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ANTIDIABETIC AND ANTIOXIDANT POTENTIALS OF COMMERCIAL AND TRADITIONAL BRAN EXTRACTS OF MALAYSIAN RICE VARIETIES

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By

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Malaysian traditional rice varieties are believed to have more nutraceutical values than the commercial rice varieties. This study intended to compare the anti-diabetic potentials, total poly phenolic contents and antioxidant activities of bran extracts of seven Malaysian traditional rice varieties (*Adan halus, Adan kasar, Salleh halus, Salleh Kasar, Beras merah, Beras hitam and Nanung*) with those of three commercial varieties collected from Selangor, Kedah and Perlis. About 10 grams of the dried rice bran samples were extracted successively with 70% ethanol (3x100 mL) by overnight soaking to obtain ethanolic extracts, which were subsequently concentrated under reduced pressure using rotary evaporator. α-amylase and α-glucosidase inhibitory potentials of the rice bran extracts (RBEs) were studied in vitro. The total polyphenolic contents (TPC) and antioxidant activities (FRAP, ABTS and DPPH) of the crude extracts were also determined in vitro. *Beras merah* and *Beras hitam* showed α-glucosidase inhibition of 96.56 % ± 0.58 and 81.52 % ± 0.96, α-amylase inhibition of 88.44 % ± 3.41 and 84.27 % ± 3.02, and total poly phenolic content of 14.94 ± 0.53 and 10.22 ± 0.25 mg Gallic acid equivalent /g of dry rice bran respectively while the commercial rice brans displayed alpha amylase inhbition of [Kedah (72.5± 0.54%), Perlis (66.0% ± 2.72) and Sekinchan (69.4% ± 3.02)] and alpha glucosidase of [Kedah (86.9% ± 0.51), Perlis (48.2% ± 1.13) and Sekinchan (70.5% ± 2.40)]. The commercial bran extracts of the rice varieties (Kedah, Perlis and Sekinchan) showed antioxidant activities of [FRAP (1.7 ± 0.3 1.8 ± 0.0 and 1.6 ± 0.0 mmol $FeSO_4$/1 g bran), ABTS (0.2 ± 0.0 0.2 ± 0.0 and 0.3 ± 0.0 mmol Trolox/1 g bran) and DPPH (1.1 ± 0.4 2.5 ± 0.0 and 2.4 ± 0.0) mmol Trolox/1 g bran]. The results showed that the traditional varieties (RBEs of *Beras merah* and *Beras hitam)* displayed significant enzyme inhibitory and antioxidant activities than the bran extracts of the commercial rice bran varieties. These two traditional RBEs found to display significantly ($p<0.05$) higher enzyme and antioxidant activities were tested for their antidiabetic potentials in vivo on normal and diabetic Sprague Dawley rats at two different concentrations (400 mg/kg and 200 mg/kg each). The results indicated that the extracts possess antidiabetic potentials with *Beras merah* having better potency than *Beras hitam* especially at 400 mg/kg. This was seen in the abilities of the rice bran extracts to lower the blood glucose levels of both the normal and diabetic rats as well as restore other biochemical markers like plasma alanine amino transferase (ALT) and

blood triglycerides (TAG). The results indicated that brans of traditional rice varieties such *Beras merah, and Beras hitam* possess better potency as antioxidants and anti-diabetic agents than the commercial rice brans, hence could be used as good sources of natural anti-diabetic and antioxidants agents.

Abstrak tesis dikemukakan kepada senat Universiti Putra Malaysia sebagai memunuhi keperluan untuk Ijazah Master Sains

POTENSI ANTIDIABETIK DAN ANTIOKSIDAN DEDAK PADI TRADISIONAL DAN KOMERSIAL MALAYSIA

Oleh

TANKO ABUBAKAR SADIQ

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Kepelbagaian padi tradisional Malaysia dipercayai mempunyai lebih nilai nutraseutikal daripada jenis padi yang telah diperbaiki. Kajian ini mengkaji potensi anti -diabetes , jumlah kandungan poli fenolik dan aktiviti antioksidan bagi ekstrak dedak padi bagi tujuh varieti padi tradisional malaysia (Adan halus , Adan kasar, Salleh halus , Salleh kasar, Beras merah , Beras hitam dan Nanung) tiga jenis varieti terbaik telah dikumpul dari Selangor, Kedah dan Perlis. Sebanyak 10 gram sampel dedak padi kering telah berjaya diekstrak dengan 70% etanol (3x100 ml) secara rendaman semalaman untuk mendapatkan ekstrak etanol. Ekstrak pekat diperoleh melalui tekanan terturun dengan menggunakan penyejat putar. Potensi rencatan α - amilase dan α -glucosidase ekstrak dedak padi (RBEs) telah dikaji secara in vitro. Jumlah kandungan fenolik poli (TPC) dan aktiviti antioksidan (FRAP, DPPH dan ABTS) daripada ekstrak mentah juga telah dikenalpasti secara in vitro. Hasil kajian menunjukkan bahawa RBEs daripada Beras merah dan Beras hitam menunjukkan enzim rencatan dan aktiviti antioksidan yang ketara, mempunyai perencatan α -glukosidase sebanyak 96.56 % ± 0.58 dan 81.52 % ± 0.96 , perencatan α – amylase sebanyak 88.44 % ± 3.41 dan 84.27 % ± 3.02 , dan jumlah kandungan fenolik poli masing-masing adalah 14.94 ± 0.53 dan 10.22 ± 0.25 mg asid galik setaraf per gram dedak padi kering, manakala dedak padi komersial menunjukkan perenjatan alpha amilase untuk [Kedah (72.5± 0.54%), Perlis (66.0%± 2.72) dan Sekinchan (69.4%± 3.02)] dan alpha glukosidase untuk [Kedah (86.9%± 0.51), Perlis (48.2%± 1.13) dan Sekinchan (70.5%± 2.40)]. Dedak padi komersial varieti tersebut (Kedah, Perlis dan Sekinchan) menunjukkan aktiviti antioksida [FRAP (1.7 ± 0.31.8 ± 0.0 dan 1.6 ± 0.0 mmol $FeSO_4$/1 g dedak padi), ABTS (0.2 ± 0.00.2 ± 0.0 dan 0.3 ± 0.0 mmol Trolox/1 g dedak padi) and DPPH (1.1 ± 0.42.5 ± 0.0 and 2.4 ± 0.0) mmol Trolox/1 g dedak padi]. Kedua-dua varieti ini menunjukkan perubahan ketara (<0.05) lebih tinggi enzim dan aktiviti antioksida berbanding dedak padi komersial. Kepelbagaian dedak padi ini telah diuji untuk potensi antidiabetik dalam vivo pada tikus normal dan tikus diabetik Sprague Dawley pada dua kepekatan yang berbeza (400 mg / kg dan 200 mg / kg setiap satu). Hasil kajian menunjukkan bahawa ekstrak-ekstrak tersebut mempunyai potensi antidiabetik dengan Beras merah mempunyai potensi yang lebih baik daripada Beras hitam terutama pada 400 mg / kg. Ini dilihat dalam kebolehan ekstrak dedak padi untuk mengurangkan kandungan glukosa darah kedua-dua tikus normal dan tikus diabetik serta memulihkan penanda biokimia yang lain seperti

transferase plasma alanine amino (ALT) dan trigliserida darah (TAG). Keputusan menunjukkan bahawa dedak padi varieti tradisional seperti Beras merah dan Beras hitam mempunyai potensi yang lebih baik sebagai antioksidan dan agen anti-diabetes daripada dedak padi komersial, dengan itu boleh digunakan sebagai sumber yang baik ejen anti-diabetes dan antioksidan semulajadi.

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I certify that a Thesis Examination Committee has met on 26 May 2016 to conduct the final examination of Tanko Abubakar Sadiq on his thesis entitled "Antidiabetic and Antioxidant Potentials of Commercial and Traditional Bran Extracts of Malaysian Rice Varieties" 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 Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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Name of Member Supervisory Committee : Associate Professor Dr. Azrina Azlan

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LIST OF ABBREVIATIONS

ABTS	2, 2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) di-ammonium salt
AH	*Adan halus*
AK	*Adan Kasar*
ANOVA	Analysis of variance
BH	*Beras hitam*
BM	Beras merah
DNS	3, 5-Dinitrosalicylic acid
DPPH	1, 1-Diphenyl-2- picrylhydrazine
FRAP	Ferrous reducing antioxidant power
GAE	Gallic acid equivalent
KED	Kedah
Na_2CO_3	Sodium carbonate
NNG	Nanung
PER	Perlis
SEK	Sekinchan
SH	*Salleh halus*
SK	*Salleh kasar*
TEAC	Trolox equivalents antioxidant capacity
TPC	Total polyphenolic contents
TPTZ	2, 4, 6-Tripyridyl-s- triazine
µg	Microgram

CHAPTER 1

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by abnormal rise in blood sugar levels known as hyperglycaemia (Son et al., 2015). It is reported to be one of the fastest growing chronic, non-communicable diseases. Diabetes leads to imbalance in the metabolisms of carbohydrates, fats and proteins (Kazeem et al., 2013; Lacroix & Li-Chan, 2014; Rajshekar & Rajshekar, 2013). According to the International Diabetes Federation, 8.3%, equivalent to 387 million people of the world population were living with diabetes in 2014 and the number was expected to increase to 592 million by the year 2035 (IDF, 2014). The prevalence of diabetes among Malaysian adults above the age of 30 years has experienced perpetually increase from 6.3 to 8.3 to 14.9% in 1986, 1996 and 2006, respectively (Letchuman et al., 2010). The overall prevalence of 22.9% of the total population was recorded in 2013 (Wan Nazaimoon et al., 2013). This shows that failure to arrest this rising diabetic trend in the country can lead to serious health, social and economic problems mainly due to diabetic complications that might ensue.

Diabetes could result from either inherited or acquired deficiency in insulin secretion, decreased sensitivity of the organs to the secreted insulin or both (Jiju et al., 2013). Most diabetes cases are broadly classified into two etio-pathogenic types (Kumar et al., 2012). Type 1, which results due to autoimmune destruction of pancreatic beta-cells triggering severe insulin deficiency (Moller, 2010; Triggle & Ding, 2014) and type 2 caused by poor sensitivity or signalling effect of insulin leading to failure to mediate glucose transport from the blood into key target cells such as muscle cells (Bathini et al., 2013). In the later situation, the insulin level is increased but the peripheral tissues become resistant to insulin (Chakrabarti, 2002; Gandhi et al., 2014; Rengasamy et al., 2013).

Hyperglycaemia is the earliest and commonest symptom of diabetes which if not early managed, could lead to diabetic complications and subsequent damage of tissues like blood vessels and nerves (Triggle & Ding, 2014). Post-prandial hyperglycaemia is normally due to the combined actions of carbohydrate hydrolysing enzymes (α-amylase and α-glycosidase) (Mohamed et al., 2012). However, in diabetic situation, the elevation of blood sugar becomes chronic (Sharma et al., 2013) inducing excessive generation of free radicals, mostly through glucose oxidation, non-enzymatic glycation, and oxidative degradation of glycated proteins (Gandhi et al., 2014). Due to their extreme reactiveness, the free radicals initiate oxidative damage of organs and tissues via mechanisms such as lipid peroxidation, oxidative DNA damage and protein oxidation (Carocho & Ferreira, 2013). Studies have shown that free radicals play an important role in the incidence of diabetic complications like cardiovascular diseases, cataract, inflammatory diseases, neurodegenerative disorders, cancer and aging (Aghdamet al., 2011). Moreover, both clinical and experimental studies have confirmed oxidative stress as one of the major causes of the pathogenesis of diabetes mellitus (Sharma et al., 2013) in which it contributes to insulin resistance, β-cell dysfunction, impaired glucose tolerance and eventually exacerbation of type 2 diabetes (Lee et al., 2014). This endangers diabetics

under unmanaged oxidative stress prone to developing diabetic complications (Yao et al., 2010).
Interestingly, reports have shown that dietary consumption of foods or beverages rich in antioxidants has inverse relation with the risk of diabetic complications that could be instigated by oxidative stress (Zujko & Witkowska, 2014). This points to the need for more studies on the exploitation of more edible plants with such potentials.

In order to mitigate chances of diabetic complications, the generation of free radicals has to be abated (Djeridane et al., 2013). One of the approaches employed to achieve this is to prevent hyperglycaemia through inhibiting activities of carbohydrate hydrolysing enzymes (Pérez-Ramírez et al., 2015). Inhibitors of these enzymes have been beneficially utilised as oral drugs for management of hyperglycaemia, especially in patients with type II diabetes mellitus (Kim et al., 2011; Kumar et al., 2012). Anti-diabetic agents like sulfonylureas, meglitinides, biguanides, thi-azolidinediones (TZDs), -glucosidase inhibitors, glucagon- like peptide (GLP)-1 receptor agonists, dipeptidyl peptidase (DPP)-IV inhibitors, amylin analogues, dopamine D2-receptor agonists and bile acid sequestrants have been in use as effective anti-diabetic therapies (Lacroix & Li-Chan, 2014; Roem et al., 2012; Tahrani et al., 2011).

Despite the achievements recorded in the treatment of diabetes using approved oral hypoglycaemic agents, search for novel alternatives continues due to a number of limitations akin to the existing synthetic drugs (Ademiluyi & Oboh, 2013; Lee et al., 2014). Among the limitations of synthetic anti-diabetic drugs are; gastrointestinal disturbances, abnormal bacterial fermentation of undigested carbohydrates in the colon, anaemia, bone fracture, oedema, congestive heart failure, and severe hypoglycaemia (Chakrabarti & Rajagopalan, 2002; Kumar et al., 2012; Wang et al., 2012; Xing et al., 2015).

Studies have already suggested that antioxidants and carbohydrate digestive enzyme inhibitors from natural sources could be better alternatives for the management of diabetes. The correlation that exists between anti hyper-glycaemic activities and antioxidant capacities reported earlier provides synergy in curbing diabetic complications (Premakumara et al., 2013). Phytochemicals such as phenolics with strong antioxidant properties have been reported to be good inhibitors of carbohydrate digestive enzymes (Djeridane et al., 2013). These phytochemicals with antioxidant properties render a holistic control of hyper-glycaemia and diabetic complications caused by oxidative stress (Ademiluyi & Oboh, 2013; Ediriweera & Ratnasooriya, 2009; Mai et al., 2007). Some dietary plants reported to have such potentials include; pea nut (*Arachis hypogea*) (Irshad & Sharma, 1981), cowpea (Piergiovanni & Gatta, 1994), lima beans (*Phaseolus lunatus*) (Johnson et al., 2013), white beans (*Phaseolus vulgaris*) (Barrett & Udani, 2011a), sorghum (Mulimani & Supriya, 1993), wheat (Heidari, 2005) etc. Inhibitory potential of starch hydrolysing enzymes have also been detected in fruits and vegetables such as raspberry (Boath et al., 2012), red grape, green pepper (McCue et al., 2005), cambucci and cupuacu fruits (da Silva Pinto et al., 2008), and carrot (Mccue *et al.*, 2005). According to some other reports, blackcurrant, blueberry (McDougall et al., 2005), strawberry (Pinto et al., 2008), apples (Barbosa & Pinto, 2012) and ginger (Oboh et al., 2010) were also found to have the ability to inhibit the activities of α-glucosidase.

Rice bran, a cheap by-product of rice milling has hitherto been investigated for the potentials discussed above (Adam et al., 2010). Although Malaysia has a host of different varieties of rice distributed in many parts of the country (Nisak et al., 2005), evaluation of locally available rice bran varieties with respect to their antioxidants and anti-diabetic properties are scanty. In a year round production, huge quantities of bran generated by the paddy industries is currently underutilized in spite of its high potentials as raw material for functional ingredient in pharmaceutical and nutraceutical production. Owing to lack of information on the potential antioxidant and anti-diabetic properties of locally available rice bran varieties, it became necessary to initiate some studies in order to explore the potentials for the local rice bran varieties.

1.1 Aim and Objectives

1.1.1 General Objective

To determine the antioxidative and anti-diabetic properties of traditional and commercial rice bran.

1.1.2 Specific Objectives

This study focused on the following specific objectives;

1. To determine and compare the antioxidant quantities and activities of Malaysian traditional and commercial rice bran extracts in vitro.

2. To screen Malaysian traditional and commercial rice bran extracts for α-amylase and α-glucosidase inhibitory activities in vitro.

3. To test the anti-diabetic potency of the best extracts on normal and alloxan induced diabetic Sprague Dawley rats in vivo.

1.2 Problem Statement

The rising trend of diabetes is a serious problem in Malaysia. Synthetic therapies currently used for diabetes management possess side effects hence the need to focus on natural products especially from dietary sources which are safer, cheaper and available yet possessing similar efficacy as the synthetic ones.

1.3 Research Questions

To check;

1. Whether Malaysian traditional and commercial rice bran have good antioxidant properties.

2. Whether Malaysian traditional and commercial rice bran can inhibit the activities of carbohydrate hydrolyzing enzymes (α-amylase and α-glucosidase).

3. Whether some of the rice brans will exhibit good anti-diabetic potencies on normal and alloxan induced diabetic Sprague Dawley rats

1.4 Hypothesis

The rice bran extracts possess anti-diabetic properties and antioxidant potentials.

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