UNIVERSITI TEKNOLOGI MARA

EFFECT OF ANTIOXIDANTS ON CORONARY RISK MARKERS IN HYPERCHOLESTEROLAEMIA

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Thesis submitted in fulfillment of the requirements
for the degree of
Master of Sciences

Faculty of Medicine

December 2009

ABSTRACT

Introduction: Antioxidant vitamins have been suggested to play a role in preventing atherosclerosis. Several vitamins with anti-oxidant properties, such as vitamin E and C, are thought to act cooperatively and possibly synergistically *in vivo*. However, the efficacy of tocotrienol, a potent vitamin E molecule as compared to α-tocopherol, in reducing risk of heart disease has not been fully explored. The optimal dose of tocotrienol in atherogenesis and the synergism of tocotrienol with vitamin C remain unclear.

Objectives: (i) To study the effects of tocotrienol-rich fraction (TRF) supplement on fasting lipid profiles (FSL), oxidative stress, inflammation and atherosclerotic lesions in hypercholesterolaemic (HC) rabbits, (ii) To determine the dose response relationship of TRF treated HC rabbits, (iii) To examine the effects of antioxidants (TRF plus vitamin C) on the inflammatory markers and endothelial dysfunction (ED) in statin treated HC patients with high coronary risk.

Materials and Methods:

(i) Animal model experiment: Twenty-eight male New Zealand white rabbits were given 1% cholesterol diet for 5 months and randomised from the second month onwards into 5 groups: Placebo (n=7), TRF 15 mg/kg (n=5), TRF 30 mg/kg (n=6), TRF 60 mg/kg (n=5) and TRF 90 mg/kg (n=5) daily. Serum FSL, C-reactive protein (CRP), malondialdehyde (MDA) and 8-Isoprostane levels were measured at baseline (BL), 1 and 2 months post-HCD, 1, 2 and 3 months post-intervention. Aortic vessels were obtained to assess the atherosclerotic lesions and immunohistochemical studies for Intercellular Adhesion Molecule-1 (ICAM-1) and Nuclear Factor Kappa-B (NFκB) were performed.

(ii) Clinical trial: Twenty-nine HC patients were identified in high risk category according to the National Cholesterol Education Programme Adult Panel Treatment III and treated with atorvastatin to achieve low density lipoprotein (LDL-c) target (LDL-c < 2.6 mmol/L) before being randomised into a double-blinded placebo-control clinical trial with 2 groups: Placebo and combined tocotrienols-vitamin C supplement (TRF-160mg plus C-500mg daily) for 3 months. FSL, high sensitivity CRP (hsCRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) levels and ED by brachial artery flow mediated Dilatation (FMD) were measured at entry, BL, 2 weeks and 3 months post-intervention.

Results:

(i) Animal model experiment: There were no differences in percentage changes of FSL, MDA, 8-Isoprostane, CRP levels and extent of atherosclerosis between the placebo and TRF groups. Reduced tissue expressions of ICAM-1 (57% vs. 20%, 29%, 50%, 25%: placebo vs. TRF 15, 30, 60, 90 mg/kg) and NFκB (67% vs. 40%, 50%, 25%: placebo vs. TRF 15, 30, 90 mg/kg) were found with significant decrease in area of ICAM-1 expression (Mean ± SEM; 3.8 ± 2.0 % vs. 25.1 ± 19.5 %, $p<0.05$) between the placebo and TRF 15 mg/kg groups.

(ii) Clinical trial: There were no differences in percent changes of FSL, hsCRP, IL-6, sICAM-1, sVCAM-1, E-selectin levels and percentage of FMD between the placebo and combined supplement groups. Significantly higher endothelial-dependent FMD were found between the antioxidant and placebo group at 3 months (Mean ± SEM; 8.8 ± 1.6 % vs. 4.7 ± 1.0 %, $p<0.05$).

ACKNOWLEDGEMENT

With great thanks to God and His Blessings, I have been able to experience lots of difficulties and new things during this degree of Master programme.

After all the difficult time, tears and disappointments, finally, I have completed this study and come up with this thesis. None of the project can be completed without the help, cooperation and support of many individuals. I am deeply indebted to all who have directly or indirectly assisted me towards the completion of this study.

First and foremost, I would like to express my most sincere appreciation and deepest gratitude to my supervisor, Prof Dr Hapizah Mohd Nawawi, for her encouragement, guidance, advice, constructive criticisms and suggestions. Without her, I would not be able to present this work as it is today.

I wish to extent my heartiest thanks to my dear parents, Ir Dr A. Razak Yaacob and [redacted] and my entire siblings for their endless prayers, support, encouragement and sacrifice. I also wish to express my gratitude to my beloved auntie, Prof Dr Maimon Abdullah for making me appreciate my examiners on their precious comments and proof read my draft of the corrected thesis, even in the very nick of time.

Sincere thanks to all closed researchers, Prof Dato' Dr Khalid Yusoff, Dr Tengku Saifudin Tengku Ismail, Associate Prof Dr Zaiton Zakaria, Dr Effat Omar, Mrs Rafezah Razali and Mrs Suhaila Abd Muid, for your great dedication in the joint research collaboration, kindness in thoroughly scrutinized this write up and supportive efforts. To Prof Dr Nafeeza Mohd Ismail, Dr Muhammad Huzaimi Haron, Dr Sushil Kumar, Associate Prof Dr Normalina Mansor and Dr Anis Safura Ramli, special appreciation is extended for your committed cooperation in running the animal model experiment and clinical trial.

Beside that, I am really grateful for all the sweet and sour memories in conducting research with all the staff of the animal house, clinical trial centre and laboratories. I truly hope that this study will benefit greatly to the research community and enlighten the future direction in the related research area.

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CHAPTER 1

INTRODUCTION

1.1 General background

According to World Health Organization (WHO) estimation in 2003, almost 17 million people around the globe die of cardiovascular disease (CVD) each year. This is over 29 percents of all deaths globally. CVD has become the leading cause of mortality in developing countries (Yach *et al.*, 2004), where countries like Malaysia and China experience an upward trend for CVD mortality (Khor, 1997). In Malaysia, CVD accounted for 30% of all deaths in 2002 (WHO, 2002). The importance to understand CVD to the health of the world and our country, Malaysia, can be easily seen in Figure 1.1 and 1.2.

The current high burdens of CVD is highlighted by the global burden of disease (GDB) study which projected that ischaemic heart disease (IHD) and cerebrovascular disease (CVAD) would be the first and second leading causes of death globally by 2020 (Murray & Lopez, 1997). Updated projections of mortality and burden of disease from 2002 to 2030, which were made by Mathers and Loncar (2006) using a similar method of original GDB study have also shown that both IHD and CVAD will continue to lead the percentage of total deaths in 2030 (Table 1.1).