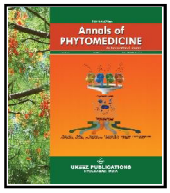
Annals of Phytomedicine 11(2): 400-404, 2022

DOI: http://dx.doi.org/10.54085/ap.2022.11.2.48

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Hepatoprotective and antioxidant activity of allicin on the polycystic ovarian syndrome in rats

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Article Info

Article history

Received 1 August 2022

Revised 17 September 2022

Accepted 18 September 2022

Published Online 30 December-2022

Keywords

Allicin

Polycystic ovarian syndrome

Letrozole

High-fat diet

Hepatoprotective

Antioxidant

Abstract

In polycystic ovarian syndrome (PCOS), oxidative stress is recognized to serve a major part. It is also possible that it is the factor or outcome of hepatic dysfunction. In recent years, there has been mounting proof of a link between hepatotoxicity and PCOS. In this work, we evaluated the impacts of allicin on the liver and antioxidant parameters in letrozole and high-fat diet-induced PCOS rats. Administration of a high-fat diet and letrozole (0.5 mg/kg) resulted in hepatotoxicity and increased oxidant levels. The amounts of liver enzymes such as alanine transaminase, total protein and bilirubin as well as antioxidant enzymes such as catalase, malondialdehyde, glutathione and superoxide dismutase were altered in PCOS rats. Treatment with a high dose of allicin resulted in the restoration of these levels and improved activity of antioxidant enzymes, thus protecting liver tissues from damage due to oxidative stress. Hence, it can be concluded that allicin has potential hepatoprotective and antioxidant activities in PCOS rats.

1. Introduction

One of the most widely accepted definitions of the polycystic ovarian syndrome (PCOS) is based on the deliberations of a professional symposium organized by the National Institutes of Health (NIH) in April 1990, which described the disease as characterized by (i) hyperandrogenism, (ii) oligoovulation and (iii) invalidation of other recognized comorbidities. PCOS is characterized by the existence of 2-3 of the eligibility principles: hyperandrogenism, oligoovulation and cystic ovaries (12 follicles ranging 2-9 mm in size and/or an ovarian capacity greater than 10 ml in minimum one of the two ovaries).

In recent times, indications of a connection between hepatotoxicity and PCOS have increased. To elucidate questions about the examination and care of such individuals, it is necessary to understand the pathogenetic relationship and clinical implications of such a connection. Liver injury is more likely in PCOS individuals, especially teenagers, according to investigations (Carmina, 2007; Brzozowska *et al.*, 2009). In PCOS animal models created by a high-fat diet, fat buildup sensitizes the liver to enlargement and downstream effects like oxidative stress (Sugasawa *et al.*, 2021; Sinha-Hikim *et al.*, 2011). Therefore, lipid structures in the cells are considered a target for lipid oxidation, resulting from exposure to reactive oxygen species (ROS) created by inefficient scavenging and/or impeded antioxidant activity of enzymes. Certainly, oxidative stress may be regarded as a trigger or consequence of liver problems (Delli Bovi *et al.*, 2021; Farzanegi *et al.*, 2019). When ROS dominates the antioxidant capacity, this reaction occurs.

Antioxidants ameliorate PCOS-mediated hepatic injury *via* the increase in quality of hepatocellular histology by limiting inflammatory responses, stabilizing glutathione (GSH), avoiding oxidative stress and boosting the protective antioxidant system and sometimes rejuvenation of liver cells, intensifying superoxide dismutase (SOD) function, ramping up the GSH cellular concentration, reducing oxidative stress and improving hepatocellular protein expression (Cheng and He, 2022). Allicin's hepatoprotective action may be clarified by the antioxidant characteristics of its flavonolignans, which are chemically phenols. In addition, it promotes hepatocellular regeneration and biological membrane stability to inhibit the penetration of hepatotoxic substances into hepatic cells (Eugenio-Pérez *et al.*, 2016; Hamid *et al.*, 2020).

Various models studied for induction of PCOS includes dihydro-testosterone, estradiol-valerate, dehydroepiandrosterone, letrozole (LET) and testosterone (Bhatnagar, 2007; Kim *et al.*, 2018). LET shows good ovarian cysts but fails to show metabolic abnormalities, whereas, a high-fat diet (HFD) in rodents shows inflammatory reactions in the hypothalamus which contribute to irregular glucose as well as lipid metabolism and increased testosterone levels that results in obesity and insulin resistance (Kakadia *et al.*, 2018). In the present study, combination of LET and HFD was used to induce PCOS (Nazia Begum *et al.*, 2022). The use of antioxidants for treating PCOS has garnered considerable interest, antioxidant therapy

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has been documented to have hepatoprotective activities and improve various health-compromising illnesses (Oyebanji *et al.*, 2020; Gharaei *et al.*, 2021; Amini *et al.*, 2015). The antioxidant capability of allicin owing to its ability to scavenge chain-carrying radicals from targets by transferring its allylic H atom to create hydroperoxides has been demonstrated (Okada *et al.*, 2006). Therefore, we evaluated the hepatoprotective and antioxidant properties of allicin in letrozole and high-fat diet-induced PCOS rats.

2. Materials and Methods

2.1 Experimental animals

Twenty-four female adult albino Wistar rats weighing 150-200 g were obtained from GENTOX Bio Services Pvt. Ltd. Hyderabad, India. The research was conducted following the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) with the approval of Institutional Animal Ethics Committee (GPRCP/IAEC/23/19/02/PCL/AE-6B-rats-F-36). The rats were kept in standard clean polypropylene cages and acclimatized for seven days in a laboratory setting with 20-22°C temp., 55 ± 5% RH and a 12 h light/dark cycle.

2.2 Drugs and chemicals

Allicin 5% was procured from Vijay Herbal Products (New Delhi, India) and metformin 500 mg (Obimet) was obtained from Corona Remedies Pvt. Ltd. (Ahmedabad, India). Open-Source Formula-Research Diets offered the following formulas for the control and high-fat diets: control diet (D12450H) containing 10% fat-based energy and HFD (D12451) containing 45% fat-based energy (New Brunswick, USA) (Nazia Begum *et al.*, 2022).

The ingredients for HFD were supplied by Behlawa Enterprises (Mumbai, India). Choline bitartrate was purchased from Universe Industries (Maharashtra, India). LET (Letero) was purchased from Hetero Health Care Pvt. Ltd. Tris buffer, disodium salt, pyrogallol, hydrochloric acid, trichloroacetic acid, thiobarbituric acid (TBA), disodium hydrogen phosphate, dipotassium hydrogen phosphate, hydrogen peroxide, ammonium molybdate, potassium dihydrogen-phosphate, 5, 5-dithiobis-2-nitrobenzoic acid, sodium nitrate and crystal violet were obtained from S.D. Fine Chemicals; saline and methanol was purchased from local source. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and direct bilirubin kits were obtained from Trans-Asia Biomedicals Ltd. ADVIA Centaur testosterone (TSTO) kit, were procured from Infobio, Delhi, India.

2.3 Experimental design

Wistar rats were split into four groups (n=6).

Group I (Control): Control diet + Vehicle (1% CMC p.o.)

Group II (PCOS Control): HFD + Letrozole (0.5 mg/kg p.o.)

Group III (Allicin LD): HFD + Letrozole + Allicin (160 mg/kg, 5% Allicin extract p.o.)

Group IV (Allicin HD): HFD + Letrozole + Allicin (320 mg/kg 5% Allicin extract p.o.)

All the groups received respective diets for 84 days and letrozole for the first 42 days. Allicin was administered from the 43rd day to the 84th day. During the study period, the estrous cycle was determined daily. The estrous cycle was determined with the help of the vaginal smear technique (Nazia Begum *et al.*, 2020).

The fasted rats were anesthetized on the 85th day of the investigation, using isoflurane and the blood sample was withdrawn by the retro-orbital sinus puncture. The samples were centrifuged (Eltek/RC4100F and 2011) to separate serum for biochemical estimations using semi auto-analyser (Aspen/Star 21 plus and 2011).

2.4 Antioxidant assay

The antioxidant assay was performed on serum. SOD levels were assessed by the pyrogallol oxidation assay, *i.e.*, Marklund and Marklund methods (Deba *et al.*, 2017). The catalase technique is founded on the interaction between unreacted H_2O_2 and ammonium molybdate, which produces a yellow color with an absorbance value of 374 nm (UV-1800 & 2013) (Hadwan and Abed, 2016). GSH was estimated using trichloroacetic acid and Ellman's reagent; the absorbance was read at 412 nm and serum GSH levels were represented in mg/dl of serum (Turgut *et al.*, 2006). Lipid peroxidation was estimated based on the bonding of lipid peroxidation products with TBS, mainly malondialdehyde (MDA), resulting in the production of thiobarbituric acid reactive substances (TBARS). TBARS produces a reddish-pink hue, which may be quantified spectrometrically at 532 nm (Yadav *et al.*, 2021).

2.5 Statistical analysis

Data values are represented as mean ± standard error of the mean (SEM). To analyze two different groups, statistical analysis was performed with the help of a one-way analysis of variance (ANOVA) coupled with Tukey's post hoc test using Graph Pad Prism 5 (Graph Pad Software, Inc., San Diego, CA, USA). Differences were regarded statistically significant when $p<0.05$.

3. Results

3.1 Effect of allicin on estrous cycle

The vaginal smear of the PCOS group demonstrated the dominant cell, *i.e.*, leucocytes in the diestrous phase/persistent cornification in the estrus phase, showing absolute acyclicity. In comparison with the control group, continuous cornification was substantially enhanced in the PCOS rats as the research continued. Administration of allicin gradually induced cyclicity in the PCOS-induced rats (Nazia Begum *et al.*, 2022).

3.2 Effect of allicin on hormonal profile

A rise in testosterone level was noted in the PCOS control in comparison with the control group ($p<0.001$) and allicin LD and HD groups showed a decrease in testosterone levels when compared with the PCOS control group ($p<0.001$). However, in allicin high dose group the testosterone levels were restored to normal (Nazia Begum *et al.*, 2022).

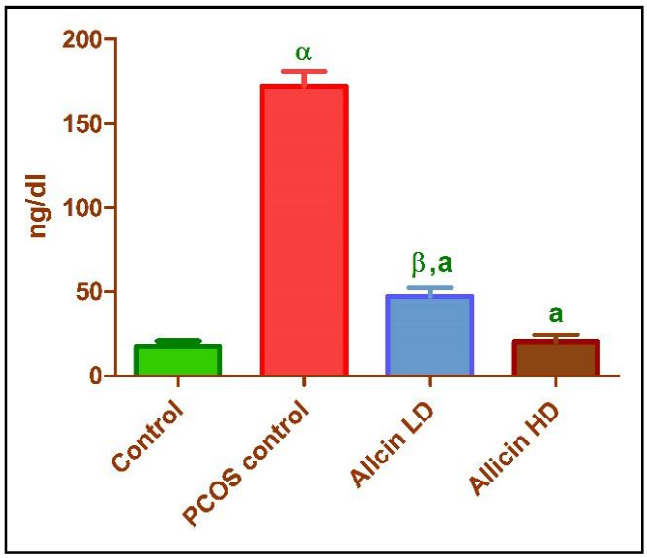

Figure 1: Effect of allicin on testosterone levels.

Data are represented as mean ± SEM (n=6) and assessed by one-way analysis of variance (ANOVA) along with Tukey's post hoc test for comparison of means. $^{\alpha}p<0.001$ and $^{\beta}p<0.01$, when compared to the control group; $^{a}p<0.001$, when compared to the PCOS control group. PCOS, polycystic ovary syndrome; LD, low dose; HD, high dose.

3.3 Effect of allicin on liver parameters

Direct bilirubin concentrations were decreased in PCOS control in comparison to the control group ($p<0.001$), allicin HD has shown an increase in direct bilirubin levels when compared to the PCOS control group ($p<0.05$) and they were re-established to normal levels, however, allicin low dose did not exhibit any remarkable rise in direct bilirubin concentrations.

Total bilirubin levels were lower in the PCOS control in comparison to the control group ($p<0.001$), allicin HD have shown an increase in total bilirubin levels in comparison tothe PCOS control group ($p<0.05$), and the levels were restored to normal. However, the allicin low dose showed no remarkable increase in total bilirubin levels.

Total protein concentrations were improved in PCOS control when compared with the control group ($p<0.01$) and significance was not noted in the allicin LD-treated rats in comparison with the PCOS control group. When compared to PCOS control group, allicin HD has shown a decrease in total protein levels ($p<0.05$) and the levels were restored to normal.

PCOS control group has shown an elevation in ALT levels ($p<0.001$). When compared to PCOS control group, allicin HD has shown a decrease in ALT levels and restored to normal levels ($p<0.001$), but significance was not observed in the allicin LD group (Table 1).

Statistically, there was no variation observed in AST levels in PCOS rats in comparison with control rats (data not shown) (Nazia Begum *et al*., 2022).

Table 1: Effect of allicin on serum liver parameters

S. No	Parameter	Control	PCOS control	Allicin LD	Allicin HD
1	**Direct bilirubin** (mg/dl)	0.45 ± 0.023	0.25 ± 0.029$^{\alpha}$	0.27 ± 0.026$^{\hat{a}}$	0.36 ± 0.021^{c}
2	**Total bilirubin** (mg/dl)	1.1 ± 0.065	0.60 ± 0.039$^{\alpha}$	0.58 ± 0.072$^{\alpha}$	0.93 ± 0.079^{c}
3	**Total protein** (mg/dl)	5.9 ± 0.19	7.8 ± 0.41$^{\alpha}$	7.7 ± 0.25$^{\alpha}$	6.4 ± 0.36^{c}
4	**ALT** (IU/l)	25 ± 2.5	53 ± 2.3$^{\alpha}$	48 ± 3.6$^{\alpha}$	34 ± 2.1^{a}

Data are expressed as mean ± standard error of the mean (SEM) (n=6) and assessed by one-way analysis of variance (ANOVA) along with Tukey's post hoc test for comparison of means. $^{\alpha}p<0.001$, $^{\gamma}p<0.05$, when compared with the control group; $^{a}p<0.001$, $^{c}p<0.05$, when compared with a PCOS control group. PCOS, polycystic ovary syndrome; LD, low dose; HD, high dose.

3.4 Effect of allicin on antioxidant parametrs

3.4.1 Serum antioxidant parameters

Catalase levels were diminished in PCOS control rats ($p<0.001$) when compared to control rats and the activity was increased in treatment groups (allicin LD-$p<0.01$ and allicin HD-$p<0.001$) in comparison with PCOS control rats, the levels were restored to normal levels in the allicin HD-treated rats. MDA concentrations were elevated in PCOS control ($p<0.001$) in comparison to control rats, these levels were decreased in treatment groups (allicin LD- $p<0.001$ and allicin HD - $p<0.001$) when compared to the PCOS control group, the levels were restored to normal in allicin LD and allicin HD group. GSH levels were decreased in the PCOS control ($p<0.001$) when compared to the control group, these levels were increased and restored to normal in treatment groups ($p<0.001$) in comparison to PCOS control rats. SOD levels were reduced in PCOS control rats ($p<0.001$) when compared to the control rats, the levels were remarkably increased and restored to normal in the treatment groups ($p<0.001$) (Table 2).

Table 2: Effect of allicin on serum antioxidant levels

S. No	Parameter	Control	PCOS control	Allicin LD	Allicin HD
1	**Catalase** (kU)	1.9 ± 0.094	0.47 ± 0.095$^{\alpha}$	1.2 ± 0.15$^{\beta,b}$	1.8 ± 0.13^{a}
2	**MDA** (µM)	1.4 ± 0.14	5.9 ± 0.31$^{\alpha}$	2.0 ± 0.15^{a}	1.6 ± 0.17^{a}
3	**GSH** (mg/dl)	4.0 ± 0.32	1.4 ± 0.20$^{\alpha}$	3.5 ± 0.19^{a}	4.3 ± 0.21^{a}
4	**SOD** (U/ml)	20 ± 1.2	7.9 ± 0.98$^{\alpha}$	17 ± 0.94^{a}	19 ± 0.95^{a}

Data are represented as mean ± SEM (n=6) and assessed with the help of one-way analysis of variance (ANOVA) along with Tukey's post hoc test for comparison of means $^{\alpha}p< 0.001$, $^{\beta}p< 0.01$, in comparison withthe control group, $^{a}p<0.001$, $^{b}p<0.01$, $^{c}p<0.05$, when compared to PCOS control. PCOS, polycystic ovary syndrome; LD, low dose; HD, high dose.

4. Discussion

Administration of a high-fat diet and letrozole (0.5 mg/kg) resulted in hepatotoxicity and increased oxidant levels. Altered liver parameters and oxidative stress have been implicated in the etiology of hepatotoxicity elicited by letrozole and HFD (Jyothilekshmi *et al*., 2020; Puri *et al*., 2020). The formation of ROS such as superoxides and H_2O_2, which serve a crucial role in peroxidation, is increased in LET+HFD-induced PCOS rats.

Allicin HD restored the modified quantities of liver enzymes in a concentration-dependent manner and these findings are following those of prior research by Mallhi *et al*. (2014). Allicin's hepatoprotective activity may be caused by the existence of phytochemicals comprising flavonoids, saponins and phenols. The crucial role of flavonoids in hepatoprotection has been demonstrated by (Tapas *et al*., 2008).

MDA is a by-product of the peroxidation of lipids by radicals. It is produced when hydroxyl radicals, particularly ROS, interact with the fatty acids found in the cellular membrane. As an index of the counteraction of hepatic lipids peroxidation, the MDA blood levels were measured. LET+HFD treatment increased MDA levels in rats which were restored after allicin treatment. Elevated MDA contents in the liver indicate that lipid peroxidation has escalated, causing hepatic damage and that antioxidant defense systems have been unable to limit the accumulation of uncontrolled radicals (Dash *et al*., 2007; Saber *et al*., 2020).

The contents of SOD offer a good indicator of the amount of oxidative injury in different organs. Impaired or restricted SOD functioning causes greater oxidative alterations of the cell surface and cytoplasmic biomolecules. In our study, LET+HFD treatment resulted in diminished levels of SOD in rats and these levels were increased upon allicin treatment. The findings are consistent with previous investigations on the antioxidant activity of allicin (Shahsavani *et al*., 2012; Hamed *et al*., 2021; Ma *et al*., 2018).

Catalase is a cytoplasmic scavenging enzyme that participates in the conversion of H_2O_2 to H_2O and molecular oxygen and much of it is localized in the peroxisomes and cytoplasm of cells. Resulting from the deposition of superoxide radicals and H_2O_2, a decline in the functioning of this enzyme potentially causes several negative side effects. In our study, letrozole and HFD treatment resulted in decreased catalase levels which were restored in the allicin-treated group. These results correlate with those of previous studies (Vimal and Devaki, 2004; Huang *et al*., 2020). Such reduction in enzymatic activity may have been triggered by the formation of ROS in PCOS women with oxidative stress.

Tripeptide GSH functions as a cytosolic natural antioxidant but is found in extremely low amounts in all live cells. This research demonstrates that PCOS rats' blood GSH concentrations were substantially lower than those of the control group. Diminished GSH values may have potential ties to insulin sensitivity (Sabuncu *et al*., 2001; Dincer *et al*., 2005). The outcomes of our investigation showed that GSH levels were increased in the allicin-treated group and these findings are following prior research (Zhang *et al*.,2012; Gong-Chen *et al*., 2014)

In the present work, the drop in MDA and the rise in SOD, GSH, and catalase concentrations contribute to the potent antioxidant activity of allicin in ameliorating LET+HFD-treated PCOS rats. Allicin could exert its antioxidant action directly by scavenging free radicals or indirectly by triggering and boosting the function of the natural antioxidant activity of cellular enzymes (Kelsey *et al*., 2010).

5. Conclusion

The oxidative stress indicators in the rats' hepatocytes and serum were impacted by the induction of PCOS by letrozole and a high-fat diet. In the present study, allicin at high doses was reported to possess considerable hepatoprotective and antioxidant activity in PCOS rats. However, the exact dose required to see optimum activity needs to be determined. Additional research should be done to thoroughly comprehend the mechanism of activity and to assess the effectiveness of allicin on hepatic organelles that may have been harmed during experimental liver toxicity.

Acknowledgments

The authors are grateful to Dr. B. Madhava Reddy, Principle, G. Pulla Reddy College of Pharmacy, for providing the necessary facilities for carrying out the research work.

Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Nazia Begum, Rahathunnisa Begum, Kandavalli Manipriya and B. Veeresh (2022). Hepatoprotective and antioxidant activity of allicin on the polycystic ovarian syndrome in rats. Ann. Phytomed., 11(2):400-404. http://dx.doi.org/10.54085/ap.2022.11.2.48.**