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Effects of Curcumin on The Changes in Some Acute Phase Proteins in Aflatoxin B1 Applied Rats

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Abstract

This research was carried out to evaluate the possible effects of curcumin on acute phase proteins in aflatoxin applied rats. In the study, 38 healthy male Wistar Albino rats were used. Group I animals was no applied. Animals in Group II were orally given 1 ml 10% DMSO daily for 60 days. Animals in Group III were orally given 300 mg/kg curcumin dissolved in 10% DMSO daily for 60 days. Animals in Group IV were orally given 250 µg/kg aflatoxin B1 dissolved in 10% DMSO daily for 60 days. Animals in Group V was orally given 250 µg/kg aflatoxin B1 dissolved in 10% DMSO and 300 mg/kg curcumin dissolved in 10% DMSO daily for 60 days. At the end of the study, nitric oxide, amyloid-A, haptoglobin and ceruloplasmin were determined in blood samples taken from all animals. In this study, nitric oxide, amyloid-A, haptoglobin and ceruloplasmin levels with aflatoxin B1 administration were found to be significantly higher than the control group ($p<0.05$). In the group in which aflatoxin and curcumin were administered together, nitric oxide, amyloid-A, haptoglobin and ceruloplasmin levels were lower than in the aflatoxin group ($p<0.05$). In conclusion, the obtained data indicated that administration of curcumin may be useful to alleviate the abnormalities in acute phase proteins resulting from aflatoxicosis.

Key words: Aflatoxin, Curcumin, Amyloid-A, Haptoglobin, Rats

INTRODUCTION

Food and feed products can be contaminated with aflatoxins, which are secondary metabolites produced by Aspergillus widely occurring genus of mold fungi. Aflatoxin B1 is the most hazardous mycotoxin in this group. The main target of aflatoxin B1 is liver and it undergoes transformations in hepatocytes: biotransformation to active aflatoxin B1-8,9-epoxide (8, 9, 18, 38, 40, 46). While infections, traumas and toxic events cause the onset of inflammatory reactions in the organism, aflatoxins also cause inflammation related to tissue damage and chemical reactions occurred in various organs, especially the liver. Inflammation is a protective tissue response against injury or various factors. This event includes different cellular populations, extracellular matrix components and a series of complex cellular and plasma events performed by mediators. The inflammatory response occurs in three different phases, each developed by different mechanisms. These are an acute transient phase characterized by local vasodilation and increased capillary permeability, a subacute phase characterized by infiltration of leukocyte and phagocytic cells from the blood into tissues, and finally a chronic proliferative phase in which tissue degeneration and fibrosis develop (30). It is stated that macrophages and proinflammatory

cytokines play an important role in the onset and continuation of chronic inflammation (13, 49). In particular, TNF-α and IL-1β are active in this process (41). With haptoglobin and CRP, which are acute phase markers, prostaglandins, leukotrienes, nitric oxide are other factors known to assist this process (4, 6, 7, 21, 22, 31).

Curcumin obtained from the rhizome of Curcuma longa L. (Zingiberaceae) is one hydrophobic polyphenol. There is a great interest to anti-inflammatory and antioxidant properties of curcumin in the last two decades. Some studies established its effectiveness in wide variety of diseases including inflammatory disorders (1, 5). It is important that curcumin retains and effectively scavenger free radicals formed during inflammation and released from macrophages and other tissue cells (25, 26, 44). There are also studies related to antimicrobial, insecticidal and anti-inflammatory properties (3, 16, 27).

The aim of this study was to determine the possible effects of curcumin on some acute phase proteins in aflatoxin applied rats.

MATERIALS AND METHODS

In the study, 38 healthy male Wistar Albino rats (2 weeks old) were used. The animals were divided into five groups. These animals fed for 60 days with standard rat food as ad libitum. Group I (K) (n=6) animals was no applied. Animals in group II (DMSO) (n=6) were orally given 1 ml 10% DMSO daily for 60 days. Animals in group III (Cur) (n=6) were orally given 300 mg/kg curcumin (Sigma Aldrich, St. Louis, MO, USA) dissolved in 10% DMSO daily for 60 days. Animals in group IV (AFB1) (n=10) were orally given 250 µg/kg aflatoxin (Acros Organics, Geel, Belgium) B1 dissolved in 10% DMSO daily for 60 days. Animals in group V (AFB1+Cur) (n=10) was orally given 250 µg/kg aflatoxin B1 dissolved in 10% DMSO and 300 mg/kg curcumin dissolved in 10% DMSO daily for 60 days (24, 45). This study protocol was approved by Selçuk University Experimental Medicine Research and Application Center Ethics Committee (Report no. 2018-26).

At the end of 60 days, blood was taken from animals in all groups. Nitric oxide, amyloid-A, haptoglobin and ceruloplasmin were determined in these blood samples taken from all animals. While nitric oxide and amyloid-A levels were determined with ELISA (Biotek ELx800, Biotek Instrumentations, Inc, Winooski, VT, USA) in accordance with the prospectuses via sandwich enzyme-linked immunosorbent measurement method using commercial kits (Bioassay T. Lab. ELISA kit), haptoglobin and ceruloplasmin levels were determined with Siemens BN2 nephelometer using nephelometric method via Siemens kits.

The data obtained from the study were analyzed by one-way ANOVA (SPSS 19). Differences among the groups were determined by Duncan's multiple range test. Differences were considered significant at $p<0.05$.

RESULTS

In the study, the effects of curcumin application in rats treated with aflatoxins on nitric oxide, amyloid-A, haptoglobin and ceruloplasmin levels are given in Table 1.

Table 1. The effects of curcumin on nitric oxide, amyloid-A, haptoglobin and ceruloplasmin levels in aflatoxin-applied rats (Mean±SE).

	Nitric Oxide (µmol/l)	Amyloid-A (µg/ml)	Haptoglobin (mg/dL)	Ceruloplasmin (mg/l)
Group I	21.75±2.35^{c}	36.56±2.02^{c}	29.43±1.02^{c}	146.77±5.93^{bc}
Group II	20.19±1.26^{c}	35.39±1.49^{c}	29.60±1.44^{c}	148.39±3.35^{bc}
Group III	19.93±1.51^{c}	36.12±1.39^{c}	28.04±1.25^{c}	139.05±2.74^{c}
Group IV	34.78±0.90^{a}	47.72±0.95^{a}	43.52±1.13^{a}	194.68±6.47^{a}
Group V	28.34±1.03^{b}	41.25±1.39^{b}	35.34±1.70^{b}	162.26±6.59^{b}

$^{a-c}$ The difference between mean values with different superscripts in the same column is significant at the $p<0.05$ level.

DISCUSSION

Acute phase response; it is an early and non-specific systemic reaction of the immune system to restore and improve homeostasis against local or systemic disorders caused by trauma, infection, stress, operation, neoplasia or inflammation (11, 14, 19, 42). Cytokines and chemokines are released at the location where any infection or tissue damage occurs (19). Cytokines and chemokines are protein and peptide mediators and these mediators are released from cells that play a key role in the immune and inflammatory response (51). These inflammatory mediators initiate and modulate an acute phase reaction by diffused into extracellular fluid and circulation. Cytokines and chemokines along with nitric oxide and also glucocorticoids activate hepatocytic receptors and alter protein synthesis and secretion. As a result, significant changes in concentrations of some plasma proteins known as acute phase proteins occur within a few hours. Although changes in plasma concentrations of acute phase proteins depend on the severity of the stimulus, these changes can also be determined at longer periods (19, 42). Acute phase response may become chronic after receptor stimulation begins and with repeated stimuli (19). Measurements of acute phase proteins are widely used in humans and animals for prognosis or as a disease biomarker. In the acute phase reaction, these proteins may decrease or increase. Increased ones are called positive acute phase protein and decreased ones are called negative acute phase proteins. For example, albumin, the most abundant plasma protein, represents the major negative acute phase protein (42). Amyloid-A and haptoglobin are positive acute phase proteins. These proteins are associated with chronic inflammatory conditions and are synthesized in mainly the liver and in other tissues such as adipose tissue (34, 47, 52).

Under some conditions, inflammatory processes persist for a long time and can cause further damage. Refer to observation of chronic elevations of acute phase proteins, have been used the terms metainflammatory and parainflammatory. Atherosclerosis, cardiovascular diseases, obesity, asthma and diabetes are examples of these elevations (12, 37, 50).

Nitric oxide is a regulatory agent in almost every stage of the development of inflammation. The regulation of the proinflammatory properties of the endothelium and regulation function in the early stages of inflammatory cell migration to the inflammatory area are important (20). In addition, it is a powerful immunoregulatory factor. It has antiapoptotic effects with inhibition of mainly the expression of developmental genes and cellular proliferation (29). The antioxidant properties of nitric oxide also mediate its anti-inflammatory properties (10, 32, 33). Modulatory effects of nitric oxide on inflammation and immunoregulation occurs as a result of its interaction with many signal transduction pathways and transcription factors (20). In our study, while the amount of nitric oxide, which has very important roles in inflammation, significantly increased in the group with aflatoxicosis compared to the control group ($p<0.05$, Table 1), it was determined that in the group in which aflatoxin and curcumin were administered together, the amount of nitric oxide significantly decreased compared to the aflatoxin group ($p<0.05$, Table 1).

Amyloid-A, the most important function of which is to modulate lipoprotein transport and metabolism during the acute phase response, also allows the immune cells to be localized in the inflammation area, while showed preventive effect against oxidative tissue damage (42, 48). In this study, amyloid-A level with application of aflatoxin B1 was found to be significantly higher compared to the control group ($p<0.05$, Table 1), while it was found to be significantly lower in the group in which aflatoxin and curcumin were administered together when compared to aflatoxin group ($p<0.05$, Table 1).

Haptoglobin, another positive acute phase protein, acts as a hemoglobin cleanser. Haptoglobin binds to free hemoglobin and this complex is phagocytosed by macrophages (12, 35). Haptoglobin also prevents the oxidative activity of hemoglobin and helps the recycled iron in heme (28). In the study, it was determined that the amount of haptoglobin in the aflatoxin B1 group was higher than the control group ($p<0.05$, Table 1). It was determined that the amount of haptoglobin in the group in which aflatoxin and curcumin were administered together was lower than the aflatoxin group ($p<0.05$, Table 1).

Ceruloplasmin is a multifunctional protein that provides both transport and storage of copper within the body. Ceruloplasmin is also an antioxidant protein and functions to scavenge reactive oxygen species, while preventing their

formation. It is among the notifications that it protects from iron-induced oxidative stress regarding iron homeostasis (17, 42). In this study, ceruloplasmin, which is a positive acute phase reactant, depend on aflatoxin application significantly increased compared to the control group ($p<0.05$, Table 1), while it was found to be significantly lower than aflatoxin group in group with the curcumin application together with aflatoxin for the same duration ($p<0.05$, Table 1).

In this study, significant changes in acute phase proteins were determined with oral administration of curcumin, which is mentioned it's positively effects in various diseases and inflammations, at dose of 300 mg/kg together with aflatoxin for 60 days. These findings determined in acute phase proteins support the reports that curcumin administration has corrective effects on hepatic functions and related acute phase proteins in inflammatory conditions and inflammations related to aflatoxicosis (2, 15, 34, 36). Studies in recent years offer various propositions about the preventive effects of curcumin against aflatoxicosis. It was shown that the first is the antioxidative effects of curcumin against DNA lesions, lipid peroxidation, reactive oxygen species and glutathione reduction, that the second is the inhibitory effect of the aflatoxins and their active epoxide derivatives against the cytochrome p450 isoenzyme-mediated biotransformation effects and that the third is its immunomodulator effects on IL-1β and TGF-β (39). In this regard, curcumin has been shown to inhibit proinflammatory prostaglandins and leukotrienes, prevent the uptake of arachidonic acid by macrophages, thereby limiting the availability of these substrates in terms of eicosanoid production. It is also reported that curcumin is a potential lipid peroxidation inhibitor and free radical scavenger (23, 43, 44).

CONCLUSION

Consequently, it has been thought that the data obtained in the study were beneficial and important for further studies considering the positive effects of curcumin at dose of 300 mg/kg for 60 days on acute phase proteins in aflatoxicosis.

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