IDENTIFICATION OF COMMONLY USED MEDICINAL PLANTS IN KANGKAR PULAI AND THEIR THERAPEUTIC EVALUATION AS ANTI-DIABETIC

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Specially dedicated goes to:

My dear parents

My wife

My siblings

My friends

For their love, understanding and support through my endeavour

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ABSTRACT

Medicinal plants have been used as traditional medicines for treatment of diseases such as diabetes mellitus. However, scientific information to support the claims of herbal medicine practitioners based on Use Value (UV) and Informant Consensus Factor (ICF) is largely unexplored. The aim of this study is to screen common medicinal plants and to evaluate their traditional use through an ethnopharmacological survey at Kangkar Pulai, Johor, Malaysia. Data were collected from the community through open interviews, determining the relative importance of the species surveyed and calculating the UV and ICF in relation to the medicinal plant uses. A total of 38 plant species belongs to 28 families were documented. Based on the results of ethnopharmacological survey, *Orthosiphon stamineus* Benth and *Momordica charantia* L recorded the highest Use Values (0.32 and 0.24) to treat diabetes. The results of antioxidant tests revealed that the total phenolic content (TPC) of *O. stamineus* is 71.70 ± 0.85 mg (GAE)/g and total flavonoid content (TFC) is 44.71 ± 0.75 mg (CE)/g. Further study was carried out to examine the effects of oral administration of *O. stamineus* extract in the treatment of diabetes in normal and alloxan-induced diabetic rats. Forty rats were divided into four groups of 10 each. Group A (control) consisted of normal rats receiving 2 mL (10 mL/kg bwt) of normal saline on daily basis, whereas group B consisted of diabetic rats treated with 1 mL (120 mg/kg bwt) of *O. stamineus* extract. Group C consisted of diabetic rats treated with 1 mL (150 mg/kg bwt) of Metformin. Group D consisted of untreated diabetic rats acted as negative control. Group B, C and D were injected intrapertonially with alloxan (150 mg /kg bwt). Diabetic group B rats treated with *O. stamineus* extract showed significantly (p <0.05) low blood glucose level compared to group D (untreated diabetic rats). Similarly diabetic group B rats consumed significantly lower daily food and water intake at significant level p <0.05 compared to group D (untreated diabetic rats). Diabetic group B rats treated with *O. stamineus* extract showed significantly higher body weight at significant level p <0.05 compared to group D (untreated diabetic rats). Diabetic group B rats treated with *O. stamineus* extract showed lower serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and higher high-density lipoprotein cholesterol (HDL-C) at significant value (p < 0.05) compared with group D (untreated diabetic rats). A significant decrease of total protein, albumin and creatinine was observed in the plasma of group B rats after being treated with *O. stamineus* extract compared with group D. Additionally, immunohistochemistry results showed that the levels of heat shock protein 70 (HSP70) and inducible nitric oxide synthase (iNOS) of group B diabetic rats were brought back to near normal range after being treated with *O. stamineus* extract at significant value (p < 0.05) compared with group D (untreated diabetic rats). In conclusion, O. *stamineus* extract exhibited antidiabetic activity in alloxan-induced diabetic rats. Thus, the present findings also support the potential use of *O. stamineus* extract as a remedy for hyperglycemia

ABSTRAK

Tumbuhan perubatan telah digunakan sebagai ubat-ubatan tradisional untuk merawat penyakit seperti diabetes mellitus. Walaubagaimanapun, maklumat saintifik berdasarkan Nilai Gunaan (UV) dan Persetujuan Pemberi Maklumat (ICF) bagi menyokong dakwaan pengamal perubatan tumbuhan masih belum diterokai. Tujuan kajian ini adalah untuk meninjau tumbuh-tumbuhan perubatan biasa dan untuk menilai penggunaan tradisional mereka melalui kaji selidik ethnopharmacology di Kangkar Pulai, Johor, Malaysia. Data-data telah didapati dari masyarakat melalui temuduga secara langsung, menentukan perbezaan kepentingan spesies yang ditinjau dan mengira Faktor Persetujuan Pemberi Maklumat (ICF) dan Nilai Gunaan (UV) berhubung penggunaan tumbuhan perubatan. Sebanyak 38 spesies tumbuhan yang dimiliki oleh 28 keluarga telah didokumenkan. Berdasarkan hasil kajian ethnopharmacological, Orthosiphon stamineus Benth dan Momordica charantia L mencatatkan nilai penggunaan yang tertinggi sebagai rawatan penyakit diabetes dengan nilai penggunaan, 0.32 dan 0.24, masing-masing. Keputusan ujian antioksidan menunjukkan ekstrak O. stamineus mengandungi jumlah kandungan fenol (TPC) 71.70 ± 0.85 mg (GAE) / g dan jumlah kandungan flavonoid (TFC) 44.71 ± 0.75 mg (CE)/g. Kajian lanjut telah dijalankan untuk mengkaji kesan pengambilan ekstrak O. Stamineus melalui mulut terhadap rawatan penyakit diabetes pada tikus normal dan diabetes yang disuntik dengan alloxan. Empat puluh ekor tikus telah dibahagikan kepada empat kumpulan dengan 10 ekor bagi setiap kumpulan. Kumpulan A terdiri daripada tikus-tikus normal yang menerima 2 mL (10 ml/kg bwt) larutan garam biasa (kawalan) pada setiap hari, manakala kumpulan B terdiri daripada tikus-tikus diabetes yang dirawat dengan 1 mL (120 mg/ kg bwt) ekstrak O. stamineus. Kumpulan C pula terdiri daripada tikus-tikus diabetes yang dirawat dengan 1 mL (150 mg/kg bwt) Metformin. Manakala kumpulan D terdiri daripada tikus-tikus diabetes yang tidak dirawat bertindak sebagai kumpulan kawalan negatif. Kumpulan B, C dan D telah disuntik intraperitoneally dengan Alloxan (150 mg / kg bwt). Tikus-tikus diabetes kumpulan B yang dirawat dengat ekstrak O. stamineus menunjukkan dengan ketara ($p < 0.05$) tahap glukosa darah yang rendah berbanding dengan kumpulan D (tikus-tikus diabetes yang tidak dirawat). Demikian juga tikus-tikus kumpulan B menunjukkan dengan ketara ($p < 0.05$), pengambilan makanan harian dan air yang lebih rendah berbanding dengan kumpulan D (tikus diabetes yang tidak dirawat). Mereka (kumpulan B) juga menunjukkan dengan ketara ($p < 0.05$) berat badan yang lebih tinggi, lebih rendah jumlah kolesterol, trigliserida, kolesterol lipoprotin ketumpatan rendah dan lebih tinggi kolesterol lipoprotin ketumpatan tinggi dalam serum berbanding dengan kumpulan D (tikus diabetes tidak dirawat). Penurunan yang ketara didapati bagi jumlah protein, albumin dan kreatinin dalam plasma tikus-tikus kumpulan B selepas rawatan dengan ekstrak O. stamineus. Selain itu, keputusan immunohistokimia menunjukkan tahap protein kejuthaba 70 (HSP70) dan inducible nitrik oksida sintase (iNOS) telah dikembalikan kepada julat hampir biasa selepas rawatan dengan ekstrak O. stamineus dalam Kumpulan B pada nilai signifikan ($p < 0.05$) berbanding dengan kumpulan D (tikus-tikus diabetes yang tidak dirawat). Kesimpulannya, ekstrak O. stamineus menunjukkan aktiviti anti-diabetes pada tikus-tikus diabetes yang disuntik Alloxan. Maka oleh kerana itu, penemuan ini juga menyokong potensi penggunaan ekstrak O. stamineus sebagai ubat untuk hiperglisemia.

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LIST OF ABBREVIATIONS

ADP	-	Adenosine diphosphate
AGEs	-	Advanced glycosylation end products
AIDS	-	Acquired immunodeficiency syndrome
AlCl3	-	Aluminium chloride
ATP	-	adenosine triphosphate
CAE	-	catechin equivalents
cNOS	-	Constitutive NOS, including eNOS and nNOS
DAB	-	3,3'- diaminobenzidine
DMEM	-	Dulbecco's Modified Eagle's Medium
DMSO	-	dimethyl sulphoxide
DNA	-	Deoxyribonucleic acid
DPPH	-	1,1-Diphenyl-2-picrylhydrazyl
DPX	-	Dextrune plasterizar xylene
EDTA	-	Ethylenediaminetetraacetic acid
EMEM	-	Eagle's Minimum Essential Medium
eNOS	-	Endothelial NOS
GAE	-	Gallic Acid Equivalents
GLUT2	-	glucose transporter 2
HDL	-	High density lipoprotein
HIV	-	Human immunodeficiency virus
HSPs	-	Heat shock proteins
I	-	Type one
ICF/Fic	-	informant consensus factor
IDDM	-	Insulin-dependent diabetes mellitus
IGT	-	impaired glucose tolerance

II	-	Type two
IKK-β	-	inhibitory protein κB kinase β
iNOS	-	inducible Nitric Oxide Synthase
IPNI	-	International Plant Names Index
IR	-	Insulin receptor
IRS	-	insulin receptor substrate
LDL	-	Low-density lipoprotein
LMIC	-	Lower middle income countries
MafA	-	musculoaponeurotic fibrosarcoma protein A
MAPK	-	mitogen-activated protein kinase
MODY	-	maturity-onset diabetes in youth
mRNA	-	Messenger RNA
MTT	-	methyl tetrazolium
N	-	number of informants
Na_2CO_3	-	Sodium carbonate
$NaNO_2$	-	Sodium nitrite
NaOH	-	Sodium hydroxide
NEFAs	-	non-esterifies fatty acids
NFkB	-	Nuclear transcription factor kB
NF-kB	-	nuclear factor-kB
NIDDM	-	Non-insulin-dependent diabetes mellitus
nm	-	Nanometers
nNOS	-	Neuronal NOS
NO	-	Nitric oxide
Nt	-	number of taxa used
Nur	-	number of use reports per each category
O_2	-	superoxide anoin
OGTT	-	oral glucose tolerance test
PCV	-	Packed cell volume
PDX-1	-	Pancreatic and duodenal homeobox 1
PI3K	-	phosphotidylinisitol-3-OH kinase
PKB	-	Akt/ protein kinase B
PKC	-	Protein kinase C

R	-	Reagent
RBC	-	red blood cell
ROS	-	Reactive oxygen species
STZ	-	Streptozotocin
T2DM	-	Type 2 Diabetes Mellitus
TG	-	Triglyceride
U	-	number of uses per species
UCP-2	-	uncoupling protein-2
UN	-	United Nations
UNESCO	-	United Nations Educational, Scientific and Cultural Organization
US$	-	United States dollar
USA	-	United States of America
UV	-	Use value
UV light	-	Ultraviolet
V	-	Volume
VLDL	-	Very-low-density lipoprotein
W	-	Weight
WBC	-	white blood cell
WHO	-	World Health Organization

LIST OF SYMBOLS

G	-	Gram
Kg	-	Kilogram
Dl	-	Deciliter
Ml	-	Milliliters
µL	-	Microliters
M	-	Molarity
mm	-	Millimeters
°C	-	Celsius
°F	-	Fahrenheit
Mg	-	Milligram
Ng	-	Nanograms
Pg	-	Pictogram

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CHAPTER 1

INTRODUCTION

1.1 Background of Research

In the last few decades, there have been many studies on ethno-medicine (Krippner, 2003; Williams, 2006). Ethno-medicine is the study of traditional medical practice. It is related to the cultural interpretation of health, diseases, and illnesses. It basically addresses matters concerning healthcare seeking and healing processes and practices (Krippner, 2003; Williams, 2006). Ethno-medicine is a highly complicated multi-disciplinary system that explores the use of plants, spirituality, and the natural environment, which has been the main source of treatment and healing for many people over the years (Lowe *et al*., 2001).

With the emergence of the discipline, research in the field of ethno-medicine has significantly contributed towards a better understanding of traditional subsistence, as well as medical knowledge and practice. A vast amount of literature on ethno-medicine has been motivated by the increasing awareness about the consequences of forced displacement and acculturation of the local people, the recognition of indigenous health practices and concepts to maintain ethnic identity, and the search for new medical cures and technologies (Williams, 2006).

The World Health Organization, (2003) reported that ethno-medicine has sustained its popularity in the developing world and its use is fast gaining roots in the developed world as well. The traditional herbal preparations of China accounts for 30–50% of the total consumption of medicines (WHO, 2003). In African countries, such as Ghana, Nigeria, Zambia, and Mali, herbal medicine is used to treat 60% of the children affected with malaria. In London, San Francisco, and South Africa, 70% of people suffering from HIV/AIDS are also reported to use herbal medicines at a cost of more than US$60 billion (WHO, 2003).

The World Health Organization has defined traditional medicine as the body of knowledge and practices used to recognize, prevent, and/or reduce some physical, mental, or social diseases that may rely on past experience and observation handed down from one generation to another in either verbal or written form (WHO, 1999a). In developing countries, complementary traditional medicines are often used. According to estimates by the World Health Organization, almost 80% of people living in rural areas in many countries are looked after by traditional medical practitioners. Another approximation is that about half of industrialized countries reportedly use traditional medicines regularly. Modern pharmaceutical agents, including many plant-derived therapeutic agents, are also supported by traditional herbal plants (Alzweiri *et al.*, 2011; Alsarhan *et al.*, 2012)

Over the years, people have used different materials from nature to improve their health and to treat their diseases. For this purpose, various substances were derived from animals, plants, and mineral resources in areas where people lived, as well as from very remote places (Ghorbani *et al.*, 2006). Nature has been the main source of medicinal agents for thousands of years. A large number of natural drugs have been isolated from natural sources to treat various diseases by keeping in mind the use of traditional medicine. This type of plant-based traditional medicine continues to play an important role in the practice of healthcare. About 80% of the world population uses conventional medicine prepared from various traditional medicinal plants as their primary healthcare (Ghorbani *et al.*, 2006).

Throughout the years, traditional medicines have been proven to be an invaluable source and guidance for screening of drugs. Many important and famous modern drugs, such as digitoxin, reserpine, tubocurarine, ephedrine, ergomentrine, atropine, vinblastine, and aspirin, were discovered on the basis of traditional folk medicine (Anyinam, 1995). In many parts of the world, medicinal herbs are considered an important element of the medical system of the indigenous people, and these resources are also an essential part of the traditional knowledge of the culture (Ghorbani *et al*., 2006).

Although reports have revealed improvements in the quality of life and life prolongation in diabetic patients after using traditional medicines, the biological activity of such medicines has not been documented (Bailey and Day, 1989). In general, with regard to traditional medicines in Asian countries, many herbal medicines are put together to make a multi-herbal formula to enhance its function (Bailey and Day, 1989).

Herbal medicines are still popular despite the abundance of modern medicine for cultural and historical reasons. Information is also available about the uses of herbal plants for the treatment of different diseases all over the world. However, there is a need to further investigate, correlate, and document these plants (Alzweiri *et al.*, 2011; Alsarhan *et al.*, 2012).

Diabetes belongs to a group of metabolic diseases having high blood sugar (glucose) levels, which are the result of defects in insulin secretion or action, or even both. Insufficient action of insulin results in increased blood-glucose concentration. The most common metabolic disorder (hyperglycemia) in the world is diabetes mellitus (Tierney *et al.*, 2002).

In the progress of diabetes, numerous pathogenic events are involved, ranging from autoimmune damage of β-cells in the pancreas resulting in insulin insufficiency to abnormalities that results in resistance to the insulin action (Alberti and Zimmet, 1998; American Diabetes Association, 2013).

The cause for defects in carbohydrate, lipid, and protein metabolism in diabetes is incomplete action of insulin on the specific tissues. The reason for deficient insulin action is inadequate insulin excretion or diminishing tissue responses to insulin action at one or more points in the complicated paths of hormone activity. Deficiency of insulin production and defects in insulin activity frequently exist in the same patient, and it is often indistinct which anomaly, if either alone, is the main reason for the hyperglycemia (Gavin *et al.*, 1997; American Diabetes Association, 2013).

Hyperglycemia symptoms include polyuria, polydipsia, weight loss, polyphagia and blurred vision. Weakness of growth and exposure to certain infections may induce chronic hyperglycemia. The life-threatening and acute after-effects of uncontrolled diabetes is hyperglycemia with ketoacidosis or non-ketotic hyperosmolar disease (Gavin *et al.*, 1997; American Diabetes Association, 2013).

The complications of diabetes include retinopathy or vision loss, and nephropathy. This leads to renal insufficiency and peripheral neuropathy with the risk of foot sores, amputations, and Charcot joints. Autonomic neuropathy causes gastrointestinal, genitourinary, and cardiovascular diseases, and even sexual dysfunction. Those patients with diabetes complications have increased prevalence of peripheral arterial and cardiovascular diseases. As well as this, diabetes patients have hypertension and abnormalities of lipoprotein metabolism (American Diabetes Association, 2013).

Insulin is a hormone that helps glucose enter the cells in the body to provide energy. Symptoms that appear in patients are frequent urination, lethargy, excessive thirst, and loss of appetite. Diabetes can be treated with dietary changes, timely medication, and, in some cases, by administering insulin injections on a daily basis. This depends on the type and severity of the problem (Bhikha and Glynn, 2013).

Type 1 diabetes is normally treated by using insulin, doing exercise, and through maintaining a diabetic diet. Type 2 diabetes is initially treated by weight loss measures, maintaining a diabetic regimen, and exercise. When these measures do not reduce the problem of raised blood sugars, then oral medications are used. In the case of failure of oral medication, insulin medications are considered. Natural herbs are also traditionally used to treat type 2 diabetes mellitus (Thomas *et al.*, 2004).

Diabetes can be treated through diet, exercise, oral hypoglycemic agents, and insulin. Today, a synthetic drug is available and is considered as an anti-diabetic agent, but it is expensive and produces serious side effects. In addition to the currently available therapeutic options, numerous herbal medicines are mentioned for treating diabetes mellitus. Generally, medicinal plants are advantageous due to the lack of side effects (Ayodhya *et al.*, 2010; Elavarasi *et al.*, 2013).

1.2 Problem Statements

Medicinal plants continue to play an important role in the treatment of diabetes, particularly in developing countries where most people have limited resources and do not have access to modern treatment. The increase in demand in industrially developed countries to use alternative approaches to treat diabetes, such as plant-based medicines, is also due to the side effects associated with the use of insulin and oral hypoglycemic agents (Anumsima, 2011).

Testing of the biological activity of medicinal plants for the treatment of diabetes mellitus based on ethnopharmacological studies may be hindered by inaccurate information collected from indigenous people regarding the use of medicinal plants, the weak points in these studies that might be overcome in the design of studies and interpretation of data. In Malaysia, there are about 12,000 kinds of flowering plants, of which about 1300 have been documented as medicinal plants, and only about 100 have been extensively studied for their medicinal effect (Anumsima, 2011).

Even with the several medicinal plants documented by ethnopharmacological studies for the treatment of diabetes, there are weak points in the determination of the use value for each plant and the informant consensus factor, because the use value explains the number of medicinal plants that have highest use value for the treatment of diabetes mellitus. Additionally, this knowledge is required to prove the validity of the claimed medicinal uses as recommended by traditional healers for the treatment of diseases, including diabetes. In order to overcome this situation, systematic research is needed to identify inexpensive, harmless, and effective anti-diabetic drugs.

Many studies have been conducted based on traditional knowledge and phytochemical analysis, but the combination of ethnopharmacological study and animal research is more reliable. Keeping in view the importance of using medicinal plants for the treatment of diabetes, this study aimed to identify and document the major medicinal plants being used by people in the Kangkar Pulai area, Johor, Malaysia, for treating human diseases. This study investigated the informant consensus factor and the use value of the plants in Kangkar Pulai area for treating diabetes and other diseases. Moreover, this ethno-medicine survey used certain equations to determine the types of medicinal plants and diseases that are treated by these plants. This study used specific biomarkers (HSP70 and iONS) to evaluate the effect of selected plants on the treatment of diabetic rats induced by alloxan.

1.3 Objectives of the Study

The main objective of this study was to investigate the anti-diabetic properties of one of the Malaysian herbs based on the ethnopharmacological survey combined with an animal model study. The objectives can be sub-classified as follows:

1. To determine the use value and informant consensus factor of traditional medicinal plants used for the treatment of diabetes based on an ethnopharmacological survey in Kangkar Pulai, Johor, Malaysia.

2. To determine the total phenol and flavonoid content, as well as the antioxidant activity, of selected medicinal plants.

3. To investigate the anti-diabetic properties of selected medicinal plant in a rat model of type 1 diabetes.

1.4 Scope of the Study

The following scopes of the study were identified:

1.4.1 To determine the informant consensus factor and use value of local herbs, particularly for diabetic treatment based on open interviews of 25 volunteers in Kangkar Pulai, Johor, Malaysia.

1.4.2 To determine the total phenol and flavonoid content, as well as the DPPH values of phytochemicals in selected anti-diabetic plants based on spectrophotometric method.

1.4.3 To evaluate the anti-diabetic properties of selected anti-diabetic plant based on glucose level, food intake, water intake, hematological parameters, and immunohistological analysis of the pancreas and liver of Alloxan-induced diabetic rats.

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