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Lycopene stabilizes lipoprotein levels during D-galactosamine/lipopolysaccharide induced hepatitis in experimental rats

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PEER REVIEW

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Comments

This important study evaluates the ability of lycopene to maintain liver health particularly, lipid metabolism during experimentally induced hepatitis by measuring the lipid metabolizing enzymes and lipoprotein levels. The clear findings of results suggest that lycopene is a potential candidate to restore the derangement of lipid metabolism during hepatitis.
(Details on Page 978)

ABSTRACT

Objective: To investigate the effect of lycopene on lipoprotein metabolism during D-galactosamine/lipopolysaccharide (D-Gal/LPS) induced hepatitis in experimental rats. **Methods:** The efficacy of lycopene was validated during D-Gal/LPS induced hepatitis by analyzing the activity of lipid metabolizing enzymes such as lipoprotein lipase (LPL), lecithin-cholesterol acyl transferase (LCAT) and hepatic triglyceride lipase (HTGL). Lipo protein analyses were done by the estimation of very low density lipoprotein cholesterol (VLDL), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL). **Results:** The toxic insult of D-galactosamine/lipopolysaccharide (D-Gal/LPS) in experimental group of animals reduces the normal values of lipid metabolizing enzymes due to liver injury. The significant drop in the levels of HDL and concomitant increase in the values of VLDL and LDL were observed. The pretreatment of lycopene restore these altered values to near normal level in experimental group of animals. **Conclusions:** In the light of results, it can be concluded that administration lycopene stabilizes the lipoprotein levels by regulating the lipid metabolizing enzymes through its antioxidant defense and helps to maintain the normal lipid metabolism during toxic injury in liver.

KEYWORDS

Lycopene, Dyslipidemia, Galactosamine, Antioxidants, Lipoproteins

1. Introduction

The liver is the major site of biochemical modifications for both endogenous and exogenous substances including drugs. The functional integrity of liver is essential to maintain a normal metabolism and homeostasis of carbohydrates, lipids, and amino acids[1]. The insoluble lipid molecules are transported through the blood stream along the plasma with proteins and are termed as lipoproteins. Since the liver plays a crucial role in lipid and lipoprotein metabolism, the significant impairment of the hepatic function occur during liver diseases, including hepatitis[2]. The viral hepatitis particularly, Hepatitis B is the most common form of acute hepatitis. Hepatitis B virus (HBV) is a major cause of acute hepatitis, cirrhosis and hepatocellular carcinoma worldwide[3]. HBV continues to be the single most important cause of viral hepatitis in the developing and underdeveloped world[4]. To date there are nearly 360 million HBV carriers in the world with highest incidence of 10%-20% in the tropical countries. Liver diseases due to HBV infection is considered to be the fourth or fifth important cause of mortality in the most productive period of life (15 to 45 years). Hepatitis remains as a clinical challenge and a problem of great importance. Acute hepatitis

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can have serious health effects[5] including disturbance in lipid metabolism. Despite considerable progress in the treatment of liver diseases by oral hepatoprotective agents, search for newer drugs continues because the existing synthetic drugs have several limitations[6]. Hence, crude drugs or natural food diet which possesses antioxidant or free radical scavenging activity has become a central focus for research designed to prevent or ameliorate tissue injury and may have a significant role in maintaining health.

Carotenoids are a class of more than 600 natural pigments that are present in fruits and vegetables[7]. These carotenoids are ubiquitous in the plant kingdom, fruits and vegetables that are a rich source of carotenoids are thought to provide health benefits by decreasing the risk of various diseases. Lycopene is a potent antioxidant and member of the carotenoid family[8]. It is a naturally occurring compound that gives the characteristic red color to the tomato, watermelon, pink grapefruit, orange, and apricot. A number of studies have indicated the health benefits of consuming lycopene[9-14]. As a major carotenoid in human blood, lycopene protects against oxidative damage to lipids, proteins and DNA[15,16]. Lycopene is a potent quencher of singlet oxygen which suggests that it may have comparatively stronger antioxidant properties, than other major plasma carotenoids[17].

Among the numerous models of experimental hepatitis, D-GalN induced liver damage is very similar to human viral hepatitis in its morphological and functional features and widely used for pharmacokinetic investigations and inflammatory processes of the liver[18-19]. Furthermore, D-GalN-induced liver injury served as a model for testing and elucidating the protective and even therapeutic value of flavones, quinines and carotenoids that are known as antioxidants and of other plant products[20-22]. Altered lipid metabolism and dyslipidemia is the characteristic feature of D-Gal/LPS induced liver injury in experimental animals[2-23]. The scientific research to date has demonstrated an array of health benefits clearly associated with lycopene. It offers important health benefits particularly in regard to prostate, lung, heart and skin health. We have earlier reported that the antioxidant potential of lycopene proves to be valid reason for its hepatoprotective and hypolipidimic role in experimental animals[24].

The present investigation further explores the antidyslipidimic effect of lycopene during D-galactosamine/lipopolysaccharide induced hepatitis in rats.

2. Materials and methods

2.1. Chemicals

D-GalN and LPS (Sero type 011. B4 extracted by phenol water method from *Escherichia coli*) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals (acids, bases, solvents and salts) used were of analytical grade obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai, India and Glaxo Laboratoreis, CDH division, Mumbai, India. Lycopene was kindly provided as a gift by Jagsonpal Pharmaceuticals, New Delhi, India.

Lycopene (100 mg) was mixed in 2 mL Tween-80 at room temperature until a homogeneous paste was obtained. Physiologic saline at room temperature was added, drop wise and with vigorous stirring, to a final concentration of 10 mg/mL lycopene of suspension[25].

2.2. Animals

Adult male albino rats of Wistar strain weighing around 120 g to 150 g obtained from Tamil Nadu Veterinary and Animal Sciences University (TANUVAS), Madhavaram, Chennai, India were used in this study. They were housed in polypropylene cages over husk bedding and a 12-hour light and dark cycle was maintained throughout the experimental period. Rats were fed a commercial pelleted diet (Hindustan Lever Limited, Bangalore, India) and water *ad libitum*. The experiments were conducted according to the ethical norms approved by Ministry of Social Justices and Empowerment, Government of India and Institutional Animal Ethics Committee guidelines (IAEC No. 01/026/08).

2.3. Experimental design

The animals were divided into four groups of six animals each.

Group 1 was served as vehicle control and administered with Tween-80 in saline. Rats in Group 2 were given lycopene alone (10 mg/kg body weight for 6 d, *i.p.*). Rats in Group 3 were induced with D-GalN and LPS (300 mg/kg body weight and 30 μg/kg body weight, *i.p.*, 18 h before the experiment)[26]. Rats in Group 4 were pretreated with lycopene for 6 d prior to the induction of D-GalN/LPS.

2.4. Collection of samples for analysis

After the experimental period, the animals were anaesthetized by intraperitoneal injection of pentobarbital sodium (30 mg/kg body weight) and sacrificed. Blood was collected and the liver tissue was excised quickly. The tissues were washed in physiological saline to remove blood clot and other tissue materials.

2.5. Separation of serum

The blood samples collected in plain centrifuge tubes were kept in inclined position to allow complete clotting of blood and then centrifuged at 2500 r/min for 30 min. The resultant clear supernatant was pipetted out and preserved in small vials in the freezer for the purpose of biochemical investigations.

2.6. Preparation of liver homogenate

Within 3 h after sacrifice, liver samples were blotted to dryness. From this, a piece weighing about 100 mg was taken and homogenized at 4 °C in Tris-HCl buffer (0.1 mol/L, pH 7.4). The tissue homogenates were centrifuged at 2 500 r/min for 30 min. The resultant supernatant was kept under refrigeration until further biochemical analysis. All the assay procedures were carried out within 48 h after sample collection.

2.7. Lipid metabolising enzymes

Activity of lipoprotein lipase was determined by the method described by Korn[27]. The activity was expressed as mmol of glycerol liberated/h/min/mL plasma. The activity of lecithin-cholesterol acyl transferase was assayed by the method of Hitz *et al*[28]. LCAT activity in serum was expressed as μg of cholesterol esterified/min/L. Assay of the activity of the