

UNIVERSITI TEKNOLOGI MARA

**EFFECTS OF TOCOTRIENOL
ENRICHED MIXED FRACTION ON
PREVENTION AND TREATMENT
OF EARLY AND ESTABLISHED
ATHEROSCLEROSIS**

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of the requirements for the degree of
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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own, unless otherwise indicated or acknowledge as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any other degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulation for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Effects of palm tocotrienol-enriched mixed fraction (TEMF) supplementation in the prevention and treatment of early and established atherosclerotic lesion remain unclear. The objectives of this study is to determine the prevention and treatment effect of TEMF towards (i) atherosclerotic lesion (ii) lipids profile (iii) inflammation (iv) endothelial activation and (v) vascular proliferation and plaque stability in early and established experimentally-induced atherosclerosis. Forty New Zealand white rabbits were randomized into two major groups of prevention and treatment groups, which were further divided into two subgroups of early and established atherosclerosis. In the prevention group, rabbits were given normal diet (ND) for 8 weeks (8W) followed by high cholesterol diet (HCD) for either 2 weeks (2W) or 8W to induce early and established atherosclerosis respectively while in the treatment groups, rabbits were fed with HCD for either 2W or 8W followed by ND for another 8W. Supplementation of either (i) TEMF (15mg/kg) or (ii) placebo was given continuously in the prevention groups, while in the treatment groups, TEMF supplementation was given following HCD for 2W and 8W for early and established atherosclerosis respectively. Blood samples at various intervals were analyzed for fasting serum lipids (FSL) and soluble C-reactive protein (sCRP). At the end of the study, the aortas were evaluated for atherosclerotic lesions using Sudan IV and immunohistochemistry staining for the biomarkers of atherosclerosis. In the prevention of established atherosclerosis, TEMF significantly reduced both total cholesterol, TC (227%) and low density lipoprotein, LDL-c (89.6%) levels at 8W compared to placebo. At 16W, triglycerides, TG levels were increased and high density lipoprotein, HDL-c levels were reduced but TC and LDL-c levels remain unchanged in TEMF groups compared to placebo. TEMF reduced LDL-c levels in the treatment of early atherosclerosis by 55.3%, but TC, TG and HDL-c levels remain unchanged. In the prevention of early atherosclerosis groups, there were reduced atherosclerotic lesions (68.6%) and trend of reduction in tissue biomarkers. In the prevention of established atherosclerosis, TEMF reduced atherosclerotic lesions (71.2%), aortic tissue expression of interleukin-6, IL-6 (71.6%), CRP (88.7%), E-selectin (68.4%), smooth muscle actin, SMA (55.9%) and matrix metalloproteinase-12, MMP-12 (85.1%) compared to placebo. In the treatment groups, TEMF showed no reduction in atherosclerotic lesions in both early and established groups but significant reduction in aortic tissue expression of CRP (88.2%), SMA (75.9%) and MMP-12 (82%) in the early atherosclerosis group. In conclusion, TEMF is beneficial in reducing atherosclerotic lesion despite neutral effects on lipids and tissue biomarkers in prevention of early atherosclerosis. In the prevention of established atherosclerosis, TEMF is beneficial as an anti-atherosclerotic agent in terms of reducing atherosclerotic lesions, inflammation, endothelial activation, smooth muscle proliferation and migration as well as plaque stability despite non-beneficial effects on lipids. TEMF leads to LDL-lowering effects and high therapeutic potential as an anti-inflammatory and anti-smooth muscle proliferative and migration agent in the treatment of early atherosclerosis. Treatment of TEMF in established atherosclerosis is not beneficial in terms of lipids, atherosclerotic lesion and tissue biomarkers. Thus, TEMF is effective in the prevention of both early and established atherosclerosis and has therapeutic potential in the treatment of early atherosclerosis.

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