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Research Paper

Evaluation of Kojic Acid derivatives as an Iron Chelator in Mice With Iron Overload

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ABSTRACT

Background: Iron overload is a major metabolic disorder characterized by abnormal iron accumulation in various tissues, particularly the liver and heart, leading to severe tissue damage through oxidative stress, lipid peroxidation, and cellular destruction. In recent years, iron chelators have attracted considerable attention as one of the principal therapeutic strategies for controlling this condition. However, currently available chelators, such as deferoxamine are associated with several limitations, including high cost, difficult administration, and poor patient compliance. Therefore, the search for novel, effective, and cost-efficient compounds continues. The aim of the present study was to evaluate the effects of kojic acid on ferritin levels and iron overload-related parameters in mice with experimentally induced iron overload.

Materials and Methods: In this experimental study, laboratory mice were divided into different groups, including a control group, an iron overload model group, and kojic acid-treated groups. Iron overload was induced through intraperitoneal injection, and kojic acid was administered at a dose of 25 mg/kg for four weeks. At the end of the treatment period, blood samples associated with iron storage and metabolism, particularly ferritin levels, were analyzed. Statistical analysis was performed using GraphPad Prism software, version 9.5.1, and one-way analysis of variance.

Results: Induction of iron overload significantly increased ferritin levels in the control group compared with the blank group, confirming successful model induction. Deferoxamine, compound I, and compound II each significantly reduced ferritin levels versus control, with compound II showing a greater reduction than compound I. No significant differences were found between deferoxamine and either kojic acid derivative, indicating comparable efficacy. One-way ANOVA showed significant group differences (R^2=0.9347), and Brown–Forsythe confirmed equal variances.

Conclusion: Kojic acid exerted modulatory effects on several iron overload-related parameters and potentially contributed to the reduction of ferritin levels. Based on these results, kojic acid derivatives may be considered promising candidates for further investigation as potential iron chelators in the treatment or management of iron overload disorders. Nevertheless, additional studies are required to establish definitive conclusions.

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Introduction

Iron is an essential element required for cell survival and normal physiological function, playing a critical role in processes, such as oxygen transport, electron transport chain activity, DNA synthesis, and the function of numerous vital enzymes [1]. Despite its indispensable biological importance, iron homeostasis must be tightly regulated, as excessive iron accumulation can lead to detrimental consequences. When iron levels exceed the normal storage and regulatory capacity of the body, free or accumulated iron participates in oxidative reactions, generating reactive oxygen species (ROS) that cause extensive cellular and tissue damage [2]. This pathological condition, known as iron overload, can affect multiple organs, including the liver, heart, pancreas, and other tissues, ultimately leading to organ dysfunction and failure. From a pathophysiological perspective, excess iron contributes to oxidation-reduction reactions, particularly through the Fenton reaction, thereby increasing the production of ROS [3]. These reactive species induce oxidative stress through the destruction of membrane lipids, proteins, and nucleic acids, while simultaneously activating inflammatory and cell death pathways. Consequently, tissues that are highly susceptible to iron accumulation undergo structural and functional impairment [4]. The liver, as the primary organ responsible for iron storage and metabolism, is among the first tissues affected, exhibiting elevated liver enzyme activity, histopathological alterations, and functional disturbances. Similarly, the heart is highly vulnerable to oxidative stress and iron deposition [5].

Under normal physiological conditions, proteins, such as ferritin, transferrin, and hepcidin regulate iron homeostasis by controlling iron absorption, transport, and storage, thereby preventing excessive accumulation [6]. However, in pathological conditions, such as repeated iron administration, hemolytic diseases, thalassemia, hemochromatosis, or certain metabolic disorders, these regulatory mechanisms become disrupted, resulting in iron deposition within tissues [7]. In such cases, biomarkers, including serum ferritin, serum iron, total iron-binding capacity, and transferrin saturation provide valuable insight into body iron stores. Ferritin is considered one of the most important indicators of iron storage, and elevated ferritin levels are generally associated with increased body iron burden, although inflammatory conditions may also influence ferritin concentrations [8]. Therefore, ferritin should be interpreted alongside other biochemical parameters. Currently, iron chelation therapy represents one of the primary therapeutic strategies for managing iron overload. Iron chelators bind free or stored iron ions, removing them from oxidative cycles and thereby reducing iron-mediated tissue damage. Deferoxamine is one of the oldest and most widely recognized iron chelators used in the treatment of iron overload disorders [9]. Nevertheless, its clinical use is limited by several drawbacks, including high cost, the requirement for prolonged or repeated administration, difficulties in drug delivery, and, in some cases, adverse effects and poor patient compliance. These limitations underscore the necessity for identifying alternative compounds with improved tolerability and lower cost.

Among potential candidates, kojic acid, a natural metabolite produced by several fungal species, has attracted increasing attention [10]. In addition to its well-known applications in the food and cosmetic industries, kojic acid possesses metal-chelating properties and may therefore function as an iron-chelating agent. Several studies have demonstrated that kojic acid can form complexes with iron ions and may theoretically reduce free iron levels and limit their toxic effects [11]. However, previous findings regarding its efficacy have been inconsistent. Some investigations have reported limited or negligible effects, whereas others have highlighted its chelating capacity and ability to form stable iron complexes. Furthermore, concerns have been raised regarding possible adverse effects or enhanced lipid peroxidation under certain conditions. These inconsistencies indicate that further experimental studies are required to clarify the effects of kojic acid. Moreover, the identification of effective and economically affordable iron chelators is of considerable importance in healthcare systems, particularly in developing countries [12]. If kojic acid proves effective in reducing iron burden and improving related biomarkers, it may represent a promising candidate for the development of novel therapeutic approaches. Therefore, the present study was designed to investigate the effects of kojic acid on ferritin levels and other iron overload-associated parameters in mice with experimentally induced iron overload.

Materials and Methods

This experimental study was conducted using laboratory mice. A total of 25 male BALB/c mice aged 12–15 weeks and weighing 25–30 g were used (five mice in each group). The animals were maintained under standard laboratory conditions, including a 12 h light/12 h dark cycle, a temperature of 24±2°C, a relative humidity of 45–55%, and free access to standard food and water [13]. Prior to the initiation of the experiment, the animals underwent an acclimatization period to adapt to the

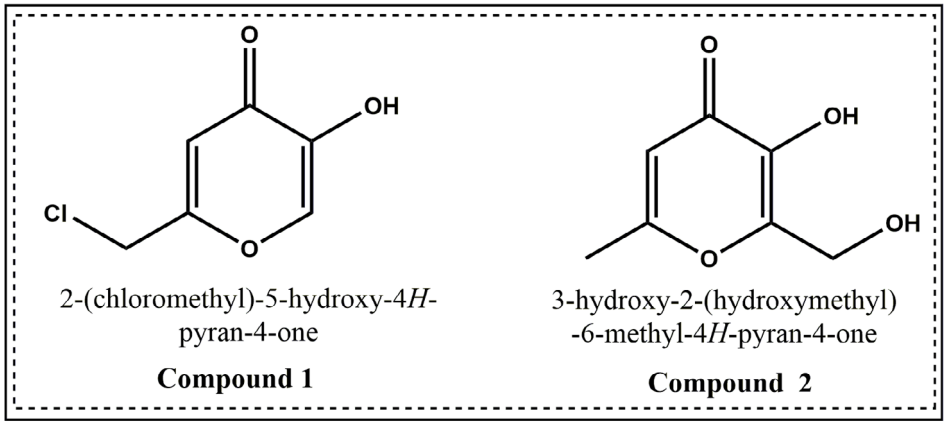


Figure 1. Chemical structure and name of kojic acid derivatives applied as iron chelator

laboratory environment. The kojic acid derivatives were administered intraperitoneally (IP) at a dose of 25 mg/kg body weight once daily for five consecutive days.

Following acclimatization, the animals were randomly assigned ito different experimental groups to evaluate the effects of kojic acid derivatives compared with the control and iron overload groups (Figure 1). Iron overload was induced via intraperitoneal injection. After confirmation of successful model induction, kojic acid was administered at predetermined doses and for a specified duration. In the presence of a reference treatment group, animals received standard chelation therapy with deferoxamine. The selected doses and treatment duration were determined based on the study protocol and previously published investigations. Throughout the experimental period, the general health status of the animals, body weight changes, and any signs of toxicity or drug intolerance were carefully monitored.

At the end of the treatment period, blood samples were collected under appropriate anesthesia and ethical considerations. The obtained data were analyzed using GraphPad Prism software. Statistical comparisons among groups were performed using suitable statistical tests according to data distribution. For normally distributed data, parametric analyses, including one-way analysis of variance (ANOVA) followed by post hoc tests were applied. Non-parametric tests were used when data did not meet normality assumptions. $P<0.05$ was considered statistically significant.

Results

Evaluation of serum ferritin levels among the experimental groups demonstrated that induction of iron overload significantly increased ferritin levels in the control group compared with the blank group, confirming the successful establishment of the iron overload model. In the deferoxamine-treated group, ferritin levels were significantly reduced compared with the control group, indicating the effective iron-chelating activity of this standard drug in reducing body iron stores. Similarly, administration of compound I resulted in a significant reduction in ferritin levels relative to the control group, suggesting its ability to inhibit iron accumulation (Figure 2). Furthermore, compound II also produced a significant decrease in ferritin levels compared with the control group, with a more pronounced reduction than that observed for compound I. However, comparisons among treatment groups revealed no statistically significant differences between deferoxamine and the two tested kojic acid derivatives, indicating comparable efficacy of the experimental compounds relative to the standard iron chelator. Overall, these findings suggest that both tested compounds were capable of reducing ferritin levels in the iron overload model and may therefore represent potential therapeutic candidates for mitigating disorders associated with iron accumulation. One-way ANOVA revealed a statistically significant difference among the experimental groups regarding ferritin levels. The coefficient of determination (R^2=0.9347) indicated that more than 93% of the observed variance in ferritin levels could be explained by differences among the experimental groups. Additionally, the Brown–Forsythe test showed no significant heterogeneity in variances between groups, confirming the assumption of equal variances required for ANOVA. These findings provide a reliable basis for interpreting the effects of the investigated interventions on ferritin levels.

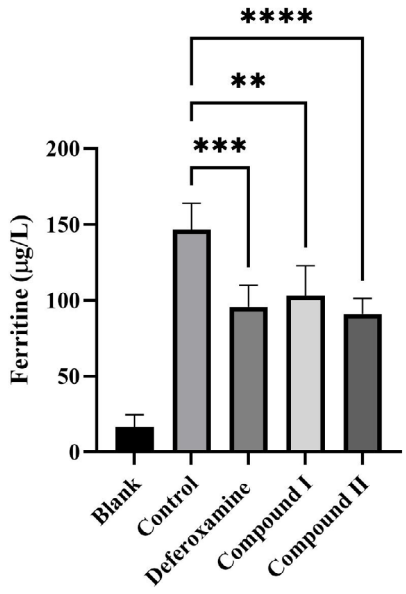


Figure 2. Effects of kojic acid derivatives on ferritin level reduction in mice with iron overload

Data are presented as Mean±SD (n=5 per group). *P<0.05, **P<0.01, ***P<0.001 versus the iron-overload control group.

Discussion

The findings of the present study demonstrated significant differences in ferritin levels among the experimental groups, as confirmed by one-way ANOVA. These overall differences highlight the potential effectiveness of the investigated interventions, including deferoxamine, compound I, and compound II, compared with the blank and control groups. Since ANOVA identifies only overall group differences, post hoc pairwise comparisons are necessary to determine which specific groups significantly differ from one another. Nevertheless, the high statistical significance observed in this study provides considerable confidence regarding the validity of the overall findings. Furthermore, the absence of significant differences in group variances, as demonstrated by the Brown–Forsythe test, further strengthens the reliability of the ANOVA results and indicates relatively homogeneous data dispersion among groups. A more detailed interpretation requires evaluation of the individual effects of compound I and compound II and comparison of their efficacy with deferoxamine, a well-established iron chelator, as well as with the control groups. Additional comparative analyses could clarify whether these compounds significantly reduced ferritin levels relative to baseline conditions and whether their efficacy is comparable to deferoxamine. Taken together, the present findings suggest that the investigated compounds possess promising therapeutic potential in the modulation of iron metabolism and reduction of ferritin levels. Future investigations should focus on elucidating the underlying molecular mechanisms and assessing their potential clinical applications.

Kotyzová et al. [14] conducted an experimental study to investigate the effects of kojic acid on oxidative stress and iron overload in two mouse strains and reported that the therapeutic effect of kojic acid on iron concentrations in the liver and kidneys was negligible. The discrepancy between their findings and the results of the present study may be attributed to differences in the experimental design, including variations in the animal models employed, the route and dosage of kojic acid administration, as well as the dependent variables evaluated, namely ferritin levels in the current study versus hepatic and renal iron concentrations in their investigation [14]. Nurchi et al. [15] reported that the incorporation of vanillin derivatives into kojic acid led to the synthesis of novel ligands with enhanced chelating properties, which demonstrated considerable potential in chelation therapy. Notably, the newly developed compounds showed lower iron-binding affinity than Desferal but affinity comparable to deferiprone, indicating moderate iron-chelating efficiency that merits further investigation.

Conclusion

The present study demonstrated statistically significant differences in ferritin levels among the experimental groups, indicating that the investigated therapeutic interventions exerted notable effects on iron metabolism. The high coefficient of determination further supports the effectiveness of the evaluated treatments. Although additional analyses are required to precisely determine the effects of each treatment relative to the control groups, the prelimi-

nary findings suggest that compound I and compound II possess therapeutic potential for modulating ferritin levels under iron overload conditions. Future studies should focus on detailed evaluation of these effects, elucidation of the molecular mechanisms involved, and determination of optimal dosages for potential clinical applications.

Ethical Considerations

Compliance with ethical guidelines

All experimental procedures involving animals were approved by the Institutional Animal Ethics Committee (Code: IR.MAZUMS.AEC.1405.030) and conducted according to guidelines. All efforts were made to minimize animal suffering and the number of animals used. This study complied with the ARRIVE guidelines and did not involve human participants.

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Authors contribution's

Investigation: Elahe Oladi; Methodology: Shima Yousefi; Conceptualization: Mehdi Mogharabi-Manzari and Sajad Molavi; Writing original draft: Mehdi Mogharabi-Manzari; Supervision and writing–review & editing: Hossein Jalali and Sajad Molavi; Resources: Hossein Jalali; Project administration and funding acquisition: Sajad Molavi.

Conflict of interest

The authors declared no conflict of interests.

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