Protective Effect of Curcumin on Acrylamide-Induced Hepatic and Renal Impairment in Rats: Involvement of CYP2E1

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Abstract
As a chemical extensively used in industrial areas and formed during heating of carbohydrate-rich foods and tobacco, acrylamide (ACR) has been demonstrated to exert a variety of systemic toxic effects including hepatotoxicity and nephrotoxicity. In the present study, we investigated the effect of curcumin, a natural polyphenolic compound in a popular spice known as turmeric, on the hepatic and renal impairment caused by ACR exposure to 40 mg/kg for 4 weeks in rats. The administration of curcumin at doses of 50 and 100 mg/kg to ACR-intoxicated rats significantly decreased the serum levels of alanine transaminase, aspartate transaminase, creatinine, and urea; improved the histological changes of liver and kidney caused by ACR; reduced the number of apoptotic cells; as well as relieved ACR-induced hepatic and renal oxidative stress. Moreover, curcumin inhibited the CYP2E1 overexpression induced by ACR in the liver and kidney tissues. Therefore, curcumin could be applied as a potential strategy for the intervention of ACR-induced systemic toxicity. The inhibition of CYP2E1 might be involved in the protection of curcumin against ACR-induced hepatotoxicity and nephrotoxicity.

Keywords
curcumin, acrylamide, hepatotoxicity, nephrotoxicity, cytochrome P450 2E1

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Acrylamide (ACR) is a well-known environmental pollutant, which exerts a variety of systemic toxic effects on human beings following either occupational or dietary exposure.1,3 As the starting monomer for polyacrylamide synthesis, ACR could lead to work-related disorders in occupational settings because of its wide use in diverse industrial processes including plastics, paper, and cosmetics manufacturing; wastewater treatment; and drinking water purification.1,3 More importantly, the well-being of the public is being adversely affected by the intake of dietary ACR that is formed during heating processes of tobacco and carbohydrate-rich foods at high temperatures.2,4 So far, in addition to its high-profile neurotoxicity, reproductive toxicity, and carcinogenicity,5 other toxic effects of ACR, for example, hepatotoxicity6-8 and nephrotoxicity,8-11 have had more attention paid to them.

As a compound with high water solubility, ACR could be easily diffused and transferred throughout the body organs including the liver and the kidney. Moreover, the capability of ACR to form adducts with hemoglobin contributes to its accumulation in these organs and subsequent damage.12-14 Accumulating evidence from animals4,8,13-16 has demonstrated that ACR exposure leads to histopathological changes which occur in the liver and kidney tissues, as well as the increment of hepatic and renal biochemical parameters. A study conducted by Wang et al12 had applied a metabolomics approach, which was based on ultra-high-performance liquid chromatography/time of flight tandem mass spectrometry and multivariate statistical analyses, to conduct a comprehensive analysis of serum metabolites in a population involving 65 individuals with occupational exposure to ACR. The results showed that liver function markers, including alanine transaminase (ALT), total bilirubin, and direct bilirubin, were significantly higher in the ACR contact group than in the noncontact group. In addition, the average levels of serum urea and creatinine were higher by 12% and 43%, respectively, in the contact group than in the noncontact group.

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noncontact group, although the differences were not statistically significant. These data suggested the potential hepatotoxicity and nephrotoxicity of ACR on humans. Therefore, extensive research has been conducted to reduce the hepatic and renal impairment induced by ACR.

Curcumin is a natural polyphenolic compound which has been reported as the most active component in the popular spice known as turmeric. The safety of curcumin, even at high doses, has been demonstrated in many clinical trials. Curcumin is currently considered as a “Generally Recognized As Safe” compound and has been marketed as a dietary supplement; there is no report on the adverse effect of curcumin on liver or kidney function. So far, a variety of health benefits, such as antioxidant, immune regulatory, anti-inflammatory, antidiabetic, anticancer, neuroprotective, and cardiovascular protective activities, have been attributed to curcumin. In particular, under the circumstance that phytochemical treatment has become one of the best ways to overcome hepatotoxicity, the hepatoprotective effects of curcumin have been well documented in many animal liver injury models caused by, for example, alcohol, acetaminophen, carbon tetrachloride, diethylnitrosamine, lindane, and heavy metals. Similarly, curcumin has been reported to exhibit a renoprotective role in experimental kidney injury associated with chronic renal failure, ischemia and reperfusion, diabetic nephropathy, and nephrotoxicity induced by adriamycin, gentamicin, iron nitritriacetate, chloroquine, hexavalent chromium, sodium fluoride, glycerol, and cisplatin. More importantly, a recent study reported that curcumin efficiently rescued ACR-induced gait abnormality and spatial memory deficits in rats, and thus was proposed as a new preventive strategy for neurotoxicity induced by ACR. However, whether curcumin exerts any beneficial effects on ACR-induced hepatic and renal impairment remained unanswered. Therefore, in the present study, we studied the protective effect and the possible mechanism of curcumin on hepatic and renal impairment caused by ACR exposure in rats, in order to examine the therapeutic potential of curcumin in ACR-induced systemic toxicity.

In order to determine whether curcumin can attenuate the liver damage in ACR-intoxicated rats, we measured the activities of serum ALT and aspartate transaminase (AST), 2 classical markers of liver function (Figure 1). The levels of serum ALT and AST were markedly higher in the ACR-intoxicated group than those in the normal control group, suggesting significant hepatocellular damage induced by ACR exposure. Importantly, when curcumin was administered at doses of 50 to 100 mg/kg, the ACR-induced elevation of ALT and AST in serum was significantly decreased in a dose-dependent manner, which highly indicated the

Figure 1. Effect of curcumin on the serum levels of aspartate transaminase (AST), alanine transaminase (ALT), creatinine, and urea in acrylamide (ACR)-intoxicated rats. Data are means ± SD of 10 animals in each group. **P < 0.01, compared with the normal control rats. #P < 0.05, ##P < 0.01, compared with the ACR-intoxicated group.
The hepatoprotective effect of curcumin on ACR-induced hepatic impairment. An increase in the serum levels of creatinine and urea can reflect renal damage. In ACR-intoxicated rats, the levels of serum creatinine and urea significantly increased by 2.68 and 3.55 times as compared with normal controls, respectively ($P < 0.01$). However, when compared with the ACR-intoxicated rats, the serum creatinine and urea levels in rats cotreated with ACR and curcumin decreased by 17.3% to 28.5% and 24.6% to 29.7%, respectively ($P < 0.05$; $P < 0.01$). The considerable neuroprotective property of curcumin has been shown in ACR-exposed rats. It is worth noting that a pharmacokinetics study demonstrated that, after intravenous administration, the average areas under the concentration-time curve (AUC) of curcumin in liver (9.06 min µg/mL) and kidney (12.0 min µg/mL) were larger than in other organs, including brain (4.04 min µg/mL). Moreover, the average half-lives of curcumin were 17.6, 19.7, and 9.20 min in liver, kidney, and brain, respectively. These data showed that curcumin accumulated more and tended to remain longer in the liver and kidney, which might contribute to the potential for curcumin to exert its pharmacological activity in these 2 organs. In line with the high accumulation of curcumin in the liver and kidney, this study demonstrated the significant protective effect of curcumin on ACR-induced hepatic and renal impairment, as indicated by reductions in the serum levels of classic hepatic and renal function biomarkers (ALT, AST, creatinine, and urea) in ACR-intoxicated rats.

To confirm further the protective effect of curcumin on ACR-induced hepatic and renal impairment, we examined the histological changes in rat livers and kidneys. As shown in Figure 2(a), rats in the ACR-intoxicated group showed drastic alterations in the internal structure of their livers, which were manifested as significant edema and intracytoplasmic vacuolization of hepatocytes, as well as inflammatory cell infiltration, with only mild disarrangement and vacuolization of hepatic cells suggesting that recovery of hepatic disruption was being observed in the curcumin-treated rats. The results from histopathological evaluation of the kidneys (Figure 2(b)) showed that the histological alterations in ACR-intoxicated kidneys included glomeruli fragmentation, glomerular congestion, hemorrhage in interstitial spaces of tubules, tubular necrosis, cell swelling, and mononuclear cell infiltration; this kidney damage was significantly alleviated by the coadministration of curcumin to ACR-intoxicated rats.

As an important element in cell number control, apoptosis is closely associated with the development of almost every hepatic or renal disease condition. Therefore, it is of extreme importance to adopt prevention strategies against cell apoptosis in an attempt to limit the liver or kidney damage resulting from cell death. So far, the antiapoptotic activity of curcumin has been commonly assumed as one of the important mechanisms underlying its beneficial bioactive properties. As shown in Figure 3, immunofluorescent staining revealed significant increases in terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)-positive apoptotic cells in the liver and kidney tissue slices from ACR-intoxicated rats, which were in line with the previous study reporting the downregulation effect of ACR on the expression of genes related to antiapoptosis in the liver. Importantly, curcumin administration effectively decreased the number of apoptotic cells, suggesting its antiapoptotic activity in ACR-damaged livers and kidneys, which might be an important mechanism underlying its hepatoprotective and renoprotective effects against exposure to ACR.

Furthermore, the protective effects of curcumin on the damaged liver and kidney have been mainly attributed to its antioxidant and radical scavenging properties. Among all phytochemicals, phenolic compounds are best known for their outstanding antioxidant activities. As a representative polyphenolic compound, curcumin is regarded as a 10-fold more potent antioxidant than vitamin E. Importantly, although the exact etiology of ACR-induced hepatic and renal impairment is unknown, oxidative stress, which can lead to cell apoptosis, has been well accepted as a critical event and a principal mechanism. During ACR metabolism in the body, excessive levels of reactive oxygen species (ROS) would be produced. On the other hand, ACR may decrease the antioxidant defense in the organs, thus resulting in the imbalance between the production of free radicals and their elimination by antioxidant defense. In order to clarify the antioxidant effect of curcumin on ACR-induced hepatotoxicity and nephrotoxicity in rats, the contents of malondialdehyde (MDA) and glutathione (GSH), as well as the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), in the tissue homogenates were measured as the indicators for evaluating the levels of oxidative stress in the liver and kidney. As shown in Table 1, compared with the normal group, the content of MDA, a classic indicator of oxidative stress, in the liver and kidney homogenates showed a strong increase, while the level of GSH (an intracellular enzymatic antioxidant acting as a free radical scavenger) and the activities of SOD and GSH-Px (2 important antioxidant enzymes for scavenging ROS) were markedly decreased in the ACR-treated group ($P < 0.05$; $P < 0.01$), suggesting ACR-induced elevation of oxidative stress and decrease of antioxidant capacity in the liver and kidney. As expected, curcumin treatment significantly reversed these alterations induced by ACR in a dose-dependent manner ($P < 0.05$), suggesting that the antioxidative property of curcumin might, at least partly, contribute to its hepatoprotective and renoprotective effects in ACR-intoxicated rats.

It has been well documented that oxidative stress, lipid peroxides, and deterioration of antioxidant defense in the liver and kidney could be attributed to the activation of cytochrome P450 (CYP) 2E1, a member of the cytochrome P450 mixed-function oxidase system constitutively expressed in the hepatic and extrahepatic tissues such as the kidney. As the most active ROS-generating CYP450 isozyme during the catalytic cycle, CYP2E1 has been considered to function as a central pathway in the formation of high levels of ROS and reactive metabolites during the metabolism of many hepatotoxins and renal toxins, including ACR. In fact, CYP2E1 is the only enzyme involved in the
biotransformation of ACR to glycidamide, the latter being a highly reactive epoxide metabolite known to be more toxic than ACR itself. Meanwhile, CYP2E1-catalyzed metabolism of ACR causes the release of ROS, triggers oxidative stress leading to an imbalance between the production and elimination of ROS, then results in lipid peroxidation.\textsuperscript{10,31,37} Moreover, there is ample evidence that ACR is not only a substrate but also an inducer of CYP2E1.\textsuperscript{31,37-39} Overexpression of CYP2E1 has been found to be induced by ACR intoxication and is associated with increased oxidant production,\textsuperscript{31,37,39} which might result in the exposed organs being more sensitive to the toxicity of ACR entering the body. Accordingly, any reagent which has the ability to either inhibit or downregulate CYP2E1 would be a strong candidate for the prevention and treatment of toxicity induced by ACR.\textsuperscript{31,39}

The present study showed that curcumin inhibited the ACR-induced CYP2E1 overexpression in the liver and kidney tissues, which was in line with previous observations that curcumin acted as a CYP2E1-positive inhibitor in the liver\textsuperscript{20,40} and kidney.\textsuperscript{41,42} In

\[ \text{ACR} \rightarrow \text{Glycidamide} \]

Figure 2. Effect of curcumin on histological changes in acrylamide (ACR)-intoxicated rat livers and kidneys. (a) Representative hematoxylin and eosin (HE) staining sections of the liver, $\times$200. (b) Representative HE staining sections of the kidney, $\times$100.
view of the essential role of CYP2E1 in the development of ACR hepatotoxicity and nephrotoxicity through the generation of free radicals and the reactive metabolites from metabolism of ACR, it could be speculated that curcumin might protect against ACR-induced hepatic and renal impairment through the down-regulation of CYP2E1 expression. As shown in Figure 4(a), CYP2E1 mRNA expression in the liver and kidney was significantly enhanced by 40% and 35%, respectively, in the ACR-treated group as compared with the control. Importantly, the ACR-induced significant rise of CYP2E1 mRNA expression levels was markedly inhibited by the cotreatment with 100 mg/kg curcumin. Accordingly, the increase of CYP2E1-positive cells in liver and kidney tissues of ACR-intoxicated rats was reversed by curcumin treatment (Figure 4(b)).

Table 1. Effect of Curcumin on the Levels of MDA, GSH, SOD, and GSH-Px in Liver and Kidney Homogenates Prepared From ACR-Intoxicated Rats (N = 10, mean ± SD).

| Groups                  | MDA (nmol/mg prot) | GSH (mg/g prot) | SOD (U/mg prot) | GSH-Px (U/mg prot) |
|-------------------------|--------------------|-----------------|-----------------|-------------------|
|                         | Liver          | Kidney         | Liver          | Kidney           |
| Normal                  | 3.7 ± 1.0        | 3.0 ± 0.8      | 6.4 ± 1.1      | 5.1 ± 0.9        | 123.4 ± 21.0    | 69.6 ± 8.1    | 38.6 ± 8.5    | 20.8 ± 9.0    |
| ACR                     | 4.8 ± 1.1*       | 4.1 ± 1.0*     | 4.1 ± 0.9**    | 4.2 ± 0.8*       | 95.6 ± 26.8*   | 59.1 ± 9.4*   | 28.8 ± 7.1**  | 12.3 ± 5.1*   |
| ACR + curcumin 50 mg/kg | 4.1 ± 1.0        | 3.9 ± 0.8      | 4.9 ± 1.2      | 4.6 ± 0.9        | 119.8 ± 20.3#  | 63.5 ± 8.7    | 30.2 ± 8.2    | 15.4 ± 5.9    |
| ACR + curcumin 100 mg/kg| 3.9 ± 0.9#       | 3.2 ± 0.9#     | 5.0 ± 1.0#     | 5.0 ± 0.9#       | 120.5 ± 23.3#  | 66.8 ± 7.1#   | 34.9 ± 6.1#   | 18.5 ± 6.1#   |

ACR, acrylamide; GSH, glutathione; GSH-Px, glutathione peroxidase; SOH, superoxide dismutase.

*P < 0.05, **P < 0.01, compared with the corresponding control rats.

#P < 0.05 compared with the corresponding ACR group.
Figure 4. Effect of curcumin on the expression of CYP2E1 in the liver and kidney tissues of acrylamide (ACR)-intoxicated rats. (a) The mRNA expression was measured with real-time PCR. (b) Immunohistochemical staining for the protein expression of CYP2E1 in the liver. (c) Immunohistochemical staining for the protein expression of CYP2E1 in the kidney. Data are means ± SD of 10 animals in each group. * \( P < 0.05 \) compared with the normal controls. \( P < 0.05 \) compared with the ACR-intoxicated group.
In conclusion, our results showed that curcumin protected against the development of hepatic and renal impairment induced by ACR exposure in rats via its antiapoptotic and antioxidant properties. Therefore, as a safe and effective component in the diet, curcumin could be applied as a potential strategy for the intervention of ACR toxicity. Importantly, the inhibition of CYP2E1 might be involved in the protection of curcumin against ACR-induced hepatotoxicity and nephrotoxicity.

**Experimental**

**Experimental Protocol**

Three-month-old Sprague-Dawley rats (male, 200-220 g body weight) were obtained from Hubei Experimental Animal Research Center (Wuhan, China). After a 1-week acclimation period, all rats were randomly divided into 4 groups, with 10 animals in each group:

1. normal control group;
2. ACR-intoxicated group;
3. low-dose curcumin treatment group;
4. high-dose curcumin treatment group.

Rats in 2 to 4 groups were intraperitoneally injected with 40 mg/kg ACR (Amresco Co., Solon, USA) dissolved in normal saline every other day for 4 weeks. The normal control animals received saline injections as a control. Meanwhile, rats in the low-dose and high-dose curcumin treatment groups were daily administered with curcumin (Sigma Chemicals Co., St. Louis, USA) at the oral administration doses of 50 and 100 mg/kg, respectively, for 4 weeks. The normal and ACR-intoxicated control rats were orally administered with distilled water. The doses of ACR and curcumin were chosen based on preliminary studies. At 24 hours after the last administration, all animals were sacrificed. The blood was quickly collected from the carotid artery and centrifuged at 1000 \(g\) for 10 minutes to prepare the serum. The liver and kidney tissues were quickly excised. This experimental protocol was approved by the Animals Care and Use Committee of Medicine College, Wuhan University of Science and Technology.

**Serum Biochemical Analysis**

Blood serum was used for the evaluation of hepatic function biomarkers including ALT and AST, as well as renal function biomarkers including creatinine and urea. All serum biochemistry was analyzed according to the protocols of commercially available assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

**Histopathological Analysis**

The same parts of the collected liver and kidney samples were fixed with 10% neutral-buffered formalin, subsequently decalcified, dehydrated, and embedded in paraffin. Then, paraffin-embedded tissue sections of 5 \(\mu\)m thickness were stained with hematoxylin and eosin dye to observe the histopathological changes.

**TUNEL Assay**

The apoptotic cells in the liver or kidney sections were detected using the TUNEL assay following the instruction manual of TUNEL Apoptosis Assay Kit (Servicebio, Wuhan, China).

**Measurement of Parameters Related to Oxidative Stress in the Liver and Kidney Homogenates**

Liver or kidney tissue homogenates were made by homogenizing each tissue with 9 times volume of PBS on ice, then centrifuging. The contents of MDA and GSH, as well as the activities of SOD and GSH-Px, in the liver and kidney homogenates were measured according to their respective manufacturer's instructions (Nanjing Jiancheng Bio-Engineering Co., Ltd, Nanjing, China). The protein contents in the tissue homogenates were detected using the bicinchoninic acid assay kit (Nanjing Jiancheng Bio-Engineering Co., Ltd).

**Real-Time PCR**

The expression levels of CYP2E1 mRNA in the liver and kidney tissues were measured by real-time PCR using all-in-OneTM qPCR master mix AOPR-1200 (GeneCopoeia, Rockville, USA). The sequences of primer sets for CYP2E1 were 5’-CTTCGGGCCAGTGTTCAC-3’ (forward) and 5’-CCCATATCTCAGAGTTGTGC-3’ (reverse). \(\beta\)-actin gene was applied as a reference.

**Immunohistochemistry**

Paraffin-embedded liver or kidney sections of 5 \(\mu\)m thickness were incubated with a rabbit anti-CYP2E1 antibody (Servicebio), then a biotinylated goat antirabbit secondary antibody (Servicebio). Immune complexes were visualized using 3,3′-diaminobenzidine tetrachloride. Then, sections were counter-stained with hematoxylin.

**Statistical Analysis**

All data were expressed as mean ± SD and analyzed using one-way analysis of variance with post hoc Tukey test by SPSS 22.0 software. \(P < 0.05\) or \(P < 0.01\) was considered statistically significant.

**Declaration of Conflicting Interests**

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