>
A_0	Absorbance of the control
A_1	Absorbance of fractions sample/standard
ABTS	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
AGE	Advanced Glycation End product
ATP	Adenosine Triphosphate
BGL_{c0}	Blood glucose level of control 1st hour after administration of water immediately before the glucose load
BGL_{c1}	Blood glucose level of control 1 hour after administration of glucose load
BGL_{t0}	Blood glucose level of test group 1st hour after administration of sample immediately before the glucose load
BGL_{t1}	Blood glucose level of test group 1 hour after administration of glucose
BHA	Butylated Hydroxyanisole
BHT	Butylated Hydroxytoluene
BSA	Bovine Serum Albumin
COSY	Homonuclear correlation spectroscopy

COX-2	Cyclooxygenase 2
DKA	Diabetic keto acidosis
DMPD	<i>N, N</i> -dimethyl- <i>p</i> -phenylendiamine
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPP-IV	Dipeptidyl peptidase 4
DPPH	2,2-diphenyl-2-picrylhydrazyl
EA/W	Ethyl acetate fraction of the water extract
EI MS	Electron ionization mass spectrometry
FAG-MS	Fast atom bombardment mass spectra
FBG	Fasting Blood Glucose
FRAP	
GDM	Gestational Diabetes Mellitus
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon-like Peptide-1
GLUT2	Glucose Transporter
HbA1C	Glycated haemoglobin (A1c), which identifies average plasma glucose concentration.
HBSS	Hanks Balanced Salt Solution, containing calcium chloride and magnesium chloride
HDL	High Density Lipoprotein
HMBC	Heteronuclear Multiple Bond Correlation
HNC	Hyperosmolar non-ketonicoma
HOCl [•]	Hydroxyl radicals, halogenated oxygen metabolites

HR-FAB MS	High Resolution Fast-Atom Bombardment mass spectrometry
HSQC	Heteronuclear Single-Quantum Correlation
IC ₅₀ value	Concentration of an inhibitor where the response (or binding) is reduced by half.
iNOS	inducible Nitric Oxide Synthase
IR Spectroscopy	Infrared Spectroscopy
J	Coupling constant
LA	Lactic acidosis
LDL	Low density lipoprotein
MGO	Methylglyoxal
MTT	tetrazolium
NADH	β -nicotamide adenine dinucleotide (NADH)
NBT	Nitro blue tetrazolium
NCEs	New chemical entities
NOESY	Nuclear Overhauser Enhancement Spectroscopy
NPH	Isophane insulin (suspension of insulin with protamine)
PG	Propyl galate
PMS	Phenazine MethoSulphate
pNPG	p-nitrophenyl- α -D-glucopyranoside
PPAR-gamma	Peroxisome Proliferator-Activated Receptor-gamma
R _f	Retention factor
RNS	Reactive nitrogen species
ROS	Reactive Oxygen species

RPHPLC	Recycling Preparative High Performance Liquid Chromatography
SOZ	Serum Opsonized Zymosan
SRB	Sulforhodamine B
TBHQ	tertiary butyl hydroquinone
TLC	Thin Layer Chromatography
t_R	Retention time
UV-visible spectroscopy	Ultraviolet–visible spectroscopy
VLDL	Very low density lipoprotein

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A study of the chemistry of *Artocarpus heterophyllus* Lam. leaves and identification of active antioxidant and hypoglycemic fractions/ compounds

Fernando K. S. S. P

ABSTRACT

The aqueous extract of the senescent leaves of *Artocarpus heterophyllus* is traditionally used in Sri Lanka as a hypoglycemic agent. It has been previously reported that the hypoglycemic activity lies in the ethyl acetate fraction of the water extract (EA/W). The main purpose of this study was to identify hypoglycemic fractions/ compounds from the EA/W fraction. The study also encompassed antioxidant, antiglycation, α -glucosidase inhibition and anti-inflammatory assays. The EA/W fraction was fractionated by chromatography on sephadex LH-20. Five fractions eluting with the following solvent systems were obtained. Fraction 1, dichloromethane/ hexane (4:1), Fraction 2, dichloromethane/acetone (3:2), Fraction 3, dichloromethane/acetone (1:4), Fraction 4, dichloromethane/ methanol (1:1) and Fraction 5, methanol. These fractions were screened for *in vivo* hypoglycemic and antidiabetic activities and as well as *in vitro* antioxidant, antiglycation, α -glucosidase inhibitory and anti-inflammatory assays. Each fraction was tested for its effect on the blood glucose levels of fasted normal and diabetic rats. None of the fractions caused hypoglycemia on normal rats. However there was significant ($p < 0.001$) reduction in the blood glucose level during the first three hours after giving the fractions 3, 4 and 5 to diabetic rats. Of the three fractions fraction 4 showed the highest hypoglycemic activity. Fractions 3, 4 and 5 were also the

most active in the glucose tolerance test carried out on both normoglycemic and diabetic rats. However fraction 3 was the most active in this assay. In both assays fractions 3, 4 and 5 at 50 mg/kg body weight showed activity of the same order as glibenclamide at 5 mg/ kg body weight. Fraction 4 was found to be the most active fraction in all the *in vitro* assays. In the DPPH radical quenching antioxidant assay it has a IC_{50} value of 21.69 ± 0.31 mg/ml compared with gallic acid which had IC_{50} value of 23.46 ± 0.43 mg/ml. In the superoxide anion radical scavenging assay it showed 98% percentage inhibition at 0.5 mg/ kg dose while quercetin showed 100% percentage inhibition. It has strong α - glucosidase inhibition activity with a IC_{50} value of 0.40 ± 0.01 mg/ml compared with acarbose which had a IC_{50} value of 0.54 ± 0.01 mg/mL. In the antiglycation assay it has a IC_{50} value 0.44 ± 0.01 mg/mL compared with rutin which had IC_{50} value of 0.18 ± 0.02 mg/mL. In the anti-inflammatory assay it has IC_{50} value of 16.9 ± 0.1 mg/mL compared with rutin which had IC_{50} value of 11.8 ± 1.91 mg/mL. As the thin layer chromatography analysis of fractions 3 and 4 indicated that they had several compounds in common, they were combined and subjected to chromatographic analysis. Five compounds were isolated using MCI gel, sephadex LH-20 and silica column chromatography, preparative thin layer chromatography and normal phase, reversed phase and size exclusion preparative high-performance liquid chromatography and their structures elucidated by using 1H NMR, ^{13}C NMR, HSQC, HMBC, COSY, NOESY, IR and UV-visible spectroscopy, EI, FAB and HR-FAB spectrometry. One of the five compounds, 3,4,6-trihydroxy-7-ene-megastigman-9-one [104], was identified as the C5 epimer of lyratol E and is a new isomer. Of the four remaining compound 4-hydroxybenzoic acid [93] has been reported previously from the twigs of *A. heterophyllus*. The other remaining compounds 3,4-dihydroxy-7-ene-

megastigman-9-one [103], 13-Hydroxy-3-oxo- α -ionol [105], 3,4-dihydroxybenzoic acid [106] are known compounds but have not been reported previously from *A. heterophyllus*. This study indicates that the obtained hypoglycemic effect of the EA/W fraction is caused by the total effect of a number of compounds of similar structures and that it may not be possible to isolate a single highly active compound with hypoglycemic activity from the senescent leaves of *A. heterophyllus*.

Key words: *Artocarpus heterophyllus*, hypoglycemic effect, antioxidant, antiglycation, alpha glucosidase inhibition, *epi*-lyratol E.