EFFECTS OF COMMON VARIETIES OF GUAVA (*Psidium guajava L*) LEAVES ON CYCLOSPORINE-INDUCED HYPERTENSION IN RATS

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ABSTRACT

Guava leaf is a folklore remedy for hypertension, however, limited scientific basis support this usage. Hence, this study investigated the molecular mechanism underlying the antihypertensive effect of the leaves of three guava varieties (white, red and pink) in normotensive and hypertensive rats with /or without captopril administration. The aqueous extract of guava leaves were prepared, and the *in vitro* antioxidant (DPPH*, Fe^{2+} chelation, ferric reducing antioxidant properties, and lipid peroxidation) and enzymes [arginase, cholinesterase (AChE and BChE), angiotensin I-converting enzyme (ACE)] inhibitory assays were carried out. Thereafter, toxicological evaluation at 50, 500, and 5000 mg/kg, 250 and 500 mg/kg of the extracts on normotensive and hypertensive rats with/without captopril on haemodynamic indices and biochemical [lipid profile, arginase, AChE, BChE, purinergic enzymes (e-NTPDase, 5'nucleotidase and adenosine deaminase (ADA)] parameters and endogenous antioxidant status as well as liver and kidney function test were carried out. The ACE mRNA gene expression in the rat's kidney was also determined. The result revealed that all the extracts exhibited strong antioxidant properties and inhibited key enzymes relevant to hypertension *in vitro*. The extracts elicited neither systemic or organ toxicity at the concentrations tested, as the LD_{50} of the extracts were greater than 5000 mg/kg. The extracts modulate systolic (SBP) and diastolic (DBP) blood pressure, enzymes activities, and significantly boosted the antioxidant status in normotensive rats. However, the extracts significantly ($p < 0.05$) lower systolic (SBP) and diastolic (DBP) blood pressure, reduced elevated plasma liver and kidney function markers and ACE, arginase and cholinesterases activities, modulated e-NTPDase, 5'nucleotidase and ADA activities lipid profile in hypertensive rats. Furthermore, the extracts significantly ($p < 0.05$) downregulated ACE mRNA expression in both normotensive and hypertensive rats. Co-administration of the extracts with captopril elicited an additive effect on the antihypertensive properties without any observable biochemical/physiological alterations. The HPLC analysis

of the extracts revealed rutin (123.90±0.26, 126.45±0.77, 123.93±0.20 mg/100 g) and chlorogenic acid (149.79±0.45, 157.17±0.41, 150.52±0.61 mg/100 g) as the dominant polyphenols in white, red and pink of guava leaves respectively. This study suggest that antihypertensive property of the leaves may be due to their rich polyphenolic content with potent antioxidant properties, and ability to modulate lipid profile, purinergic signalling, key enzymes relevant to blood pressure, as well as downregulate ACE mRNA expression, which culminated in SBP and DBP.

CHAPTER ONE

INTRODUCTION

1.1 Introduction

Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. It is a common risk factor of cardiovascular disease, which has become a worldwide problem of epidemic proportions, affecting 15 to 20% of all adults with ailments such as arteriosclerosis, stroke, myocardial infarction and end-stage renal disease (Giles *et a*l., 2009). Hypertension causes a considerable morbidity and mortality worldwide, contributing disability in about 57 million people and 7.5 million premature deaths annually (Dewhurst and Walker, 2015). Abnormality in the blood pressure is recognized as a biomarker for hypertension, and a distinction is made between the various stages of hypertension and global cardiovascular risk (Giles *et al*, 2009). Hypertension is known to be the risk factor for stroke, blindness, kidney damage, heart attack, enlarged heart and arteriosclerosis (Dewhurst and Walker, 2015; Akinyemi *et al.*, 2015).

For about two decades, studies have indicated an escalating pattern of hypertension in sub-sahara Africa (Lim et al., 2012; Murray *et al.*, 2012). The reasons for the escalating burden of hypertension in sub-Sahara Africa is thought to include rapid urbanization, adoption of unhealthy eating habits, and sedentary lifestyles (Echouffo-Tcheugui *et al.*, 2015), Addressing hypertension in sub-Sahara Africa requires multipronged interventions to achieve better prevention, detection, and control of the condition (Echouffo-Tcheugui *et al.*, 2015). Although several classes of antihypertensive drugs are available in modern medicine to achieve this purpose, the treatment of arterial hypertension in sub-sahara Africa and other developing countries is still challenging. This is because most hypertensive drugs seem unaffordable and unavailable for almost the entire population. More so, they come with different side effects