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Anti-hyperlipidemic and Anti-hypercholesterolemic effect of aqueous extract of guava (*Psidum guajava Linn*.) leaves on rats

Thesis
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Dina Hesham Sayed Hanafy

Dedication

I would like to dedicate this thesis to my family, especially my mother and my father. I will never forget their effort towards me and also for their encouragement and support. Words can't express my gratitude.

Contents

List of Abbreviations

AdipoR1 : Adiponectin receptor 1

AdipoR2 : Adiponectin receptor 2

AG : Acylated gherlin

AgRP : Agouti-related protein

ALT : Alanine aminotranseferase

ALP : Alkaline phosphatase

AMPK : Adenosine monophosphate-activated protein kinase

ARC : Arcuate nucleus

AST : Aspartate aminotranseferase

BS : Bile salt

CNS : Central nervous system

CPT : Carnitine palmitoyl transeferase

CRH : Corticotrophin releasing hormone

CVDs : Cardiovascular diseases

DIO : Diet –induced obesity

ELISA : Enzyme linked immunosorbent assay

fAD : Full length adiponectin

FFAs : Free fatty acids

gAD : Globular adiponectin

GALP : Galanin-like peptide

GHSR-1A : Growth hormone secretagogue receptor type 1A

List of Abbreviations (Cont.)

GLE : Guava leaf extract

HDL-C : High density lipoprotein cholesterol

HFHC : High- fat high- cholesterol

HMG-CoA : 3-hydroxy-3-methylglutaryl-CoA

HMW : High-molecular-weight

LDH : Lactate dehydrogenase

LDL-C : Low density lipoprotein cholesterol

LEPRb : Leptin receptor

MCAD : Medium chain acyl CoA

MDA : Malondialdehyde

mRNA : Messenger RNA

NPY : Neuropeptide Y

p.o : Per ose

POMC : Pro-opiomelanocortin

PPARα : Peroxisome proliferator activated receptor alpha

SHRSP/ZF: SHRSP.Z-Leprfa/IzmDmcr

TAC : Total antioxidant capacity

TAGs : Triacylglycerols

TC : Total cholesterol

TMB : Tetramethylbenzedine

VLDL-C : Very low density lipoprotein cholesterol

WAT : White adipose tissue

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Abstract

The aim of the present study is to investigate the ameliorative effect of aqueous guava leaves extract(AGLE) with different doses (200, 350, 500 & 650 mg/kg b.wt.) taken *p.o* in rats fed high fat high cholesterol (HFHC) diet for 8 weeks. The four doses of AGLE cause a significant decrease in food intake, final body weight, body weight gain, serum TAGs, VLDL-C, risk ratio as well as liver TAGs and malondialdehyde level. Also doses of AGLE (350, 500 and 650 mg/kg b.wt.) cause a significant decrease in relative liver weight, serum AST and LDL-C, but it was found a significant increase in HDL-C and leptin hormone. While the doses (500 & 650 mg/kg b.wt.) cause a significant decrease in serum TC. The highest dose causes a significant decrease in serum ALT and adiponectin hormone. Total liver cholesterol was decreased significantly in groups given (200&350 mg/kg b.wt.) but no significant decrease in doses (500 & 650 mg/kg b.wt.). No change in ghrelin hormone in the four treated groups fed HFHC diet and given AGLE compared to positive control.

Introduction

Hyperlipidemia is one of the major risk factors for cardiovascular diseases (CVDs). Both genetic disorders and diet enriched with saturated fats and cholesterol, contribute to the elevated lipid levels in population as well as in many other developed countries around the world ***(Jeevangi et al., 2013).***

Causative factors of hyperlipidemia are sedentary life, poor dieting and genetic factors which are the most prominent. In humans, continuous intake of high amounts of fat appears to contribute to hyperlipidemia. As in rural areas and as in most developing countries, reliance on natural sources for medications (traditional medicine) is common. Of these sources, plants (sometimes specific parts) are critical components. In therapeutic medicine, plants are also veritable sources of therapies as most of the currently available drugs are derived from plants ***(Nwibo et al., 2016).***

Guava leaf "*Psidium guajava L."* belonging to *Myrtacea* family has a long history of folk medicinal used in Egypt and worldwide as a cough sedative, in the management of hypertension, obesity and in the control of diabetes mellitus ***(Chia-Hung et al., 2010).***

The leaves of guava are rich in flavonoids, in particular, quercetin. Much of guava's therapeutic activity is attributed to these flavonoids. The flavonoids have demonstrated anti-bacterial activity. Quercetin is thought to contribute to the anti-diarrhea effect of guava, it is able to relax intestinal smooth muscle and inhibit bowel contractions. In addition, other flavonoids and triterpenes in guava leaves show anti-spasmodic activity. Guava also has antioxidant properties which are attributed to the polyphenols found in the leaves ***(Kumari et al., 2013).***

Psidium guajava L. leaves aqueous extract possesses hypolipidemic effect. Further studies on the activity guided isolation of the extract of this plant may yield valuable therapeutic compounds which may be useful for developing powerful hypolipidemic agent ***(Shinde et al., 2013).***

The crushed leaves are used as applications on wounds, ulcers and rheumatic spots, and the leaves can be chewed to relieve toothache. The leaf decoction is usually taken as a remedy for throat and chest ailments. Also it is gargled to relieve oral ulcers and gum inflammations. It is effective in stopping vomiting and diarrhea in cholera patients. A decoction of the new shoots can be taken as a febrifuge. The leaf infusion is currently prescribed in India for cerebral ailments, nephritis and cachexia. An extract can be given in epilepsy and chorea ***(Stalin, 2013).*** Guava leaves infusion not only reduced postprandial glycemia and improved hyperinsulinemia in animal models but also contributed to reduce hypercholesterolemia, hypertriglyceridemia ***(Deguchi and Miyazaki, 2010).***

Aim of the work

This work aimed to investigate the ameliorative effect of aqueous guava leaves extract with different doses on rats fed high fat high cholesterol diet and to deduce its protective effect against hyperlipidemia.

Review of literature

❖ Cholesterol synthesis, metabolism and importance.

Cholesterol is a 27-carbon sterol compound with amphipathic properties that exerts both structural and physiological functions in the human body. It is an essential component of the plasma membrane of all eukaryotic cells and also it serves as a precursor for the biosynthesis of bile acids, steroid hormones, and vitamin D ***(Segatto et al.,2014).*** Cholesterol is prevalently synthesized in the hepatic tissue, where the major part of its metabolism takes place. However other tissues, such as intestine, muscle and skin are able to produce significant amounts of this sterol ***(Dietschy, 1984).*** Cholesterol is a water-insoluble lipid, believed to be dissolved in normal bile by incorporation into molecular aggregates (micelles) of bile acids and lecithin ***(Ingelsinger, 1968).***

Cholesterol is required by all eukaryotic cells, which have specialized methods of recruiting and synthesizing the lipid only when it is needed. While effectively maintaining intracellular cholesterol homeostasis, but these processes leave excess circulating cholesterol through the body, leading to atherosclerotic plaque development and subsequent coronary artery disease. So, levels of cholesterol and related lipids circulating in plasma are important predictive tools utilized clinically to indicate the risk of a cardiac event ***(Stamler et al., 2000).***

In eukaryotic cells, most cholesterol is located in either the outer and inner leaflet of the plasma membrane, whereas a smaller amount of this sterol is found in the intracellular membranes of the endoplasmic reticulum, golgi apparatus and in the nucleus ***(Dietschy and Turley, 2004).***

In circulation, cholesterol, being a lipid, requires a transport vesicle to shield it from the aqueous nature of plasma. This vesicle