# EFFECT OF SOME ORGANIC COMPOUNDS IN MONITORING THE LIPID METABOLISM IN RATS

## THESIS

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BY

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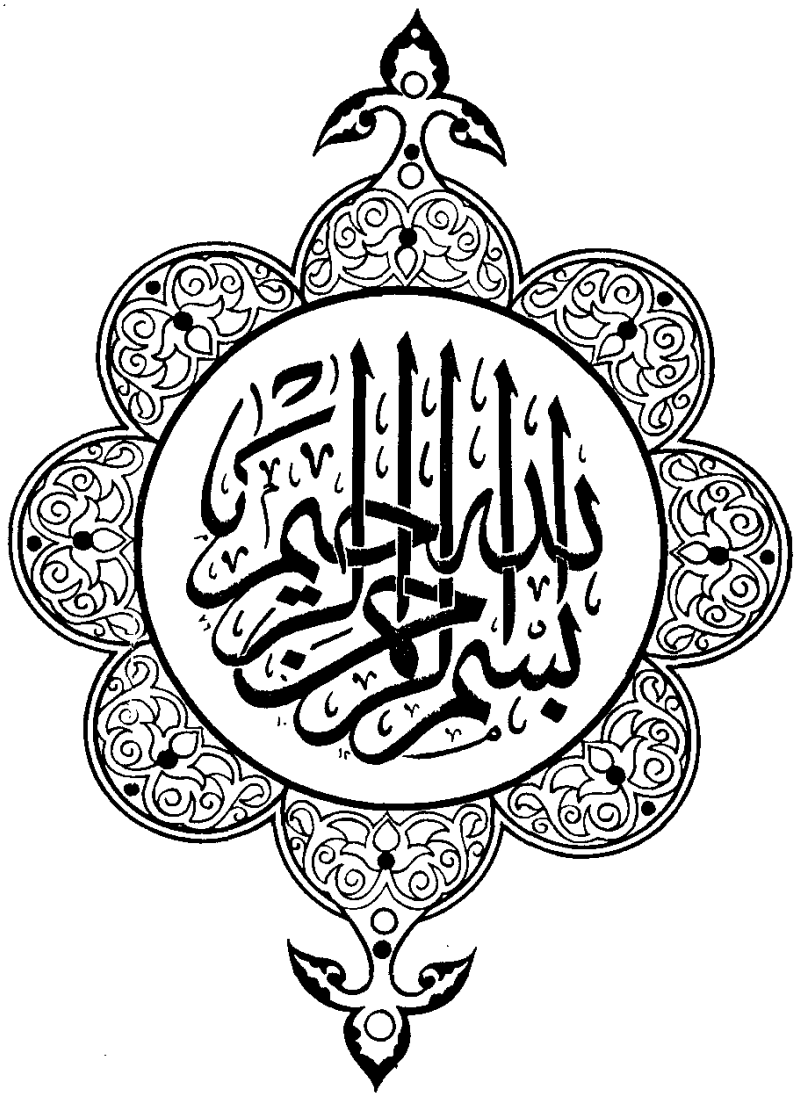

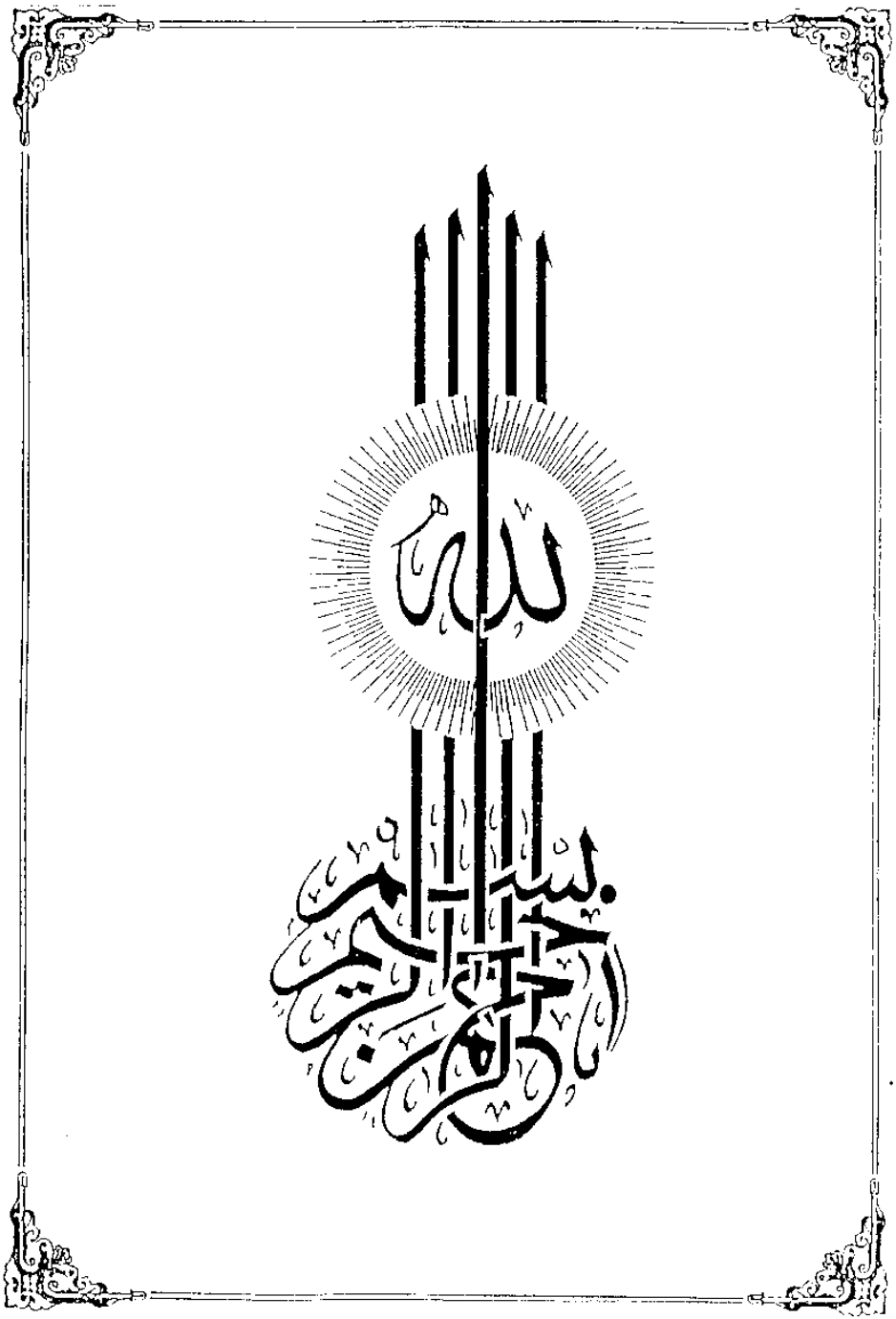

This thesis has not been submitted for a degree at this or any other University.

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## ABBREVIATIONS USED

| | |
|---|---|
| A | atherogenic |
| AR | analytical grade |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| B.p. | boiling point |
| C | concentration |
| C | degree centigrade |
| ch | cholesterol |
| CHD | chronic heart disease |
| CPIB | x-chlorophenoxy isobutyrate |
| DDC | diethyldithiocarbamate |
| FFA | free fatty acid |
| FAS | fatty acid synthetase |
| GABA | x-aminobutyric acid |
| g. | gram. |
| HDL | high density lipoprotein |
| hr. | hour |
| HMG-CoA | 3-hydroxy-3-methylglutryl CoA reduction |
| IHD | inherited heart disease |
| i.m. | intramuscular |
| LDL | low density lipoprotein |
| M | molar |
| m. | micro- |
| mol. | mole |
| N | normal |
| PL | phospholipid |
| PLP | pyridoxal-5-phosphate |
| PM | pyridoxamine |
| PN | pyridoxine |
| s.c. | subcutaneous |
| TG | triglyceride |
| TL | total lipid |
| TP | total protein |
| vol. | volume |
| VLDL | very low density lipoprotein |
| wt. | weight |

CONTENTS

# AIM OF THE WORK

There is a great evidence that atherosclerosis is related to the level of saturated fatty acids in blood . Moreover , it has been found that in pyridoxine deficiency there were significant decrease of serum tetraenoic acids , and cholesterol deposition in aorta was also significant , and hence pyridoxine deficiency may acount for hyperlipidemia and atherosclerosis .

On the other hand , it has been reported by several investigators that pyridoxal-5-phosphate (PLP) inhibit in vitro the activity of both yeast and fatty acid synthetase .

Since vitamin $B_6$ deficiency was found to increase the cholesterol deposition in veins , this coupled with the fact that PLP would inhibit the fatty acids synthetase , therefore, it is conceivable that high doses of PLP alone or in combination with other chemical compounds could lower the total lipid concentration in blood . This study has not been investigated yet .

# PART I

# INTRODUCTION

# INTRODUCTION

Cardiovascular diseases remain the major cause of death and disability in many countries all over the world, especially western society. As the principal disease underlying most cardiovascular deaths, atherosclerosis deserves the central focus of attention, since atherosclerosis and thrombosis are the two etiological causes of coronary heart disease (World Health Organization, 1982). Atherosclerosis is manifested by occulsion effects of different parts of circulation giving rise to occulsive vascular disease. Atherosclerosis is a multifactorial disease since at least three major and other secondary risk factors have been assumed to be etiological. The best established of these risk factors are hypercholesterolemia, hypertension and cigarette smoking. In addition to these, diabetes mellitus, stress, lack of exercise and obesity may contribute also to the disease. So, hyperlipidemia represents a single causal factor of the atherogenic process (World Health Organization, 1982).

In humans, there is a close relationship between plasma cholesterol and arterial lipoprotein cholesterol concentration (Smith and Slatter, 1972). Possibly the

accumulated lipid in arterial wall with increasing age results from infiltration of plasma lipoproteins. Many evidences demonstrated that cholesterol is a major component of atherosclerotic plaque (Kannel et al., 1979; Castelli et al., 1979).

Clinical studies in humans revealed that hyperlipidemia may be suspected in people with contineous manifestations of hyperlipidaemia, premature atherosclerosis or a strong family history of premature heart disease (Jim and Madeleine, 1985).

Ross and Glomset (1973), indicated that accelerated atherogenesis in hyperlipidemia is related to low density lipoprotein (LDL) ability to stimulate proliferation of arterial smooth muscle cells. In ischemic heart disease, hypercholesterolemia (over 230mg%) has been observed in a significant number of patients who later developed myocardial infarction (Neill, 1964; Hashimoto & Kato ; 1976). The serum cholesterol level was found to be high in cerebrovascular diseased patients in comparison with normal individuals (Feldman and Albrink, 1964; Randrup and Pakenberg, 1967). Therefore, it appears that there is a statistically significant correlation between the incidence of chronic heart disease (CHD) and the high serum cholesterol level.

Cross sectional studies, however, have reported high triglycerides level in chronic heart disease (CHD) patients when compared with controls (Carlson, 1960; Albrink et al., 1961). Rifkind et al. (1968) studies, suggested that triglyceride levels provide better discrimination of CHD patients from control subjects than do cholesterol levels.

Etiology of Atherosclerosis:

The etiology of atherosclerosis has been known to be a subject of controversy. Many factors are involved and reported to be related to atherogenesis.

(1) Hypertension:

Recorded level of blood pressure is only one factor which operates in the pathogenesis of arterial disease. the evidence that supported this fact was derived from observation in animals with experimental hypertension. Hollander and Madoff (1975) demonstrated that hypertension induced by coarctation in combination with atherogenic diet raised lesions in rats. It is abundantly clear that hypertension accelerates atherosclerosis, several possibilities have been suggested:

1. High intraarterial pressure, the possibility that pressure may have an effect on the metabolism of arterial wall (Strong and Eggen, 1972).

2. Increased endothelial permeability (increased filtration pressure) caused by high levels of circulating vasoactive substances.

3. Endothelial injury resulting from abnormalities that accompany hypertension.

The effect of hypertension is the greatest in the cerebral arteries less in the coronaries and still less in the aorta (Solberg and McGany, 1972). Some of the antihypertensive drugs which affect the mediators of hypertension in various way may augment coronary atherosclerosis instead of preventing it (Hollander, 1973).

On the other hand, hypertension markedly increases lysosomal enzyme activity, persumably owing to stimulation of the cellular disposal by the internal utilization of increased amounts of plasma substances, this might lead to increased cell degeneration and release of the highly destructive enzymes (within the lysosomes) into the arterial wall (Wolinsky, 1977).

(2) Diabetes Mellitus:

According to statistical data performed by Schettler and Wall (1969), diabetes mellitus is the most frequent precursor to severe type of coronary sclerosis followed by hypertension and gallstones.

Hyperglycemia is known to affect aortic wall metabolism. Sorbitol a product of the insulin independent aldose reductase pathway of glucose metabolism, accumulates in the arterial wall in the presence of high glucose concentration resulting in osmotic effects including increased cell water content and decreased oxygenation (Morrison et al., 1972). Preliminary in vitro results suggest that increased glucose also stimulates proliferation of cultured arterial smooth muscle cells (Turner and Bierman, 1976).

(3) Emotional Stress:

On the other hand emotional stress appears to play a role in atherogenic process. Lang (1967) reported that animals subjected to abnormal stressful conditions developed higher serum cholesterol level followed by incidence of coronary atherosclerosis.

(4) Age:

Kannel (1971) reported that the correlation between the total cholesterol level and the risk of developing chronic heart disease (CHD) is relatively low and that a closer correlation can be obtained with the low density lipoprotein (LDL)-cholesterol level.

The level of high density lipoprotein (HDL)-cholesterol which rises with age is in itself a good indicator of CHD risk, being negatively related to the onset of the disease.

The amount of cholesterol ester in the vascular tissue increases progressively with increasing age (Boberg et al., 1972) but this is not the only form of lipid to increase. The phospholipid content of the vascular wall also increases, but whereas between 10 and 90 years the cholesterol ester content increases 2-5 fold, the phospholipid level only increases by 60%. Hence the ratio of cholesterol ester to phospholipid increases four-fold over this period.

(5) Smoking:

Cigarette smoke is a major source of cadmium in the human body (Lewis et al., 1972). There is a correlation between Cd/Zn ratio in the kidney and the extent of atherosclerosis (Voors et al., 1974). One or more of the many chemicals in cigarette smoke may alter endothelial permeability, stimulate smooth muscle cell proliferation or increase the rate of mutation.

(6) Diet:

Mahley and his coworkers (1981) studied intensively the effect of feeding a diet high in saturated fat to the postprandial accumulation of light and an apolipoprotein E-