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HYPERLIPIDEMIA: INFLAMMATORY PATHWAY AND PHYTOCHEMICAL APPROACH

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Abstract:

Hyperlipidemic condition serve as a major risk factor for cardiovascular events as they contribute to free fatty acid circulation. Co-occurrence of obesity, hyperglycemia and cardiovascular disease is the major health concern resulting in increased mortality. It activates JNK pathway interfere with RAAS pathway contributing to cardiovascular complications. Tumor necrosis factor α (TNF α), interleukins (IL-1, IL-6, IL-18) and C-Reactive Protein (CRP) are the most important inflammatory cytokines implicated in hyperlipidemic condition which accelerates systemic inflammation. Elevated level of TNF α remains the independent factor for cardiovascular mortality. Chronic inflammation is the hall mark of cardiovascular progress which results from elevated concentration of CRP. CRP promotes endothelial dysfunction and has been recognized as key factor for cardiovascular. Further it enhances the production of IL-6 which worsens the condition by increasing triglyceride concentration. Oxidative stress in hyperlipidemia induces IL-18 concentration which results in atherosclerotic plaque and arterial stiffness.

Medicinal plants are rich in antioxidants and metabolites act as source to inhibit the cholesterol synthesis and reduced inflammation with their antioxidant properties. This paper discuss the antihyperlipidemic properties of fenugreek, cumin and fennel based on previous research studies.

Keywords: *Antioxidants, Antihyperlipidemic Cardiovascular events, Inflammation, Obesity.*

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INTRODUCTION:

Hyperlipidemia and obesity are the most common hypothesis in describing the pathophysiology of cardiovascular events. Obese condition contributes to hyperinsulinemia by elevating insulin secretion as a result of excess free fatty acid circulation. Likewise abundance of free fatty acid enhance production of triglycerides, very low density lipoproteins and leptin thus contributing to cardiovascular events.[1] Insulin resistance accompanying obesity elevates circulating angiotensinogen II by striking renin angiotensin system which in turn generates reactive oxygen species(ROS).[2] Surplus ROS is the key factor for oxidization of poly unsaturated lipids that induce atherosclerosis.[3] Inflammation of the vessel is recognized to play the vital role in rupture of plaques in addition to that of initiation and progression of cardiovascular disease. Insulin resistance enhance release of pro coagulant factors by their mechanism of endothelial dysfunction that result in platelet aggregation.[4] Insulin resistance accompanying obesity alters renin-angiotensin-aldosterone system and elevates angiotensinogen II concentration. This eventually ends in myocardial fibrosis.[5]

Life style changes to reduce body weight, pharmacological therapy focusing on inflammatory pathway in addition to regulation of hyperlipidiemic condition prevent progress of cardiovascular events and mortality.

PATHOGENESIS

C-Reactive Protein being accelerated in hyperlipidemia contribute to platelet aggregation by inhibiting nitric oxide synthesis whereby initiating the Insulin resistance syndrome. C-Reactive Protein alters insulin receptor substrate and spleen tyrosine kinase which eventually impair insulin signaling and resulting in type 2 diabetes mellitus.[6] IL-6 that in due course results in reduced level high density lipoprotein and raised triglyceride level whereby exerting its contribution to cardiovascular diseases.[7] Interleukin 18 level elevates with acute hyperglycemic condition through oxidative stress mechanism play a key role in immune responses.[8] Over time this results in insulin resistance and induces atherosclerotic plaque.[9] Higher concentration of IL 18 is observed to cause arterial stiffness which emerge as future risk of cardiovascular mortality. IL-18 is a pro inflammatory cytokine activate Nuclear Factor – kappa B cell pathway which control genes involved in pathology of arthrosclerosis. [10]

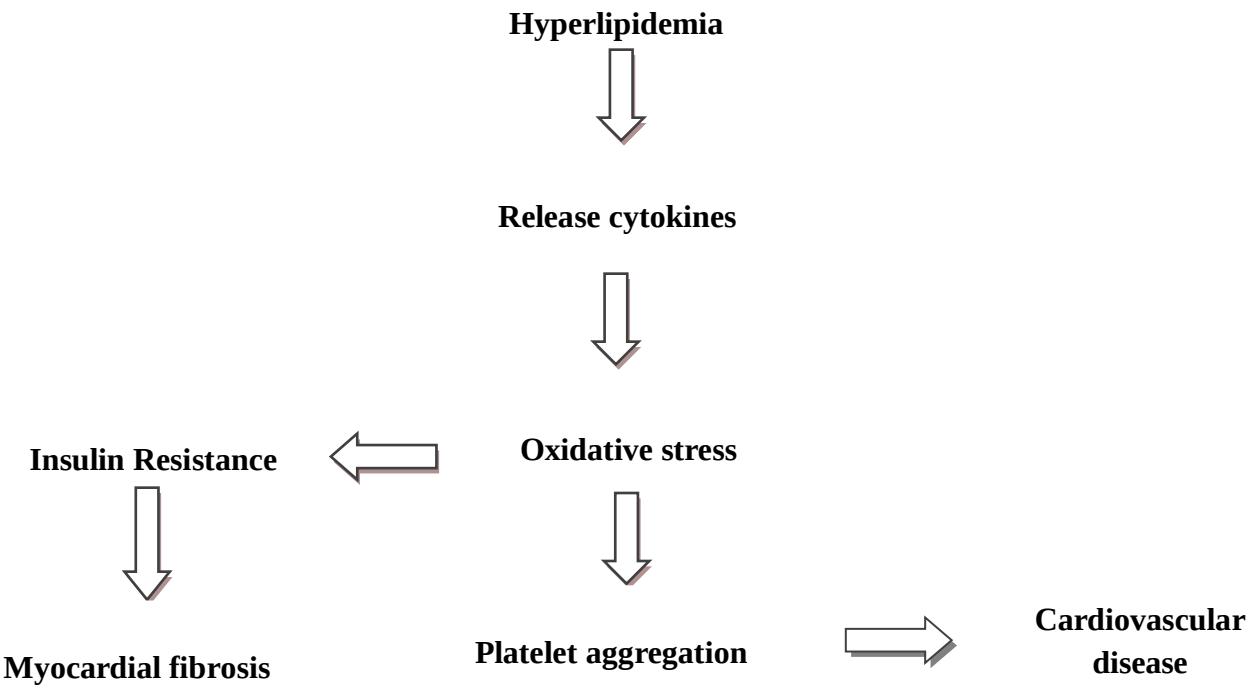

Fig 1: A brief pathway of co-morbid conditions of hyperlipidemia

PHYTOCOMPOUNDS WTH ANTIHYPERLIPIDEMIC PROPERTIES FENUGREEK

Fenugreek contains helpful flavanoids and polyphenol including quercetin, luteolin, vitexin, and 7, 4′dimethoxy flavan ones in the alcoholic extracts.[11] On focusing antioxidant properties, about 32 to 73% was identified thus aiding in prevention of hyperlipidemic complications.[12]

Fenugreek belongs to the *Fabaceae* family and has been used as an important spice since ancient times.[13] The fenugreek seeds have 58% carbohydrates, 23-26% proteins, 0.9% fats and 25% fibre. Fenugreek also contains potassium (603 mg/100 g), magnesium (42 mg/100 g), calcium (75 mg/100 g), zinc (2.4 mg/100 g), manganese and copper (0.9 mg/100 g) and iron (25.8 mg/100 g). Vitamin C (220 mg/100 g) and β carotene (19 mg/100 g) are also considered as the important components of fenugreek.[14, 15]

Even though fenugreek is considered harmless, certain side effects are linked to individuals who are allergic to fenugreek cross-reactivity can occur. The reaction may result in severe bronchospasm, wheezing diarrhea, dizziness and flatulence.[16]

ANTIHYPERLIPIDEMIC STUDIES WITH FENUGREEK

A study conducted with three-week-old male, Sprague-Dawley rats which are fed with high fact high sucrose diet was conducted to determine the antihyperlipidemic activity of fenugreek. Fenugreek dose-dependently reduced the hepatic triglyceride and total cholesterol levels by inhibiting lipid accumulation in the liver. This occurs as a result of increasing the lipid and bile acids excretion in the feces. The study concluded that the mechanism underlying the inhibition of lipid accumulation in the liver and the adipose tissue would have enhanced the total cholesterol and the bile acid excretion in feces.[17] There exist reference that daily administration of fenugreek seed powder at 2 and 8g per Kg body weight for 4 weeks resulted in significant drop in serum total cholesterol and triglyceride levels in alloxan induced diabetic rats. The study conducted with thirty two male golden hamsters, eight weeks old weighing about 120g fed with high fat diet results that fenugreek prevents hyperlipidemia and hepatic damage following high cholesterol diet. The mechanism behind hypocholesterolemic action was increasing LDLR gene expression.[18]

CUMIN

On focusing cumin seeds, the major volatile substances found are terpenoids, cymene and cumin aldehyde, myrcene, 1-8-cineole, α-pinene, ρ-mentha-1, 3-dien7-ol, β-bisabolene, β-farnesene, limonene, caryophyllene, β-phellandrene, cuminyl alcohol and some oleoresin, gum, protein compounds, mucilage, and malates.[19]

Cumin (Cuminum cyminum L.) belonging to the Apiaceae family is a multipurpose plant species cultivated in the Middle East, India, China, and several Mediterranean countries. Cumin has used in traditional medicine to hypolipidemia, cancer, and diabetes. [20] Phytochemical analysis of Cuminum cyminum includes alkaloid, anthraquinone, coumarin, flavonoid, glycoside, protein, resin, saponin, tannin and steroid.[21] Cumin powder tends to reduce cholesterol, triglyceride, and LDL levels in plasma and increased HDL. [22]

EXPERIMENTS TO REVEAL ANTIHYPERLIPIDEMIC PROPERTIES

Based on the study conducted with ten to twelve weeks old twenty-four male Wistar rats of 185–200 g weight which were fed with high fat diet to determine the antihyperlipidemic activity, the ethonolic extracts of cumin seed powder had shown significant reduction or neutralization of oxidative stress induced ROS indicators. This result documented the antioxidant property of cumin seeds in alleviating the progress of hyperlipidemia and restoration of tissue antioxidants.[23, 24]

The crude powder of cumin was extracted with 95% ethanol. 8 to 10 weeks old male Sprague-Dawley strain rats weighing 160 ± 20 g were ncluded in the study. High fructose and high fat diet animals were treated with extract at the dose of 100 mg/kg body weight. The result showed decline in their serum total cholesterol (22.7%), serum triglycerides (21.0%) and LDL levels (16.9%) level. HDL level was elevated (12.2%) when treated with cumin extract. This experiment serves as another example for hypolipidemic effect ethanolic extract of cumin seeds.[25]

FENNEL

Foeniculum vulgare commonly called fennel is a medicinal plant belonging to the Umbelliferae (Apiaceae) family. It is known to be effective for treatment of ailments related to digestive, endocrine, reproductive, and respiratory systems. It has antioxidant, antitumor, chemopreventive, cytoprotective, hepatoprotective, hypoglycemic, and oestrogenic activities.[26] Some of the publications stated that *F. vulgare* has memory-enhancing effect

and can reduce stress.[27] *F. vulgare* seeds showed a potent hepatoprotective effect against acute hepatotoxicity in rats. The aqueous extract of *F. vulgare* revealed notable hypolipidemic and antiatherogenic activity against Triton WR-1339 induced hyperlipidemia in mice. Extracts of fennel seeds revealed significant reduction in, cholesterol, triglycerides, LDL and apolipoprotein-B while increasing the serum level of HDL. [28]

ANTIHYPERLIPIDEMIC PROPERTIES OF FENNEL

A study conducted with six groups of female albino rats with induced hyperlipidemia. The biochemical parameters showed significant increase in the body weight, serum glucose, ASAT, ALAT, GGT, LDH, total protein, albumin and total lipids in liver. The fennel seed powder of weight 10mg/100g body weight were fed orally to these rats. This resulted in ameliorated parameters and reduced lipid levels proving the antioxidant and antihyperlipidemic activity of fennel seeds.[29]

Experiment to determine antihyperlipidemic effect of fennel seed contributed to the alcoholic extraction of fennel with 70% ethanol. This extract upon inductin to streptozotocin induced diabetic rats with high lipid profile showed significant alleviation in the lipid level and blood glucose level on experimental animals.[30]

A study with 28 male Wistar rats of weight 190-220 g were performed. 80% ethanolic extract of Fennel seeds were used to observe the antihyperlipidemic property. The study concluded that Fennel extract has a favourable effect on hyperlipidemia. It was also suggested that antioxidant property of fennel prevents cardiovascular disorders, protects the liver against hypercholesterolemia.[31]

CONCLUSION:

Hyperlipidemia is a metabolic modification characterized by elevated blood levels of total cholesterol, low-density lipoprotein, triglycerides, and reduced levels of high-density lipoprotein. Hyperlipidemia is a major risk factor for development insulin resistance, endothelial dysfunction, hypertension, cardiovascular disease. Hypercholesterolemia is a significant risk factor for atherosclerosis Antioxidant activity is also a function of the individual and synergistic effects of numerous bioactive compounds, and its interaction with endogenous enzymatic antioxidants. An outcome of interest in the antioxidant effect and its potential impact on the management of hyperlipidemia has emerged as a better alternate to alleviate the morbidity with no or very less side effects. This manifest positive outcome on public health and in turn on healthcare sectors.

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