Research Article

Effects of Curcumin on Iron Overload in Rats

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Abstract

Background: Iron overload, common in patients with hematological disorders, is a key target in drug development. This study investigated the effects of curcumin on iron overload in rats.

Methods: Forty male Wistar rats weighing 139.78 ± 11.95 gm (Mean $\pm$ SD) were divided into three equal groups: (i) controls; (ii) iron overload group that received six doses of iron dextran 1000 mg/kg^{-1} by intraperitoneal injections (i.p.); and (iii) iron overload curcumin group that received six doses of curcumin (1000 mg/kg BW by i.p.). In addition to six doses of iron dextran 1000 mg/kg^{-1} by i.p., we studied the effects of curcumin on liver function enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]); antioxidant enzymes (malondialdehyde [MDA], total oxidant status [TOS], total antioxidant status [TAS]); hematological parameters (hemoglobin [Hb], hematocrit [Hct], red blood cells [RBC], white blood cells [WBC], mean corpus volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]); and iron parameters (serum iron profile, transferrin, total iron-binding capacity [TIBC], ferritin, and transferrin saturation [TS%]).

Results: Curcumin caused a significant decrease in the Hct and Hb concentrations in Group III ($P < 0.05$). It also significantly reduced the serum levels of ALT (52.45 ± 4.51 vs 89.58 ± 4.65 U/L) and AST (148.03 ± 6.47 vs 265.27 ± 13.02 U/L) at the end of the study ($P < 0.05$). The TIBC, transferrin levels, and TS significantly decreased when the rats were administered curcumin serum iron ($P < 0.05$). The TAS level significantly increased in Group III in comparison to Group I (the control group) ($P < 0.05$). At the end of the study, curcumin significantly reduced the serum levels of TOS (12.03 ± 2.8 vs 16.95 ± 5.05 mmol H_2O_2/L) while the TAS (1.98 ± 0.42 vs 1.06 ± 0.33 mmol Trolox equiv./L) was increased.

Conclusion: The findings of the present study suggest the therapeutic potential of curcumin against iron overload.

1. Introduction

Iron is crucial for all living organisms, including humans and animals. It is required as a cofactor for a multitude of proteins with diverse biological functions. However, because iron is a transition metal, it can participate in the Fenton reaction resulting in the generation of reactive oxygen and free radicals [1, 2]. In the body, iron is an essential element involved in numerous physiologic processes, such as mitochondrial respiration, energy production, ATP production, DNA synthesis, and oxygen consumption [3, 4].

While iron is tightly regulated physiologically, the human body has no controlled mechanism to excrete its excess amounts. Iron overload occurs when excess iron accumulates in the body, causing organ dysfunction. Under such circumstances, iron chelation therapy is required, particularly in repeatedly transfused patients suffering from sickle cell anemia or β-thalassemia [5–8]. At the same time, iron becomes potentially more toxic since the redox cycling catalyzes the production of hydroxyl radicals. Iron can readily undergo redox cycling between its two predominant oxidation states, Fe^{3+} and Fe^{2+}, acting as an electron donor or acceptor [9, 10]. However, when iron is present in excess, iron-mediated oxidative stress occurs. In the presence of molecular oxygen generating oxygen-derived free radicals such as hydroxyl radicals, the highly reactive hydroxyl radicals attack the cell membrane, destroying DNA base sequences and sugar groups [11–16].

Iron chelation therapy is the optimum alternative for treating iron overload. Currently, three iron chelators are licensed to treat iron overload, the most widely used of which is Desferrioxamine-B. The principal drawbacks of Desferrioxamine are lack of oral activity, high cost, and low compliance. Moreover, the two oral chelators that are currently available have various disadvantages. Therefore, there exists an urgent clinical need for new chelation agents for iron. Consequently, the successful design of a nontoxic, orally active, selective iron chelator has become a much sought-after goal [11–20].

Desferrioxamine, also known as deferoxamine (DFO; generic and Desferal [brand name]), is a drug that is commonly utilized in the treatment of iron overload. In addition to its iron-chelation property, other features have been identified. DFO is injectable iron chelator indicated for chronic iron overload in patients aged three years or more [23–26]. This iron chelator has proven effective in preventing lipid peroxidation, reducing deaths by cardiac disease, and extending the lifespan in iron overloaded patients; it also has a mild toxicity profile. The most common adverse effects of DFO are discomfort at the injection site and gastrointestinal disturbances. Although rare, ototoxicity, nephrotoxicity, and visual impairment are other side effects of DFO. Fortunately, most of the toxicity is

reversible when DFO therapy is discontinued. However, this therapy increases the risk of infections, including those caused by vibrio and yersinia [27–30].

Deferiprone (DFP), a tablet orally administered three times daily, was first introduced in clinical trials in the 1980s and approved in 2011. It was also the first oral iron chelator to be clinically assessed, and it is pharmacologically effective in achieving iron excretion [13]. DFP is indicated for the treatment of transfusional iron overload. It appears to be particularly effective with regards to cardiac iron removal [28]. However, although DFP has good compliance, some serious side effects have been reported, including agranulocytosis, gastrointestinal disturbances, arthropathy, neutropenia, and a transient rise in serum transaminases. In comparison to Deferasirox (DFX), DFP appears to be less successful in controlling iron overload in thalassemia. DFX is used as the second-choice treatment in thalassemia when DFP is not available [29–31].

DFX is an orally administered iron chelator that has been successful in clinical trials in patients with transfusional iron overload; it has demonstrated high effectiveness in the reduction of iron burden. Although DFX is well-tolerated with a high safety profile, it leads to several adverse side effects, including gastrointestinal disturbances, increased liver enzymes, increased serum creatinine levels, and maculopapular skin rash. It also entails changes in kidney and liver function, diarrhea, nausea, abdominal pain, auditory impairment, skin rash, and headaches [32, 33].

Curcumin (diferuloylmethane) is the biphenolic active compound of turmeric. Various studies have shown that it has anti-arthritic, anti-infectious, cardioprotective, anti-inflammatory, antioxidant, hepatoprotective, chemo preventive, thrombo suppressive, and anti-carcinogenic activities. This compound is a polyphenol, and it readily complexes with several different metal ions. It has been found to be an effective chelator of Fe (III) [34–39].

This study aimed to investigate the effect of curcumin on iron overload in rats by measuring the activities of hematological parameters (hemoglobin [Hb], hematocrit [Hct], red blood cells [RBC], white blood cells [WBC], mean corpus volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), Serum iron profile, transferrin, total iron-binding capacity (TIBC), transferrin saturation (TS%), total oxidant status (TOS), total antioxidant status (TAS), malondialdehyde (MDA), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

2. Materials and Methods

Forty male Wistar rats weighing 139.78 ± 11.95 gm (Mean ± SD) were divided into three groups: (i) the control group; (ii) the iron overload group receiving six doses of iron dextran 1000 mg/kg i.p. injection; and (iii) the iron overload curcumin group receiving six doses of curcumin (1000 mg/kg BW by i.p. injection). In addition to six doses of iron dextran 1000 mg/kg by i.p. injection, at the end of the experiments, the rats were anesthetized with ketamine/xylazine. Blood samples were collected by a heparinized tube. Hematological parameters were assayed by an automated hemoanalyzer. Blood samples were centrifuged at 1000 x g at 4°C for 10 min, and serum samples were separated to measure the serum ALT and AST levels using standard diagnostic kits (Roche). Serum transferrin levels were measured using a transferrin kit by ELISA method. The TIBC was measured by a colorimetric, spectrophotometric method using the Randox TIBC kit and Fe serum levels were measured using Randox kit. TAS and TOS were measured spectrophotometrically using a commercially available kit.

2.1. Determination of MDA as an indicator of oxidative stress

A total of 200 µl of liver tissue homogenates were used to estimate the MDA content, which was measured spectrophotometrically [40, 41].

2.2. Statistical analysis

Differences between the two groups were assessed using Student's *t*-test and ANOVA. Data are shown as Mean ± SEM. *P*-values < 0.05 were defined as statistically significant.

3. Results

We examined the hematological parameters of all three groups. Based on our results, curcumin administration did not significantly affect the Hb and Hct in group-III rats (Table 1).

MDA levels significantly increased in Group-II rats compared to the controls and Group III. Curcumin significantly reduced the levels of MDA (34.52 ± 6.34 compared with 152.46 ± 6.99 U/L in Group II) ($P < 0.05$) (Table 2).

TAS level increased significantly in Group III compared with Group I ($P < 0.05$). The TOS was found to be higher in the second group compared with the first ($P < 0.05$).

TABLE 1: Comparison of hematological parameters (Hb, Hct, RBC, WBC, MCV, MCH, MCHC) in the three groups of rats.

Hematological parameters	Group I	Group II	Group III
WBC count	3.22 ± 0.16	3.24 ± 0.65	4.02 ± 0.42
RBC (×10/μL)	7.524 ± 0.08	5.642 ± 1.35	7.795 ± 0.28
Hemoglobin (gm/dL)	14.52 ± 0.18	12.98 ± 0.54	12.96 ± 0.48
Hematocrit (%)	45.12 ± 0.88	39.89 ± 1.12	40.75 ± 1.45
MCV (fl)	60.95 ± 0.52	59.45 ± 1.32	60.06 ± 0.22
MCH (pg)	19.58 ± 0.15	19.52 ± 0.18	20.28 ± 0.14
MCHC (gm/dl)	32.45 ± 0.33	32.87 ± 0.46	34.07 ± 0.24

The results are expressed as Mean ± SD.

TABLE 2: The effect of iron overload and curcumin on MDA (nmol/gm tissue), TOS (mmol H_2O_2/L), and TAS (mmol Trolox equiv./L) activities of rats.

	Group I	Group II	Group III
MDA (nmol/gm wet tissue)	59.12 ± 4.02	152.46 ± 6.99[a]	34.52 ± 6.34[b]
Serum TOS (mmol H_2O_2/L)	34.86 ± 2.76	46.95 ± 5.05[a]	30.03 ± 2.8[b]
Serum TAS (mmol Trolox equiv./L)	15.32 ± 0.24	14.06 ± 0.33[a]	18.58 ± 0.42[b]

The results are expressed as Mean ± SD. [a]Significant difference with Group I; [b]Significant difference with Group II; [c]Significant difference with Group III at $P < 0.05$.

At the end of the study, curcumin significantly reduced serum TOS levels (46.95 ± 5.05 vs 30.03 ± 2.8 [mmol H_2O_2/L]) and increased TAS (14.06 ± 0.33 vs 18.58 ± 0.42 [mmolTroloxEquiv./L]).

The enzyme assays of serum transaminases demonstrated that iron overload significantly increased the levels of ALT and AST to 89.58 and 265,27 U/L, respectively ($P < 0.05$). Curcumin was able to effectively inhibit the enzyme activity. The levels of AST and ALT were reduced to 52.45 and 148.03 U/l, respectively ($P < 0.05$) (Table 3).

In this study, serum iron, TIBC, and transferrin levels were significantly increased in the iron overload rats. At the end of the study, curcumin significantly reduced the serum levels of iron (205.24 ± 4.50 vs 330.45 [μg/dL]), transferrin (1.49 ± 0.07 compared with 2.35 ± 0.04 [gm/L]), and TIBC (96.43 ± 6.46 compared with 109.22 ± 9.74 [μg/dL]) (Table 4) ($P < 0.05$).

TABLE 3: The effect of iron overload and curcumin on ALT and AST activities.

	Group I Control	Group II	Group III
ALT (U/L)	65.14 ± 8.85	89.58 ± 4.65[a]	52.45 ± 4.51[b]
AST (U/L)	160.15 ± 10.62	265.27 ± 13.02[a]	148.03 ± 6.47[b]

[a]Significant difference with the control group; [b]Significant difference with the iron overload group at $P < 0.05$.

TABLE 4: The effect of iron overload and curcumin on the serum iron profile of rats.

	Group I	Group II	Group III
Transferrin (gm/L)	1.45 ± 0.02	2.35 ± 0.04[a]	1.49 ± 0.07[b]
Transferrin saturation (%)	66.76 ± 4.12	76.16 ± 3.38[a]	68.24 ± 3.65[b]
Iron (μg/dL)	220.38 ± 3.45	330.45 ± 6.11[a]	205.24 ± 4.50[b]
TIBC (μg/dL)	104.25 ± 5.30	109.22 ± 9.74[a]	96.43 ± 6.46[b]

The results are expressed as Mean ± SD. [a]Significant difference with Group I; [b]Significant difference with Group II; [c]Significant difference with Group III at $P < 0.05$.

4. Discussion

Iron overload condition in the body can be defined as an increase in iron deposition with no consideration as to the presence of tissue destruction. Curcumin, also known as diferuloylmethane, is a bright yellow chemical produced by plants of the *Curcuma longa*. Curcumin molecule has been reported to be the active site involved in the chelation of iron. It has chemical properties consistent with iron chelator activity [42–44]. This study aimed to investigate the effect of curcumin on iron overload in rats. We studied the effects of curcumin on liver function enzymes (AST, ALT), antioxidant enzymes (TOS, TAS, MDA), hematological and iron parameters (serum iron profile, Transferrin, TIBC, Ferritin, TS%). Based on our results, curcumin administration did not significantly affect Hb and Hct in rats in group III. Yadav *et al.* reported a statistically nonsignificant change in the RBC and WBC counts and the Hb values observed in rats administered with extract of curcumin. Hussain reported that curcumin caused a significant decrease in RBC and MHC in aged rats [45, 46]. Iron overloaded rats had a significantly higher level of MDA in the liver than controls. Treatment with curcumin significantly lowered the level of MDA. The decrease in the level of MDA suggests that curcumin might be effective in the prevention of lipid peroxidation. MDA in the liver of iron-overloaded rats was statistically higher than that in other corresponding groups ($P < 0.01$). These changes may be the result of oxidative damage associated with ROS production and hepatic iron accumulation, which may ultimately lead to chronic diseases [47].

These results confirmed that curcumin significantly elevated the levels of TAS and that TOS was found to be higher in the second group compared with the first and the third groups. At the end of the study, curcumin significantly reduced serum TOS levels. This study also demonstrated that curcumin significantly reduced pathological changes in the liver by reducing AST and ALT levels as shown in Table 2. Iron overload was associated with significant increases in the activities of the ALT and AST ($P < 0.05$) compared with Group I. The injection of curcumin significantly decreased the serum levels of

AST and ALT compared to iron overloaded rats ($P < 0.05$). A previous study did not find any significant changes in AST and ALT levels following curcumin administration [48]. Other studies showed that curcumin treatment reversed the elevated enzymes; ALP, ALT, and AST. Moreover, Fu *et al.* found that curcumin significantly protected the liver from injury by reducing the activities of serum ALP, AST, and ALT [49]. In another study by Manjunatha *et al.*, rats injected with iron showed hepatic toxicity as measured by elevated serum enzymes, LDH, ALT, and AST and an increase in lipid peroxides [50]. In the present study, serum iron, TIBC, and transferrin levels were significantly elevated in the iron-overloaded rats. In rats administered with curcumin TIBC, serum iron, transferrin levels, and TS% significantly decreased ($P < 0.05$). Evidence for iron toxicity in another study was exhibited by the significant increase in serum, liver, and kidney iron concentrations, serum TIBC, transferrin, and TS% in iron-overloaded rats while serum UIBC was significantly reduced. Such increases have been associated with increased oxidative stress state and changes in antioxidants. These results are in agreement with those recorded in several models of iron overload [51].

5. Conclusion

In conclusion, the present study confirms previous reports on the therapeutic potential of curcumin. Our results confirm the hypothesis that curcumin acts as an iron chelator and our in-vivo results suggest that curcumin-oxime has the potential to exhibit a positive effect on iron overload.

Acknowledgements

None.

Ethical Considerations

This study was performed in accordance with the Declaration of Helsinki. Ethical approval was obtained for the studies from the Hatay Mustafa Kemal Animal Experiments Local Ethics Committee (2018/10-1).

Competing Interests

None to declare.

Availability of Data and Material

All relevant data and methodological details pertaining to this study are available to any interested researchers upon reasonable request to corresponding author.

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