UNIVERSITI PUTRA MALAYSIA

SOME MECHANISMS FOR WOUND HEALING ENHANCING EFFECTS OF BITTER GOURD (Momordica charantia L.) EXTRACT IN DIABETIC RATS

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IB 2013 23

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By

ALIREZA REZAEIZADEH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July 2013

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DEDICATION

To my parents who always encourage and be there in my life, my wife Maryam Abdollahi who is always my best friend, and my children Kimia and Pouria who are my inspiration, and my colleagues.

Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfilment of the requirement of the Degree of Doctor of Philosophy

SOME MECHANISMS FOR WOUND HEALING ENHANCING EFFECTS OF BITTER GOURD (*Momordica charantia L.*) EXTRACT IN DIABETIC RATS

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Chairman: Prof Md Zuki Bin Abu Bakar, PhD

Faculty : Institute of Bioscience

Wound healing is greatly delayed in diabetes mellitus. About 15-25% of patients with diabetes will suffer a wound problem in their lifetime. The aim of the current research was to determine the effects of *Momordica charantia* L. (MC) whole fruit extract on wound healing in streptozotocin (STZ)-induced diabetes in neonatal rats.

The antioxidant activity of water, methanolic, and chloroformic extract of the whole fruit of MC extracts was determined by ferric thiocyanate (FTC), thiobarbituric acid (TBA), free radical scavenging activity (DPPH). Total phenol and flavonoid components were measured as well. The malondialdehyde (MDA) level of wound tissue and serum was determined. The level of endogenous defense enzymes (catalase, superoxide desmotase, and glutathione peroxidase) was determined.

Diabetes mellitus was induced in 160 one day-old male Sprague-Dawley ratsby injection of STZ (85 mg/kg). Twelve weeks later a 3 cm^2 wound was placed in the back of each rat and the wounds were treated 2 times per day with either the topical MC aqueous extract (DMT) or vehicle alone (DV). In a parallel experiment some diabetic animals were treated with either oral MC (DMO, 20mg/kg) or both. Diabetic rats treated by povidone iodine, glibenclamide, or a combination of both were used as positive control groups, these were termed diabetic plus glibenclamide (DPG), diabetic plus povidine iodine (DPP), or diabetic plus glibenclamide and povidine iodine (DPM).Similarly treated non diabetic animals acted as control.At termination, blood samples were collected to measure blood glucose and serum insulin level. Additionally to confirm the presence of diabetes intraperitoneal glucose tolerance tests (IPGTT) and intraperitoneal insulin tolerance tests (IPITT) were also performed. The animals were terminated on days 5, 10 and 15 and wound area, wound reepithelialisation, granulation tissue fibroblast, myofibroblast, vessel number, inflammatory cell infiltrate, growth factors and collagen content was determined by immunohistochemistry (IHC). Hydroxyproline content was measured by colorimetry.

Prior to the treatment of the wounds, antioxidant activity of three different types of MC extract (aqueous, methanolic and chloroformic) was measured by ferric thiocyanate (FTC), thiobarbituric acid (TBA), and diphenyl-picryl-hydrazyl (DPPH) methods. These assays showed that the antioxidant activity of aqueous extract of MC was significantly ($P \leq 0.05$) higherthanthe methanolic and chloroformic extract. For this reason the effect of the aqueous extract on diabetic control and wound healing (mentioned above) was determined.

The effect of the aqueous extract of MC on diabetic control was determined by measurement of the malondialdehyde (MDA) profile of plasma and wound. These studies showed that MDA level in serumand wound tissue was significantly ($P \leq 0.05$) highest in the DC group and this increase was prevented in the DMO and DMM treated groups. TheMC aqueous extract also improved glucose tolerance and increased insulin sensitivity in the treated diabetic rats.

With regard to the effect on wound closure, MC has significantly improved the wound closure observed in the DC rats. The improvement in wound closure was also evident in the histological studies which showed an increase of collagen fibers, fibroblast and myofibroblast cells in the granulation tissue in diabetic animals treated with MC.Additionally, the studies on the growth factor level by ELISA and histological methods in wound area have illustrated that there was a significant increase in the growth factor's level in the DMT and DMM groups as compared to DC group.

In conclusion, the studies in this thesis indicate that the oral administration of aqueous extract of MC fruit was effective in reducing hyperglycemia and also manifested improvement of glucose tolerance and insulin sensitivity. The results of this research also showed that the topical use of aqueous extract of MC fruit capable to improve the wound in treated diabetic rats. Furthermore, oral administration of MC also alleviates damage induced by diabetes in some of the wound parameters in treated diabetic rats.

Keywords: diabetes mellitus, neonatal rats, streptozotocin, wound healing, *Momordica charantia,* growth factor

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan Ijazah Doktor Falsafah

BEBERAPA MEKANISMA UNTUK MENINGKATKAN PENYEMBUHAN LUKA KESAN DARI EKSTRAK PERIA (*MOMORDICA CHARANTIA* L.) PADA TIKUS DIABETES

Oleh

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Pengerusi : Prof Md Zuki Bin Abu Bakar, PhD

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Penyembuhan luka amat lewat bagi pesakit diabetes melitus. Kira-kira 15-25% pesakit diabetes akan mengalami masalah luka dalam hidup mereka. Tujuan kajian semasa adalah untuk menentukan kesan ekstrak buah *Momordica charantia* L. (MC) ke atas penyembuhan luka dalam tikus neonatal diabetes diaruh oleh streptozotocin (STZ). Aktiviti antioksidan bagi ekstrak akueus, metanol dan klorofom bagi buah MC ditentukan oleh ferik tiosianat (FTC), asid thiobarbituric (TBA), dan aktiviti memerangkap radikal bebas (DPPH). Jumlah komponen fenol dan flavonoid juga diukur. Tahap malondialdehid (MDA) tisu luka dan serum ditentukan. Tahap enzim pertahanan dalaman (catalase, desmotase dismutase dan glutathione peroxidase) juga telah ditentukan. Diabetes telah diaruh ke atas 160 ekor tikus Sprague-dawley jantan berusia satu hari melalui suntikan STZ (85 mg/kg). Dua belas minggu kemudian luka

seluas 3 cm^2 telah diaruh pada belakang setiap tikus dan dirawat dua kali sehari sama ada dengan MC topikal ekstrak akueus (DMT) atau DV sahaja. Dalam masa yang sama beberapa haiwan diabetes telah dirawat sama ada secara oral MC (DMO, 20mg/kg) atau kedua-dua oral dan topikal. Tikus diabetes yang dirawat dengan iodin povidone, glibenclamide, atau gabungan kedua-duanya telah digunakan sebagai kumpulan kawalan positif, kumpulan ini dipanggil sebagai diabetes serta glibenclamide (DPG), diabetes serta iodin povidine (DPP), atau diabetes serta glibenclamide dan iodin povidine (TPM). Haiwan diabetes yang tidak dirawat juga bertindak sebagai kawalan. Pada penghujung eksperimen, sampel darah telah diambil untuk mengukur glukosa darah dan tahap insulin serum. Selain itu, untuk mengesahkan kehadiran diabetes, ujian toleransi glukosa intraperitoneal (IPGTT) dan ujian toleransi insulin intraperitoneal (IPITT) juga telah dilakukan. Haiwan telah dimatikan pada hari ke 5, 10 dan 15 selepas rawatan dan kawasan luka, reepithelialisation luka, tisu granulasi fibroblast, myofibroblast, bilangan salur darah, sel radang menyusup, faktor-faktor pertumbuhan dan kandungan kolagen ditentukan melalui immunohistokimia (IHC). Kandungan hydroxyproline telah diukur dengan kalorimetri. Sebelum rawatan luka, aktiviti antioksidan bagi tiga jenis ekstrak MC (akueus, metanol dan klorofom) telah diukur dengan kaedah ferik tiosianat (FTC), asid thiobarbituric (TBA), dan Diphenyl-picryl-hydrazyl (DPPH). Ujian-ujian ini menunjukkan bahawa aktiviti antioksidan ekstrak akueus MC adalah lebih tinggi ($P \leq 0.05$) daripada ekstrak metanol dan klorofom. Atas sebab inilah kesan ekstrak akueus ke atas diabetes kawalan dan penyembuhan luka (yang disebutkan di atas) telah ditentukan. Kesan ekstrak akueus MC diabetes kawalan telah ditentukan oleh ukuran (MDA) Profil malondialdehid plasma dan luka. Kajian-kajian ini menunjukkan bahawa tahap MDA dalam tisu serum dan luka adalah ketara

(P≤0.05) tertinggi dalam kumpulan DC dan peningkatan ini telah dihalang dalam kumpulan dirawat DMO dan DMM. Ekstrak akueus MC juga telah meningkatkan toleransi glukosa dan sensitiviti insulin dalam tikus diabetes yang dirawat. Dengan mengambil kira kesan ke atas penutupan luka, MC telah meningkatkan dengan ketara kadar penutupan luka yang rendah yang diperhatikan dalam tikus DC. Peningkatan dalam penutupan luka juga telah dibuktikan dalam kajian histologi yang menunjukkan peningkatan dalam gentian kolagen, sel-sel fibroblast dan myofibroblast dalam tisu granulasi dalam haiwan diabetes dirawat dengan MC. Selain itu, kajian mengenai tahap faktor pertumbuhan dengan ELISA dan kaedah histologi di kawasan luka telah menunjukkan bahawa terdapat peningkatan yang ketara dalam tahap faktor pertumbuhan dalam kumpulan DMT dan DMM berbanding dengan kumpulan DC. Kesimpulannya, kajian ini menunjukkan bahawa pemberian secara oral ekstrak akueus buah MC adalah berkesan dalam mengurangkan hiperglisemia dan juga menunjukkan peningkatan toleransi glukosa dan sensitiviti insulin. Hasil kajian ini juga menunjukkan bahawa penggunaan topikal ekstrak akueus buah MC mampu untuk meningkatkan penyembuhan luka pada tikus diabetes. Tambahan pula, pemberian secara oral MC juga mengurangkan kerosakan disebabkan oleh diabetes pada beberapa parameter luka pada tikus diabetes yang dirawat.

Keywords: diabetes melitus, tikus neonatal, streptozotocin , penyembuhan luka, *Momordica charantia* , faktor pertumbuhan

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest appreciation to the chairperson of my supervisory committee, Prof. Dr. Md Zuki Bin Abu Bakar for giving me the opportunity to conduct this research under his supervision. He sacrificed his time out of his busy schedule to guide me constantly throughout my study period. I am also indebted to the members of the supervisory committee, namely, Prof. Dato' Dr. Tengku Azmi Tengku Ibrahim, Assoc. Prof. Dr. Goh Yong Meng, Prof. Dr. Noordin Mohamed Mustapha, and Assoc. Prof. Dr. Muhajir Hamid for their continuous encouragement, valuable advice, and insightful suggestions. I would like to further extend my deepest and sincere appreciation to the Director of Institute of Bioscience, Dean of Faculty of Veterinary Medicine, and Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia. I would like to additionally extend my deepest and sincere appreciation to the Assoc. Prof. Dr. Sussan McLennan and Dr. Charmaine Tam for the best scientific advice and editing thesis and my gratitude also goes to the staff members of the Laboratory of Histology, Physiology, Parasitology, and Histopathology, Faculty of Veterinary Medicine, for their cooperation and support. I would also like to thank my friends Mr. Mehdi Ebrahimi who had kindly helped me in completing this project.

I wish to express my thanks to my beloved parents who have placed my needs above their own and help me in this way. I would like to extend my special thanks to my wife Maryam who had been a great friend, helper, and source of inspiration throughout this endeavor. Finally, I am also grateful to my sisters Azam, Akram, and Elham who had lent their constant support. Special thanks are also due to my children Kimia and Pouria who steadfastly help their father to complete this project.

I certify that a Thesis Examination Committee has met on 16 July 2013 to conduct the final examination of Alireza Rezaeizadeh on his thesis entitled "Some Mechanisms for Wound Healing Enhancing Effects of Bitter Gourd (*Momordica charantia* L.) Extract in Diabetic Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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DECLARATION

I hereby declare that the thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously and is not currently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

ALIREZA REZAEIZADEH

Date: 16 July 2013

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure **Page**

LIST OF ABBREVIATIONS

4-HNE	4- hydroxynonenal
α-SMA	Alpha-smooth muscle action
AEGs	Advanced glycation end products
AR	Aldose reductase
ATP	Adenosine triphosphate
AST	Aspartate amino transferase
ANOVA	Analysis of variance
ACT	Alanine amino transferase
BFGF	Basic fibroblast growth factor
BHT	Butylated hydroxytoluene
BHA	Butyrate hydroxyanisole
BC	Before Christ
BFGF	Basic fibroblast growth factor
CCL4	Carbon tetrachloride
CAT	Catalase
DM	Diabetes mellitus
DETC	Dendritic epidermal-T-cells
DC	Diabetic control
DV	Diabetic Vaseline
DMO	Diabetic *Momordica charentia* oral
DMT	Diabetic *Momordica charentia* topical
DMM	Diabetic *Memordica charentia* mixed
DPG	Diabetic positive glibenclaimide

DPP	Diabetic positive providine iodine
DPM	Diabetic positive mixed
DPPH	1,1-dipheny 1-2-picry 1-hydrazyl
DW	Distilled water
DAB	3,3-diaminobenzzidine
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
EDTA	Ethylenediaminetetraacetic acid
ELLSA	Enzyme-linked immunosorbent assay
EMCD	19-epoxy-25-methoxy-cucurbita-6,23-diene-3/3, 19-diol
ERK	Extracellular signal-regulated kinase
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
FGF-7	Fibroblast growth factor-7
FGF-2	Fibroblast growth factor-2
FTC	Ferric thiocyanate
GLUT4	Glucose transporter type 4
GSH	Glutathione
GPx	Glutathione peroxidase
GAGS	Glycosaminoglycans
GM-CSF	Granualocyte macrophage colony stimulating factor
G-CSF	Granulocyte colony stimulating factor
GAE	Gallic acid equiralents

GTT	Glucose tolerance test
g	Gram
HO	Hydroxyl radical
H_2O_2	Hydrogen peroxide
HA	Hyaluronic acid
HS	Heparin sulfate
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IDDM	Insulin- dependent diabetes mellitus
IGF-1	Insulin growth factor-1
IL-6	Interlukine-6
IL-1B	Interlukine-1b
IFN-G	Interferon gamma
ICAM-1	Intercellular adhesion molecule-1
IgE	Immunoglobulin-E
IGF1R	Insulin growth factor 1 receptor
IC50	50% inhibitory concentration value
IRS Protein	Insulin receptor substrate protein
ITT	Insulin tolerance test
IPGTT	Intraperitoneal glucose tolerance test
IPITT	Intraperitoneal insulin tolerance test
IL-4	Interlukine-4
IκBK	Inhibitor kappa B kinase
TCA	Trichloroacetic acid
Kg	Kilograms

LDL	Low density lipoprotein
MC	Momordica charentia
mRNA	Messenger-Ribonucleic acid
MDA	Malondialdehyde
MMPS	Matrix metalloproteinase
MPO	Myeloperoxidase
MAC-1	Macrophage-1 antigen
MAPK	Mitrogen-activated protein kinase
NIDDM	Non-insulin dependent diabetes mellitus
NHMS	The national health and morbidity survey
NO	Nitric oxide
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NC	Normal control
NF-κB	Nuclear factor kappa B
O2	Super anion radical
O	Single oxygen
PDGF	Platelet- derived growth factor
PKC	Protein kinase c
PUFA	Polyunsaturated fatty acid
PMNS	Polymorphonuclear leukocytes
PLGF	Placental growth factor
PIP3	Phosphatidylinositol -trisphosphate
PG	Propyl gallate
PGs	Proteoglycans

PI3K	Phosphatidylinositol 3-kinase
QE	Quercetin equivalents
ROS	Reactive oxygen species
RPM	Revolutions per minute
RBC	Red blood cells
RAW 246.7 macrophages	Mouse leukaemic monocyte macrophage cell line
STZ	Streptozotocin
SOD	Superoxide dismutase
SMCs	Smooth muscle cells
SDS	Sodium dodeyl sulfate
SD	Standard deviation
TGF-β	Transforming growth factor-β
TNF-a	Tumor necrosis factor
TIMPs	Tissue inhibitor of metalloproteinase
TBHQ	Tertiary butyl hydroquinone
TBA	Thiobarbituric acid
TGF-β	Transforming growth factor-Beta
VEGF	Vascular endothelial growth factor
VEGF-R	Vascular endothelial growth factor receptor

CHAPTER 1

INTRODUCTION

Diabetes mellitus is a growing public health concern in Malaysia. In association with the increased incidence the number of diabetic individuals with diabetic complications is also ascending. It was estimated that there was a total of between 700,000 to 900,000 diabetic patients in 1999. This means that there were approximately eight persons with diabetes for every 100 adults. In 2006, a study revealed that 44 percent Malaysians were obese and overweight. This number appears to be in the older age group as some 14.1 percent of those over 30 years old were diabetic. Whilst less than five percent of those aged 18 were diabetic. The estimated number of adults with diabetes in Malaysia in 2000 was 940,000, and the figure is expected to rise to 2.48 million by 2030(Freeda Cruez, 2009). Diabetes mellitus is a systemic metabolic disorder characterized by elevated blood glucose due to absolute or relative deficiency of insulin secretion from pancreatic cells (Leonardi, Mints, & Hussain, 2003). Type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM) has been increasing alarmingly worldwide and is the type of diabetes which is increasing in the Malaysia population. It has been estimated that from 1995 to 2025, the prevalence of diabetes will increase by 42% among adults living in the developed world and by 170% among adults in developing countries (Costacou & Mayer-Davis, 2003).

Type 2 diabetes is the most common form of the disease usually accompanied by insulin resistance and defective β-cell function (Lupi & Del Prato, 2008). Glucoseintolerance in

association with hyperinsulinemia and insulin resistance is early hallmarks of the prediabetic phase. Insulin resistance is a major factor in the pathogenesis of type 2 diabetes mellitus and occurs when the cellular mechanisms fail to respond to the effects of insulin (Prentki, Joly, El-Assaad, & Roduit, 2002). It has been mentioned that the predisposition toinsulin resistance results from genetic and environmental factors (Nandi, Kitamura, Kahn, & Accili, 2004). Pancreatic β-cell mass is markedly reduced in type 1 diabetes or insulin-dependent diabetes mellitus (IDDM) and is moderately reduced in type 2 diabetes(Rahier, Guiot, Goebbels, Sempoux, & Henquin, 2008). The chronic hyperglycemia of diabetes mellitus leads to disorders of carbohydrate, fat and protein metabolism and inducescomplications in many organs (Bastaki, 2005).It is largely recognized that increased oxidative stress is a central underlying abnormality that plays an important role in the development of diabetes complications (Haidara, Yassin, Rateb, Ammar, & Zorkani, 2006). This increase in oxidative stress can be caused by amongst other things increased production of free radicals and increased lipid peroxidation (Evans, Goldfine, Maddux, & Grodsky, 2002).

Diabetes mellitus causes many complications of these impaired wound healing has not received much attention(Mace, Yu, Paydar, Boudreau, & Young, 2007). Diabetic patients not only have delayed healing of acute wounds but the failure to heal in approximately 15% of cases results in a chronic non-healing wound. These wounds typically occur on the extremities such as the foot and for this reason are recognized as diabetic foot ulcers(Guo & DiPietro, 2010). Diabetic wounds have been shown to have decreased keratinocytes proliferation, endothelial cells, decreased collagen deposition and synthesis, reduced angiogenesis, delayed inflammatory response and delayed

reepithelialization. In addition, poor wound healing in diabetic patients and animal models is accompanied with decreased secretion of growth factors [such as keratinocyte growth factor (KGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF)] (Brown, Breeden, & Greenhalgh, 1994; Greenhalgh, Sprugel, Murray, & Ross, 1990; Mace*et al.*, 2007; Werner, Breeden, Hubner, Greenhalgh, & Longaker, 1994).

Although medications such as sulfonylureas are widely used to treat type II diabetes, however, they have recently been shown to be are associated with side effects. For this reason there is an increasing interest in traditional medicinal plants. Many traditional plants have been used for diabetes therapy (Modak, Dixit, Londhe, Ghaskadbi, & Devasagayam, 2007). One of these plants is *Momordica charantia* (MC) or bitter gourd that belongs to the *Cucurbitacea* family and is consumed in South Asia, South America and oriental countries as a food item and medicinal plant for treating various diseases including diabetes mellitus. The use of this kind of medicinal plant persists in many parts of the world, particularly in Asia (Grover & Yadav, 2004). The hypoglycemic activity of the MC fruit (Miura *et al.,* 2001; Virdi *et al.*, 2003), seeds (Sathishsekar &Subramaniam, 2005b) and whole plant (Krawinkel &Keding, 2006) has been previously confirmed in experimental animals. It was also reported that MC decreased fasting serum glucose in patients with type II diabetes (Ahmad *et al.*, 1999). Some studies have

shown the effects of MC on improving insulin sensitivity in high-fat fedrats and it is demonstrated that MC improved glucose tolerance in diabetic patients(Sridhar,

Vinayagamoorthi, Arul Suyambunathan, Bobby, & Selvaraj, 2008; Welihinda, Karunanayake, Sheriff, & Jayasinghe, 1986). Previous studies had also reported thatMC enhanced insulin secretion (Fernandes *et al.,* 2007; Sathishsekar &Subramaniam, 2005b) and increased the number of pancreatic β-cells in the Islets of Langerhans (Ahmed *et al.,* 2004).

There are several possible mechanisms of hypoglycemic activity of MC. Previous studies have revealed that MC increased the glucose uptake in the liver by promoting glucose-6-phosphate dehydrogenase and decreasing glucose-6-phosphatase activity (McCarty, 2004; Sekar *et al.,* 2005). It could also increase the mRNA expression of glucose transporter 4 (GLUT4) proteins in skeletal muscles (Mahomoodally, Gurib-Fakim, & Subratty, 2007; Manabe, Takenaka, Nakasa, & Okinaka, 2003).It is suggested that the MC fruit extract could reduce the glucose transport via the brush border of the small intestine.Some studies have reported that abnormally high levels of lipid peroxidation and the concurrent diminution of antioxidant defense mechanisms can lead to the destruction of cellular organelles and lead to oxidative stress (Ahmed *et al.,* 2006; Mahboob *et al.,* 2005). Dietary antioxidants associated with change in lifestyle might help to reduce damage brought about by free radical toxicity in diabetes mellitus (Srivatsan *et al*, 2009). The antioxidant compounds of MC include phenolic phytochemicals and vitamins such as C and A were isolated from this plant (Grover and Yadav, 2004). Recently, cucurbitane-type triterpenoids were isolated from the stems of MC and demonstrated their antioxidant activity (Liu *et al.*, 2010).

Most of the studies on antidiabetic activity of MC had focused on adult type 1 diabetic animal. In the work described in this thesis a diabetic neonatal rat model was used. This model previously described as one day old pup rats treated with STZ. These pups exhibit hyperglycemia and insulin reduction in the neonatal period which could be maintained up adulthood(Portha, Movassat, Cuzin-Tourrel and Bailbe, 2007). The diabetic pup rats show slightly higher blood glucose level, a slight decreased plasma insulin levels, and reduced insulin in pancreases (Arulmozhi, Veeranjaneyulu, & Bodhankar, 2004; Portha, 2007).

The present study was carried out to evaluate the effects of the MC whole fruit aqueous extract on diabetes and wound healing in the neonatal STZ- induced diabetic rat model.It was hypothesized that Bitter gourd (*Momordica charantia L.*) whole aqueous extract would improve diabetes control and wound healing in STZ-induced neonatal diabetic rats.

The objectives of the study were:

i. To evaluate different extraction methods for the antioxidant activities of the MC fruit extracts.
ii. To determine physiological and biochemical effects of the MC aqueous extract on diabetes control in the neonatal STZ-induced diabetic rats.
iii. To evaluate the histopathological effects of the MC extract on wound healing in diabetic rats.

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