ANTITHROMBOTIC PROPERTIES OF POLICOSANOL RICE (*Oryza sativa* L.) BRAN IN MODULATING BLOOD PLATELET PROPERTIES IN *IN VITRO*, *EX-VIVO* AND *IN VIVO* MODEL

By

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In recent decades, sugarcane policosanol was shown to be effective in preventing platelet aggregation by Cuban researchers. However, there were some identifiable gaps in the research in which the underlying mechanisms details were lacking. The policosanol content was not quantified and its impact on other important related markers was not assessed. Moreover, the anti-platelet effect of policosanol from other plant sources was never been investigated. The general objective of this research project was to investigate the anti-platelet functions of rice bran policosanol extract. The project started with policosanol extraction and sonication using hexane and methanol (20:1 v/v) was the best method yielded 877.99±110.11mg policosanol/100g extract. Gas chromatography mass spectrometer (GCMS) analysis showed that tetracosanol was the dominant component (371.80±45.27mg/100g extract). On the other hand, *in vitro* antioxidant analysis showed that policosanol had strong antioxidant power, with EC_{50}=8.53mg/mL and EC_{50}=10.55mg/mL respectively in both 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay and beta carotene bleaching (BCB) assay. The project was then continued with *in vitro* study using microtiter method and 500µg/mL policosanol extract was shown to inhibit adenosine diphosphate (ADP)-induced platelet aggregation up to 52.79±5.95%. The research project was further extended to *ex vivo* and *in vivo* analysis using high fat diet fed male Sprawgue Dawley rats. The results obtained revealed that 250mg/kg policosanol treatment exerted highest platelet aggregation inhibitory effect which was up to 53% . Besides, 500mg/kg policosanol treatment inhibited lipid peroxidation by 33%. On the other hand, policosanol extract did not prolong both bleeding time (521.2±97.16 secs) and coagulation time. In addition, policosanol extract was shown to modulate platelet glycoproteins and soluble biomarkers expression positively while regulating lipid profile without exerting harmful effects as revealed by *in vitro* and *in vivo* toxicity analysis. With all the solid findings, rice bran policosanol was suggested to be a good anti-platelet candidate in arterial thrombosis prevention.

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

CIRI ANTI-TROMBOSIS POLIKOSANOL DEDAK BERAS (*Oryza sativa* L.) DALAM MEMODULASI CIRI PLATELET DALAM MODEL *IN VITRO, EX-VIVO* AND *IN VIVO*

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Sejak kebelakangan ini, polikosanol tebu terbukti berkesan dalam mencegah aggregasi platelet oleh penyelidik Kuba. Namun demikian, jurang penyelidikan dikenalpasti di mana dasar mekanisme tidak diperincikan. Kandungan polikosanol tebu tidak diuji dan kesannya terhadap parameter penting lain tidak dinilai. Tambahan pula, kesan anti-platelet polikosanol daripada sumber tanaman lain tidak pernah disiasat. Objektif umum projek penyelidikan ini adalah untuk menyelidiki fungsi anti-platelet ekstrak polikosanol dedak beras. Projek dimulakan dengan pengekstrakan dan sonikasi menggunakan heksana dan metanol (20: 1 v / v) adalah kaedah terbaik yang menghasilkan 877.99 ± 110.11mg polikosanol / 100g ekstrak. Analisis spektrometer jisim kromatografi gas (GCMS) menunjukkan bahawa tetrakosanol adalah komponen dominan (371.80 ± 45.27mg / 100g ekstrak). Di sampingnya, analisis antioksidan *in vitro* menunjukkan bahawa polikosanol mempunyai kekuatan antioksidan yang tinggi, iaitu EC_{50} = 8.53mg / mL dan EC_{50} = 10.55mg / mL dalam ujian 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) dan ujian pelunturan beta karoten (BCB) masing masing. Projek ini kemudian dilanjutkan dengan kajian *in vitro* menggunakan kaedah microtiter dan 500 µg / mL ekstrak polikosanol terbukti dapat mengurangkan agregasi platelet oleh adenosin difosfat (ADP) sehingga 52.79 ± 5.95%. Projek penyelidikan ini seterusnya diperluaskan ke analisis *ex vivo* dan *in vivo* dengan menggunakan tikus Sprague Dawley jantan yang berdiet lemak tinggi. Hasil yang diperoleh menunjukkan bahawa rawatan 250mg / kg polikosanol memberikan kesan penghambatan agregasi platelet tertinggi sehingga 53%. Selain itu, rawatan dengan 500mg / kg polikosanol berjaya menghambat peroksidasi lipid sebanyak 33%. Selain daripada itu, ekstrak polikosanol tidak memanjangkan masa pendarahan (521.2 ± 97.16 saat) dan masa pembekuan. Tambahan pula, ekstrak polikosanol terbukti memodulasi glikoprotein platelet dan ekspresi biomarker larut secara positif sambil menambahbaikkan profil lipid tanpa memberikan kesan berbahaya seperti yang ditunjukkan dalam analisis toksisiti *in vitro* dan *in vivo*. Dengan semua penemuan yang kukuh, polikosanol dedak beras dicadangkan sebagai calon anti-platelet yang baik dalam pencegahan trombosis arteri.

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AA	Arachidonic acid
ADP	Adenosine diphosphate
ASA	Aspirin
BCB	Beta carotene bleaching
COX	Cyclooxygenase
CRP	C-reactive protein
CVD	Cardiovascular disease
DPPH	2,2-diphenyl-1-picryl-hydrazyl-hydrate
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial NO synthase
GCMS	Gas chromatography mass spectrometer
GP	Glycoprotein
GPx	Glutathione peroxidase
HDL	High density lipoprotein
H_2O_2	Hydrogen peroxide
LDL	Low density lipoprotein
NO	Nitric Oxide
O_2^-	Superoxide anion
OH^-	Hydroxyl radical
ONOO	Peroxynitrite
$PGF_{1\alpha}$	Prostaglandin F1 Alpha
PGI_2	Prostacyclin
PLC	Phospholipase C

ROS	Reactive Oxygen Species
SOD	Superoxide dismutase
TAG	Triacylglycerol
TXA_2	Thromboxane A_2
TXB_2	Thromboxane B_2
VTE	Venous thromboembolism
vWF	Von Willebrand factor

CHAPTER 1

INTRODUCTION

As according to the global burden of disease study reported by Feigin *et al.* (2014), the two common diseases of thromboembolism, stroke and heart disease, caused about 7 million and 5.9 million deaths respectively across the globe (Feigin *et al*., 2014). This number increased tremendously for about 35% and 25% respectively as compared to the past 20 years (Jagannathan *et al*., 2019). By referring to a statistics report by Raskob *et al*. (2014), it was also documented that one in four deaths worldwide was caused by coronary artery disease and stroke while venous thromboembolism (VTE) had lower occurrence rate. Generally, thrombosis can be divided into two types namely venous thrombosis and arterial thrombosis. Arterial thrombosis was always the clinical focus as it had been recognized as the underlying cause of stroke and heart attack. The onset of arterial thrombosis was commonly due to vascular plaque rupture or through excessive platelet accumulation (Raskob *et al*., 2014).

Platelet is requisite in primary hemostasis, endothelium repair, and play pivotal role in atherosclerosis. Scientifically, adhesion and aggregation of platelet is causal in arterial thrombosis development and this makes antiplatelet agents the key solutions for arterial thrombosis (Hamilos *et al*., 2018). Platelet adheres to vascular wall, undergoes activation through surface receptors, releases granules content, tethers additional platelets, and eventually forms aggregates. Although this mechanism is regulated in response to injury, abnormal progression of the events triggers the formation of white thrombus, subsequently causes atherothrombosis (Kearon *et al*., 2012). To date, aspirin is still the choice of prescription as anti-platelet drug. Aspirin interferes with thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) production through inhibition of cyclooxygenase (COX) enzyme activity and this suppresses platelet aggregation. However, aspirin brings the potential risk of bleeding (Meek *et al*., 2010).

Besides platelets, inflammatory markers, lipids, and free radicals are shown to participate significantly in arterial thrombosis development (Previtali *et al*., 2011). There are strong evidence showing that inflammation triggers platelet activation, sequentially drives arterial and venous thrombosis. High concentration of inflammatory marker C-reactive protein (CRP) in serum was directly proportional to the incidence rate of cardiovascular manifestations. Overall, there was a bi-directional relationship between thrombosis and inflammation (De Caterina *et al*., 2016). Apart from inflammation, oxidative stress is proved to be impactful in atherothrombosis, directly or indirectly (Martin Ventura *et al*., 2017). Both endogenous and exogenous reactive oxygen species (ROS) were involved in platelet adhesion, activation, and aggregation upon the stimulation by agonists (Masselli *et al*., 2020). Arthur *et al*. (2012) showed that ROS regulated GPVI-dependent platelet activation through the binding of ROS to collagen receptor. Last but not least, lipids have been reported to have inter-relationship with platelet functions. Lipids act on platelets directly through surface receptor binding or

indirectly by changing the platelet membrane lipid composition (Van der Stoep *et al*., 2014). More details were described in depth in the following chapters.

In recent decades, people try not to take clinical drugs and switch attention to natural remedies in thrombosis prevention. Most of the research studies skewed towards natural products to discover bioactive compounds that can reduce health complications (Weiver, 2014). Long chain fatty alcohols, collectively known as policosanol, derived from sugarcane, were reviewed to be useful in cardiovascular diseases prevention. Carbajal *et al*. (1998) showed that sugarcane policosanol decreased platelet aggregation in both healthy and hypercholesterolemia volunteers, with the reduction of thromboxane A_2 (TXA_2) but not prostacyclin (PGI_2). Valdes *et al*. (1996) proved that repeated dosage of policosanol decreased collagen, adenosine diphosphate (ADP), and apinephrine-induced platelet aggregation by reducing thromboxane B_2 (TXB_2). Besides, Arruzazabala *et al*. (1998) showed that 30 days treatment using 10mg policosanol significantly decreased platelet aggregation with no adverse effects. Furthermore, policosanol was shown to have advantages over aspirin as it decreased only TXA_2. Combination of aspirin and policosanol was shown effective in decreasing ADP-induced platelet aggregation (Arruzazabala *et al*., 1997). In addition, Castaño *et al*. (1999) successfully showed that policosanol had a better efficacy in inhibiting ADP and AA-stimulated platelet aggregation as compared to pravastatin. Later, Castaño *et al*. (2006) also presented that policosanol worked synergistically with omega-3-fatty acid in decreasing AA and collagen-induced platelet aggregation by improving serum lipid profile.

Despite of all the health benefits reported by the researchers, there were discrepancies in some studies that explained otherwise. In addition, research gaps were found in which the reported anti-platelet aggregation function of policosanol was too superficial to draw a conclusion without the knowledge of the working mechanisms. A more concise study is needed to evaluate the anti-platelet function of policosanol. Also, efficacy of policosanol from other sources, for instance wheat or rice bran, was never been investigated. Therefore, this project was aimed to study the benefits of rice bran policosanol on platelet function. Rice bran is rich in wax content and has its own composition of long chain fatty alcohols. With its unique fatty alcohols fingerprint, it could have different physiological benefits as compared to sugarcane policosanol. In addition, soluble biomolecules release and platelet glycoproteins expression were analyzed upon policosanol treatment to understand the inhibitory mechanisms better. Holistically, the anti-platelet functions of rice bran policosanol extract were assessed comprehensively including its effect on inflammatory markers, oxidative stress, and lipid profile as there is a strong interplay among all in thrombosis. Positive outcome of the studies will make rice bran policosanol a great candidate in cardiovascular diseases management. Malaysia, being one of the rice-producing countries, it provides sufficient sample for future research and utilization of rice bran for nutraceutical purposes will help to reduce waste generation during rice milling.

1.1 General objective

To study the anti-platelet effects of rice bran policosanol extract, *in vitro*, *ex vivo* and *in vivo*.

1.2 Specific objectives

1. To characterize rice bran policosanol extract and to evaluate its antioxidant capability, *in vitro*.
2. To evaluate the effect of rice bran policosanol on platelet adhesion, aggregation and protein secretion, *in vitro.*
3. To determine the effect of rice bran policosanol on platelet functions and serum arachidonic acid metabolites level, *ex vivo* and *in vivo.*
4. To examine the effect of rice bran policosanol on platelet glycoproteins expression and soluble marker release, *in vitro* and *in vivo*.
5. To study the effect of rice bran policosanol on antioxidant and blood lipid modulation capability, *in vivo*.

1.3 Hypothesis of the study

1. Rice bran policosanol is potential to inhibit platelet adhesion, activation, and aggregation with no adverse toxicity.
2. Rice bran policosanol is potential to reduce platelet aggregation in response to oxidative stress.
3. Rice bran policosanol is potential to reduce platelet aggregation by modulating glycoproteins expression and other platelet- related biomarkers.
4. Rice bran policosanol is potential to reduce platelet aggregation by improving serum lipid profile.

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