Summary

Liver is the most important organ in body due to its unique functions. In briefly, Liver functions are secretion of bile, storage of vitamins and detoxification of foreign materials beside its role in protein, carbohydrate and lipid metabolism. Thus, maintenance of liver in a healthy state is an important factor for normal human life. Exposure to environmental toxins, alcohol drinking and some prescribed drugs eventually lead to liver diseases like hepatitis, cirrhosis and finally may lead to HCC. Chemicals as TAA release free radicals by inducing lipid peroxidation and damage to liver cell membrane cause necrosis of these cells and release of liver enzymes such as ALT and AST to the circulating blood. In the present study, TAA was used as a selective hepatotoxin to induce liver cirrhosis in a short time and its harmful effect through its very reactive compound TAA-S-dioxide.

Propolis is a natural resinous substance that collected from trees by *Apis mellifera* bees which use it as a building material in the beehive and to keep it in a healthy state. Propolis has many properties and used for many purposes as anti-inflammatory, antiviral, antifungal, anti-tumor and bactericidal agent. Its main components are flavonoids, phenols, terpenes, aldehydes, aromatic acids, esters and polysaccharides. The most important ingredient of propolis is CAPE.

The efficiency of different propolis extracts (AEP and OEP) on blood analyses and immunological markers were tested to investigate anti-inflammatory and immunomodulatory properties of propolis in TAA-induced hepatotoxicity in albino rats. Liver sections were examined microscopically to support biochemical parameters and cytokines levels.

To achieve this study, 70 albino rats were divided into 7 groups 10 rat each: **1st group** is control one, **2nd group** in which rats fed on the standard diet with daily oral administration of Sunflower oil 100 mg/kg b.wt., **3rd group** in which rats administered *i.p.* with TAA twice a week 200 mg/ kg b.wt., **4th group** in which animals with daily oral administration of AEP 100 mg/kg b.wt., **5th group** in which animals with daily oral administration of OEP 100 mg/kg b.wt., **6th group** in which animals with oral administration of AEP 100 mg/kg b.wt./day and *i.p.* administrated of TAA 200 mg/kg b.wt. twice a week and **7th group** in which animals with administered *i.p.* with TAA at a dose of 200 mg/kg b.wt. twice a week plus AEP at a dose of 100 mg/kg b.wt./day.

This protocol of work continued for 8 successive weeks. At the end, animals were sacrificed and blood collected for immunological and biochemical studies. Also, liver was excised to be examined microscopically.

Administration of TAA with dose 200 mg/kg b.wt. caused liver toxicity that clearly reflected in increasing serum levels of ALT, AST, ALP, GGT, total and direct bilirubin. Also, TAA caused disturbance in protein and lipid metabolism

showed in increasing in serum total cholesterol, triglyceride, LDL and decreasing in serum HDL, total proteins content and albumin. Administration of different propolis extracts (AEP or OEP) caused recovery to a great extent from TAA effects as a hepatoprotective agent investigated by modulation of the level of liver enzymes ALT, AST, GGT and ALP beside total and direct bilirubin. Also, both extracts normalized lipid profile, serum total proteins content and albumin.

On the other hand, in regard to effect of TAA on immune system, TAA increased CRP level in serum as an indication of inflammation and liver injury, whereas it reduced IL-6 and TNF-α levels compared with control rats. Anti-inflammatory properties of AEP and OEP caused reducing in CRP level and stimulated macrophages that led to increase in IL-6 and TNF-α levels compared with TAA-treated group.

Histopathological studies supported the previous results and liver sections showed variable changes like atrophy, degeneration and cirrhosis of hepatic cells in TAA-treated group. Liver sections in AEP and OEP prophylactic groups showed nearly normal and less changes in liver tissue compared with the effect of TAA.

In conclusion, AEP and OEP extracts of propolis showed anti-inflammatory and immunomodulatory properties as evidenced by amelioration of serum IL-6 and TNF-α levels compared with TAA-administrated group. Both extracts also recovered the toxic effects of TAA as proved by modulation of liver enzymes levels, lipid profile, and protein metabolism. AEP seemed to be more efficient, in some parameters, than

OEP as an anti-inflammatory and antioxidant as proved by immunological, biochemical and histopathological studies.

Further studies are recommended to elucidate and clarify the mechanism by which propolis acts as hepatoprotective and immunomodulatory supplement and to isolate the effective compounds of propolis and explore the effect of each components.

Potential effects of different propolis extracts on anti-inflammatory cytokines in induced rat hepatotoxicity

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By

Karim Mohsen Sayed Ahmed

(B.Sc. in Biochemistry, 2006)

Under Supervision of

Prof. Dr. Kamal Ali Fathy Shalaby K. Shalab

Professor of Biochemistry
Faculty of Science
Ain Shams University

Dr. Eman Mohamed Saleh Ahmed

Lecturer of Biochemistry
Faculty of Science Eman Saleh
Ain Shams University

Dr. Eglal Mohamed Sayed Eglal Mahmoud

Researcher
Research and Training Center on vectors of diseases
Ain Shams University

2013

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