



OPEN New insight into the protective effect of *Citrullus colocynthis* loaded with ZnONP cream on glutaraldehyde-induced dermatitis in health care workers

Walaa A. Ali¹, Walaa A. Moselhy^{1,2}, Marwa A. Ibrahim³✉, Ahlam G. Khalifa⁴ & Gadallah Mohamed⁵

Glutaraldehyde (GLU) is mainly used in medicine by healthcare workers during infection control as a chemical disinfectant. It has been linked to numerous health hazards that range from asthma to irritation of the eye to contact dermatitis. *Citrullus colocynthis* (C.C.) is utilized as a supplement to combat a range of health-related problems. This study aimed to assess the effectiveness of locally applied *Citrullus colocynthis* extract and *Citrullus colocynthis* loaded with ZnONPs against dermatitis caused by the disinfectant *glutaraldehyde* (2%). The female mice were divided into five groups (G1, G2, G3, G4, and G5). Group 1 was used as a control. The other 4 groups (2, 3, 4, and 5) were sprayed with 2% GLU (2 mg/kg body weight), and the other groups (3, 4, and 5) were subjected to local application of natural products (*Citrullus colocynthis* extract cream, ZnONP cream, and *Citrullus colocynthis* loaded on ZnONP cream), respectively. Each experimental animal was followed for 5 days per week for 30 days. Our findings revealed that GLU-induced dermatitis via the upregulation of TNF- α , IL-1b, NFkB 1, and ptgs2 mRNA expression and the downregulation of TGFB1 mRNA expression caused oxidative stress and altered the biochemical markers and histological appearance. However, these effects were improved by the ZnONPs, C.C. extract, and C.C.-ZnONPs. Local application of *Citrullus colocynthis* ZnONPs and ZnONPs had preventive effects against GLU-induced dermatitis through the suppression of oxidative stress and inflammatory markers and the enhancement of antioxidants.

Keywords Oxidative stress, Dermatitis, IL-6, PTGFB1, Ptg2, Nfkb 1, *Citrullus colocynthis*, ZnONPs, Anti-inflammatory effects

Nosocomial infections, or hospital-acquired infections, affect between 5 and 20% of hospitalized patients. It poses a persistent risk to patient safety. Multi-drug-resistant organisms (MDROs) rely on workers to clean and disinfect areas effectively¹. In addition to social and economic hazards MDRO are key variables that can lead to nosocomial infections and increase the cost of medical care². Outbreaks of nosocomial infections are usually caused by contaminated tools and other medical supplies³. Disinfection is considered one of the best tactics for sterilizing reusable instruments⁴. Disinfectants can lower the number of microorganisms in the environment and obstruct their path of transmission⁵. Chemical disinfectants are the most popular and widely utilized type of disinfectant⁶. One of the most commonly used groups is the aldehyde group. *Glutaraldehyde* is now widely used as a chemical sterilant and high-level disinfectant. Agent⁷. *Glutaraldehyde* is employed in the dental and medical fields⁸. It has been linked to a number of dangerous health outcomes, including asthma, breathing difficulties, irritation of the eyes, and contact dermatitis⁹. Contact dermatitis has been observed in X-ray technicians, endoscopy nurses, dental assistants, hospital maintenance and cleaning personnel, and funeral

¹Department of Biotechnology and Life Sciences, Faculty of Postgraduate Studies for Advanced Sciences, Beni-Suef University, Beni-Suef 62511, Egypt. ²Toxicology and Forensic Medicine Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef 62511, Egypt. ³Department of Biochemistry and Molecular Biology, Faculty of Veterinary Medicine, Cairo University, Cairo, Egypt. ⁴Forensic Medicine and Toxicology Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef 62514, Egypt. ⁵Biochemistry Department, Faculty of Agriculture, Al Azhar University, Cairo, Egypt. ✉email: marwa199@gmail.com; marwaibrahim@cu.edu.eg

service workers¹⁰. Synthetic drugs used to treat dermatitis caused by *GLU* have certain side effects, such as hypersensitivity. Natural products are preferred over synthetic products because they have fewer or no negative effects, are more affordable, and are more readily available. One of these natural products is *Citrullus colocynthis*. The nutrients present in *Citrullus colocynthis* may be taken as supplements to help with a variety of health-related problems¹¹. It has many antibacterial, anti-inflammatory, and antioxidant properties¹². *Citrullus colocynthis* has been linked to a protective effect by suppressing proinflammatory release, inhibiting COX-2 expression, and lowering both TNF- α and IL-6 levels. Nanomedicine is the use of nanoparticle technology for the treatment and prevention of illnesses in humans. The second most prevalent element in the human body, controls several forms of metabolism, cell growth and proliferation, and the creation of macromolecules such as DNA, RNA, and proteins¹³. Zinc impacts the synthesis of cytokines that reduce inflammation, including interleukins such as IL-1b, IL-6, and TNF- α (tumor necrosis factor alpha). compared to other NPs, zinc oxide nanoparticles significantly reduce inflammation because of their high photocatalytic efficiency, affordability, and lack of toxicity. Therefore, our experimental research was carried out to assess the effectiveness of locally applied *Citrullus colocynthis* extract and ZnONPs loaded with *Citrullus Colocynthis* and ZnONPs to prevent dermal inflammation when a chemical disinfectant (glutaraldehyde 2%) was used.

Materials and methods

Plant materials

Dried *Citrullus Colocynthis* (fruit) raw samples were purchased from a medicinal herb dealer in Helwan, Cairo, Egypt.

Citrullus colocynthis (fruit) identification number 0E49E3V9U6.

Chemicals

1. *Glutaraldehyde* (2.2% solution) was obtained from Sigma Chemical Industries Company.

2. *Zinc oxide* purity: 99.5% w/w from the Nanotechnology Laboratory, Faculty of Postgraduate Studies for Advanced Sciences (PSAS), Beni-Suef University.

Preparation of *Citrullus Colocynthis* (C. C) extract

Fruits of C.C. extract were created, according to¹⁴ (Fig. 1).

Synthesis of Zinc Oxide nanoparticles (ZnONPs)

ZnONPs were created according to the protocol of¹⁵. Zinc oxide (ZnO) was dissolved in 100 ml of deionized water for 40 min and agitated in the solution until it was entirely dissolved. Sodium hydroxide solution was added progressively over 3 h with vigorous stirring until a white precipitate formed. The solution was recovered by centrifugation at 15,000 rpm for 10 min. The precipitate was then filtered and thoroughly washed with deionized water before being dried in an oven at 70°C for 48 h until completely dry.

Loading of *Citrullus Colocynthis* on ZnONPs (C.C-ZnONPs)

Citrullus colocynthis extract was loaded onto ZnONPs via the coprecipitation method of¹⁶. The supernatant was removed. The formed C.C-ZnONPs were dried at 60 °C for 4 h in an oven¹⁷. During the drying period, the Zn (OH)2 in the NPs fully converted into white ZnNP powder. ZnONPs and ZnONPs/C.C. will be characterized



Fig. 1. Preparation of *Citrullus Colocynthis* (C.C) Extract.

via ultraviolet visible (UV) spectroscopy, Fourier transform infrared (FTIR) spectroscopy, and transmission electron microscopy (TEM). (Fig. 2).

Experimental design

Forty healthy adult female mice, seven weeks old, were housed in eight rats per cage. The mice were obtained from the National Research Center in Dokki. All procedures for the maintenance and sacrifice (care and utilization) of the animals were performed. The empiricism processes were carried out in compliance with the ethical procedures and standards that were authorized by Beni-Suef University's local animal ethics committee (permission from Ethics Committee No.022–383). The mice were divided into five groups, each consisting of eight mice. Group 1 (control), no exposure to *GLU* or creams Group 2 (*GLU*) exposed *GLU* spray (an applied volume of 2.0 ml/kg/day) from¹⁸. Group 3 (*GLU* + *ZnONPs*) was exposed to both *GLU* spray and *ZnONP* cream. Group 4 (*GLU* + *C.C.* extract) was exposed to both *GLU* spray and *C.C.* cream. Group 5 (*GLU* + *CC-ZnONPs*) was exposed to both *GLU* spray and *C.C-ZnONP* cream. Throughout the trial, the animals in each group underwent daily examinations, and clinical indicators were monitored. At the beginning of the study, the hair of the mice was shaved on the dorsal skin surface, and then the mice were exposed to *GLU* spray (four groups) with the exception of the control group. The cream was applied 3 h after *GLU*. All mice were euthanized at the conclusion of the 30-day experiment by isoflurane inhalation (300 µL on gauze placed in a 500 ml container). The skin tissue was meticulously split into three sections according to the protocol of¹⁹.

Biochemical assays

The levels of glutathione (GSH) were estimated via an ELISA kit via sandwich-ELISA as described previously (Catalog No. SL0998Ra, Bioassay Technology Lab) and malondialdehyde (MDA) were measured via a spectrophotometric instrument to ascertain the degree of inflammation and the quantity of MDA chemical generated via the lipid peroxidation process. A commercial MDA ELISA Kit (MDA Assay Kit competitive ELISA) was used for this investigation (catalog no. ER1878, Bioassay Technology Lab).

Histopathological investigations of skin tissue

The dorsal skin of animals was freshly isolated, and the samples were fixed and stained with hematoxylin and eosin following the protocol of²⁰.

Relative mRNA expression analysis of *TNF-α*, *IL-1b*, *nfkβ1*, *ptgs2* and *tgf1b* via qRT-PCR

A Qiagen Mini-RNAeasy extraction kit was used to extract total RNA in accordance with the manufacturer's instructions. The RNA sample concentration and purity were assessed via spectrophotometry at wavelengths of 260 and 280 nm²¹. To remove any DNA contamination, DNase I treatment was performed. The Revert Aid First Strand cDNA Synthesis Kit from Thermo Scientific was subsequently used to generate complementary DNA (cDNA) in accordance with the manufacturer's instructions²².

The primer sets used for determining the target genes' mRNA levels were designed on the basis of *Mus musculus* sequences obtained from GenBank. The primer3 tool was utilized to create these primer sets. SYBR Green PCR Master Mix (catalog number: 4,309,155) and ABI Prism Step One from Thermo Scientific were used for real-time PCR measurement of relative gene expression. An instrument from Applied Biosystems was used, according to the manufacturer's guidelines. For each sample, two PCRs were run²³. The expression of the housekeeping gene beta-actin was used to standardize the expression levels of the target genes. The primer sets used for detecting the mRNA levels can be found in Table 1.

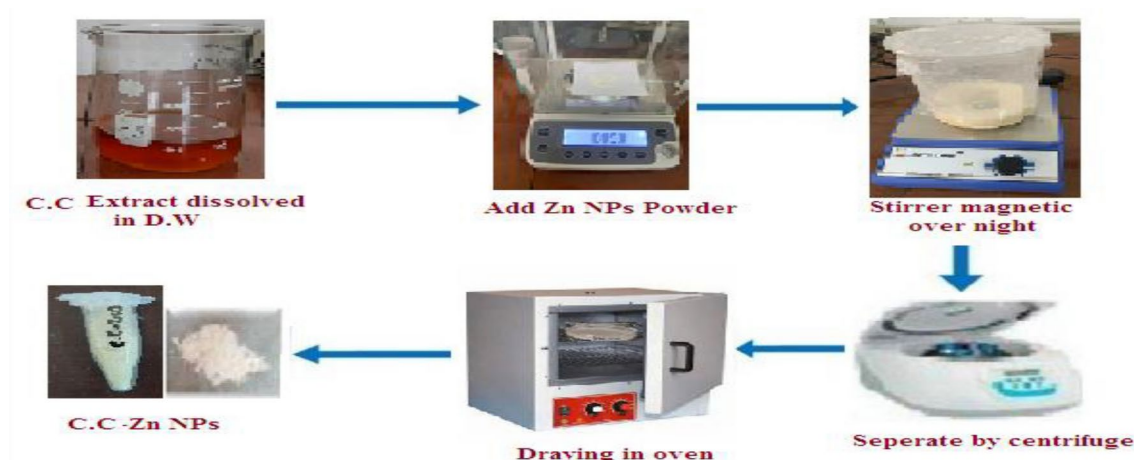


Fig. 2. Loading of Citrullus Colocynthis (C.C.) on ZnONPs.

Gene symbol	Gene description	Accession number	Primer Sequence	Amplicon size
<i>TNF-α</i>	Tumor necrosis factor	NM_013693.3	F: 5'- TGTAGCCACGTCGTAGCAA -3' R: 5'- ATAGCAAATCGGCTGACGGT -3'	216
<i>IL-1β</i>	Interleukin 1 beta	NM_008361.4	F: 5'- TGCCACCTTTTGACAGTGATG -3' R: 5'- AAGGTCCACGGGAAAGACAC -3'	220
<i>NFkb1</i>	nuclear factor kappa	AY521463.1	F: 5'- CCCTACGGAAGTGGGCAAAT -3' R: 5'- TGCAAATTTTGACCTGTGGGT -3'	241
<i>PTGS2</i>	prostaglandin-endoperoxide synthase 2	NM_011198.5	F: 5'- CATCCCCTTCCTGCGAAGTT -3' R: 5'- CATGGGAGTTGGGCAGTCAT -3'	178
<i>Tgf1b</i>	Transforming growth factor 1 beta	NM_011577.2	F: 5'- ACTGGAGTTGTACGCGAGTG -3' R: 5'- GGGGCTGATCCCGTTGATT -3'	123 111
<i>ACTB</i>	Beta actin	NM_007393.5	F: 5'- CCACCATGTACCCAGGCATT -3' R: 5'- AGGGTGTAACACGAGCTCA -3'	253

Table 1. Primer sequences of the target genes.

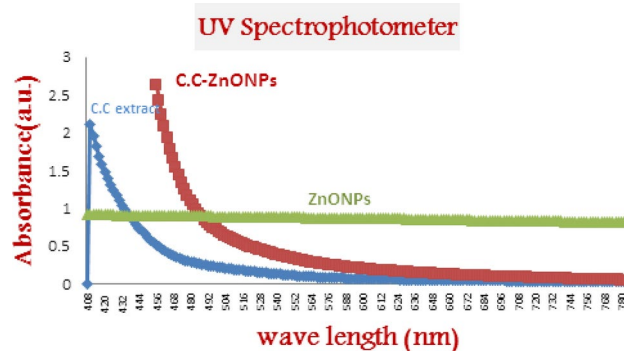


Fig. 3. UV-Vis spectra of ZnONPs, C.C extract, and C.C- ZnONPs.

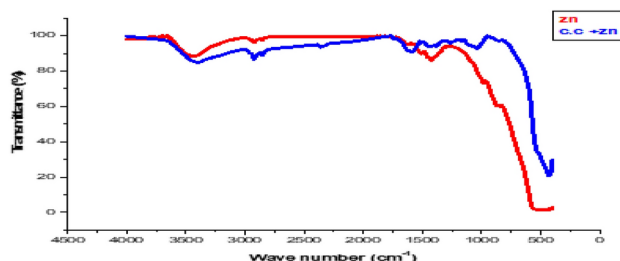


Fig. 4. FTIR spectra of zinc oxide nanoparticles and Cc – ZnONPs.

Statistical techniques

The statistical program at Social Science (IBM Corp., released 2017) was used to examine the data. Armonk, NY: IBM Corp.; IBM SPSS Statistics for Windows, Version 25.0. A P-value of less than 0.05 was considered significant.

Results

UV-VIS spectrophotometer

UV-VIS spectroscopy was employed to verify the *C.C.ZnONPs*, as shown in Fig. 3. The UV-VIS spectra showed a narrow peak at approximately 408 nm, which was attributed to adsorption of bimolecules. These absorptions are related to transitions, which correspond to the existence of polyphenolic substances found in the extract. For the *C.C.ZnONP* sample, a narrow peak with a 456 nm absorption band is characteristic of *ZnONPs* (Fig. 3).

Fourier transform infrared spectroscopy (FT-IR) analysis

The FTIR analysis of synthesized zinc oxide nanoparticles (Fig. 4) revealed that the peak, 1421.95 cm^{-1} , corresponded to the O-H groups of alcohol. The transmigration of the halo compounds (C-Cl or C-Br stretching) is indicated by the well-defined signal at 1623.19 cm^{-1} . The medium peak (1623.19 cm^{-1}) reflected the C-C=C symmetric stretching of the conjugated alkene groups (1-propane).

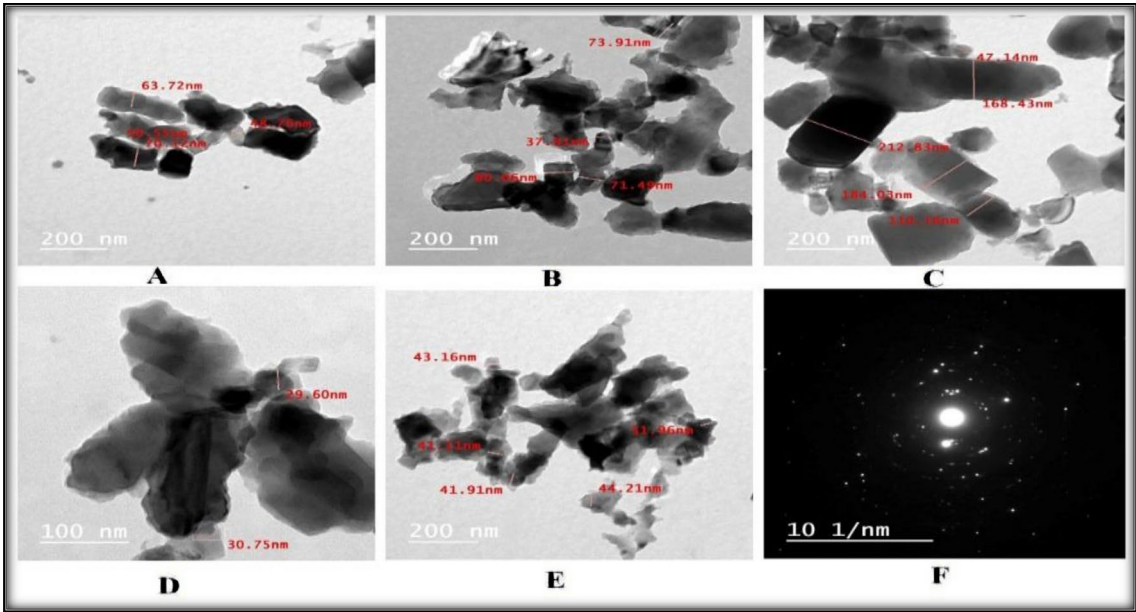


Fig. 5. TEM images of C.C-ZnONPs.

		Control	Glu	GLU + ZnONPs	GLU + C.C extract	GLU + CC-ZnONPs
GSH	Mean	167.200	46.1667	125.3000	103.6933	116.4000
	SD	0.10000 ^e	0.05774 ^a	0.10000 ^d	0.09609 ^b	0.26458 ^c
MDA	Mean	9.1500	41.8067	15.5667	23.5333	21.4667
	SD	0.1000 ^a	0.04041 ^e	0.15275 ^b	0.07234 ^d	0.05774 ^c

Table 2. Biological parameter in skin tissues among studied groups.

The transformation caused by the N = C = S stretching of the isothiocyanate group is responsible for the peak at 1508.60 cm⁻¹. Propyne (HC / C-CH₃) has an alkyne group present, and carbonic dioxide exhibits O = C = O stretching with a prominent peak at 2962.25 cm⁻¹. The presence of N-H stretching from primary and secondary amine groups is confirmed by the peak at 3444.08 cm⁻¹. The alcohol group is visible at 3444.08 cm⁻¹ due to O-H vibration. *Citrullus colocynthis* alkaloids, flavonoids, glycosides, phenols, saponins, tannins, and terpenoids are all present in this fruit extract. These phytochemicals contain compounds that increase the stability of the C.C.-ZnONP molecule, which was subjected to FTIR analysis (Fig. 6a), revealing that the ZnONP crystal structures produce wave lengths at different values and that some phytochemicals have been adsorbed onto the surfaces ZnONPs. At 3405.68 cm⁻¹ for -OH, 2922.81 cm⁻¹ for -C-H, and 2852.53 cm⁻¹ for -OH, the vibrations for -C≡C-, 1584.47 cm⁻¹ for -N-H, 1430.02 cm⁻¹ for -COOH, 1035.00 cm⁻¹ for -C-F, 1264.32 cm⁻¹ for C-O-C, 1169.99 cm⁻¹ for C-H, 464.79 cm⁻¹ for C-S, and 429.74 cm⁻¹ for C-Br, respectively. Figure 4.

Transmission electron microscopy (TEM) observations

Figure 5 shows the C.C-ZnONP flower-shaped TEM image. The TEM image displayed here demonstrates that the nanoparticles formed an assembly of asymmetric polygons (Fig. 5).

Biological assay

The levels of MDA and GSH in skin tissue varied significantly among the groups under study Table 2: Compared with that in the control group, the level of the antioxidant enzyme (GSH) in the GLU treated group significantly decreased (P ≤ 0.001), but this was also linked to a large increase (P < 0.001) in the quantity of MDA. Compared with those in the GLU exposure group, the level of the antioxidant enzyme (GSH) (P < 0.001) significantly increase, and the amount of MDA. (P ≤ 0.001) significantly decrease ZnONP-treated group. The *Citrullus colocynthis*-treated groups were compared with those in the GLU and control groups, there was a substantial increase in the GSH level (P < 0.001), which was correlated with a reduction (P ≤ 0.001) in the MDA concentration. The GSH level was significantly elevated (P < 0.001) in the C.C.-ZnONP-treated groups, which was correlated with lower MDA concentrations than those in the GLU and *Citrullus colocynthis* groups.

Histopathological findings

A shows hematoxylin and eosin (H&E) staining of skin tissues from the different groups. At 30 days after treatment (Fig. 6).

Inflammation was still severe in the *glutaraldehyde* groups, with a photomicrograph showing infiltration of the epidermis and dermis by a high number of inflammatory cells, mainly neutrophils and eosinophils (star), with congestion of dermal blood vessels (arrowhead) (Fig. 6B).

In addition, the healing process began in the groups treated with *GLU* + *ZnONPs* and the control groups as shown by photomicrographs of the normal histological structure of the epidermis and dermis Fig. 6(A, C).

Inflammation and allergies were low in areas of the skin in the *GLU* + *C.C* extract photomicrograph shows dermal infiltration by a low number of mononuclear inflammatory cells (arrow), as shown in Fig. 6(D).

The relative reduction in *GLU* + *CC-ZnONP* photomicrograph shows dermal infiltration by a low number of eosinophils (arrow) (Fig. 6E).

Relative mRNA expression analysis of $\text{TNF-}\alpha$, IL-1b, *nfk1*, *ptgs2* and *tgf1b* via qRT-PCR

QRT-PCR was employed. Compared with the control group.

GLU exposure resulted in a significant downregulation of *TGFB1* mRNA expression and an upregulation of $\text{TNF-}\alpha$, IL-1b, *nfk1*, and *ptgs2* mRNA expression.

Citrullus colocynthis extract cream alone downregulated $\text{TNF-}\alpha$, IL-1b, *NFkb1*, and *ptgs2* gene expression and upregulated *TGFB1* mRNA expression compared with that in the *GLU* group.

Compared with the *GLU* group, *C.C-ZnONP* cream treatment downregulated $\text{TNF-}\alpha$, IL-1b, *NFkb1*, and *ptgs2* gene expression and upregulated *TGFB1* mRNA expression levels.

Compared with the *GLU* group, the *ZnONP* cream alone significantly downregulated the $\text{TNF-}\alpha$, IL-1b, *NFkb1*, and *ptgs2* gene expression levels and upregulated in *TGFB1* mRNA expression levels.

Figure 7 displays the mRNA expression profiles.

Discussion

Health care workers (HCWs) are mostly exposed to chemical compounds such as disinfectants, sterilizers, and cleaners, leading to a spectrum of healthcare burdens, such as dermatological and respiratory side effects²⁴.

Glutaraldehyde is considered one of these chemical disinfectants, and can lead to dermatitis. Our study highlights the prevention of dermatitis and any side effects to the skin through the use of using medicinal plants. This material has great potential for therapeutic applications.

C. colocynthis one of the most, common biologically active chemicals, and has different phytoconstituents, including phenols and flavonoids²⁵. In the present study, our extract was generally rich in these compounds (alkynes, hydrocarbons, phenols, hydroxyl (OH), aromatics, carboxylic acids, nitro compounds, fatty acids,

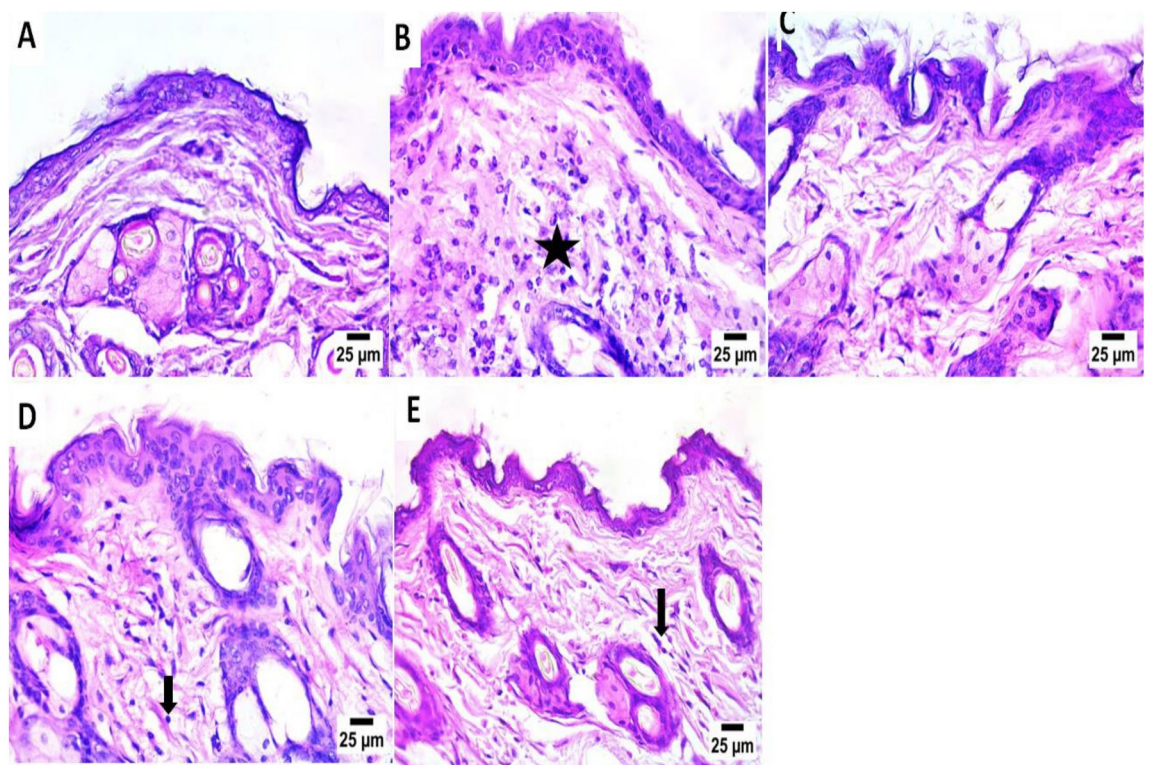


Fig. 6. Histological sections of skin from the mice Scale bar = 25 µm (H&E stain). (A) control, (B) *GLU*, (C) *GLU* + *ZnONPs* (D) *GLU* + *C.C* extract and (E) *GLU* + *CC-ZnONPs*.

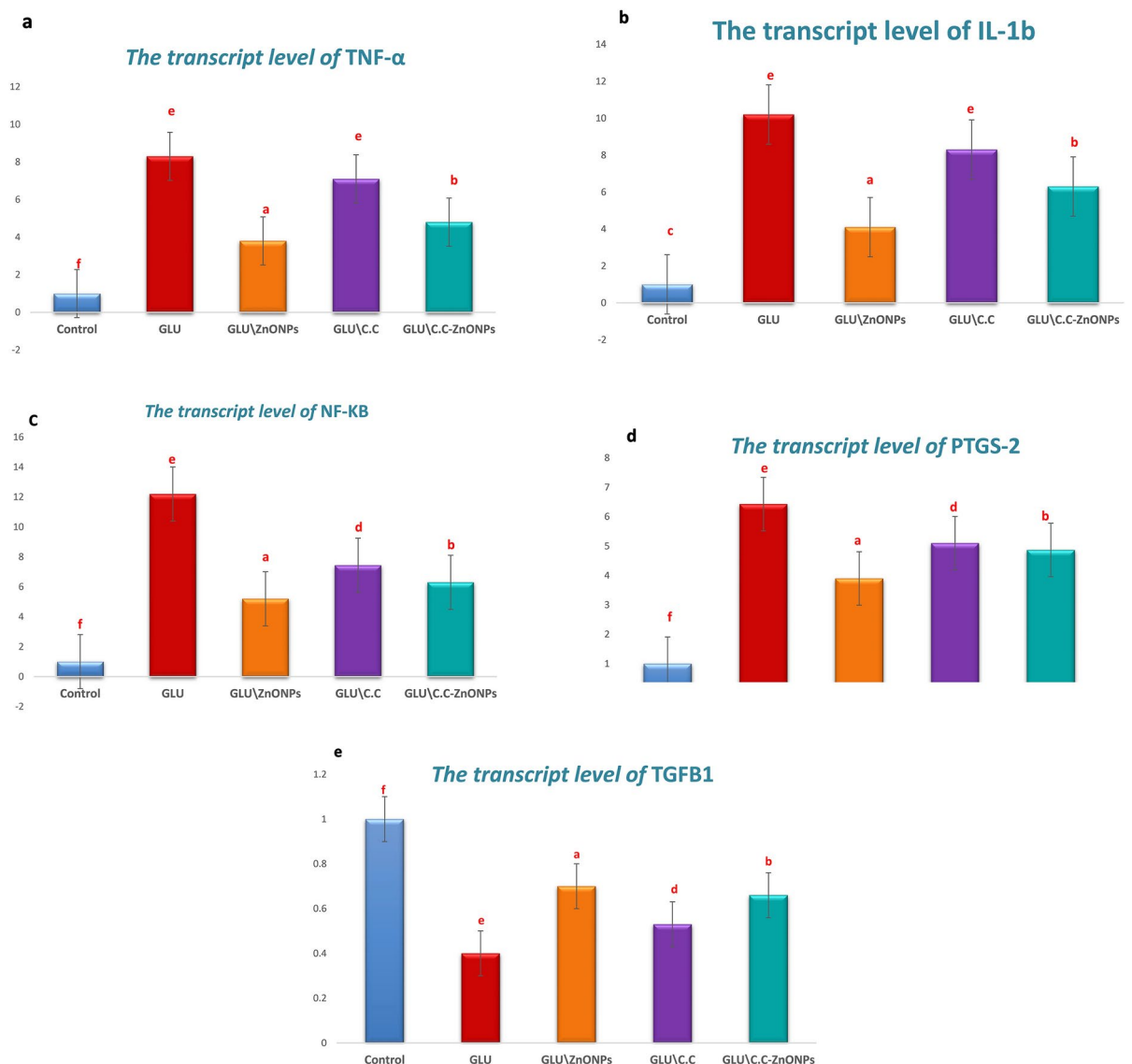


Fig. 7. The transcript levels of (a) *tnf-α*; (b) *il1b*; (c) *nfkβ*; (d) *ptgs-2*; (e) *tgfb1* genes from different groups. Values expressed as mean \pm SE, different superscripts indicate significant distinctions at $P < 0.05$ ($n = 7$).

aldehydes, alkyl alides, cycloalkanes, C–O–C, C–H, C–S, and C–Br), which were identified via the FT-IR analysis which determines the wavelength of the compound (Fig. 4). These results align with those of previous studies¹⁴. These compounds are most likely related to the antioxidant and anti-inflammatory properties of *Citrullus colocynthis*²⁶. The Loading of C.C. extract on the ZnONPs was studied via UV–Vis spectra, TEM, and FTIR spectroscopy to confirm the successful formation and stability of the CC-ZnONPs.

The characterization results of the UV–Vis spectra revealed characteristic absorption peaks at 408 nm (Fig. 3)²⁷. The TEM morphological analysis of CC-ZnONPs revealed that they were flower-shaped, and the image displayed here demonstrated that the nanoparticles formed an assembly of asymmetric polygons (Fig. 5)²⁸. FTIR spectroscopy confirmed the loading of the extract on the ZnONPs²⁹. Compared with the conventional methods, nanoparticle administration methods have many advantages (large surface area to volume ratio, greater efficacy, greater absorption)³⁰.

The current study shows the efficacy of the local application of *Citrullus colocynthis*—ZnONPs for the prevention and treatment of dermatitis induced by glutaraldehyde. Through different methods (biochemical, histological and molecular methods).

Biochemistry studies have revealed the expression of antioxidant (GSH) and oxidative damage related malondialdehyde (MDA), which are highly toxic compounds³¹.

Glutaraldehyde exposure results in significantly increased (MDA), and decreased GSH, indicating long-term stress exposure lead to oxidative stress, this result align with those of previous studies³².

Our results revealed that *Citrullus colocynthis* extract alone, a minimal decrease (MDA) in these results aligns with those of previous studies³³ and a minimal increase in the GSH content. These results align with those of

previous studies³⁴. Compared with *Citrullus colocynthis*—ZnONPs significantly increase GSH and decrease MDA, indicating that *Citrullus colocynthis*-ZnONPs are more effective and more protective, compare with *Citrullus colocynthis* alone.

In the ZnONP- treated group, the MDA content decreased³⁵, and there was an exponential increase in the GSH level, indicating low stress exposure and increased protection.

Histopathological examination revealed that *glutaraldehyde* resulted in infiltration of the epidermis and dermis by a high number of inflammatory cells, mainly neutrophils and eosinophils, with congestion of dermal blood vessels. These findings indicate severe inflammation, which align with the findings of previous studies³⁶.

Photomicrographs of ZnONPs revealed a normal histological structure of the epidermis and dermis where ZnONPs have the ability to modulate the degranulation process in neutrophils to protect skin tissue^{37,38}.

Photomicrographs of *Citrullus colocynthis* alone revealed that a dermal infiltration by a low number of mononuclear inflammatory cells, compared with that caused by *glutaraldehyde*.

A photomicrograph of *C. colocynthis*-ZnONPs revealed that a dermal infiltration by a low number of eosinophils, there is no mononuclear inflammatory cells, unlike that caused by *Citrullus colocynthis* alone. The anti-inflammatory effect of *C. colocynthis*-ZnONPs was greater than that of *Citrullus colocynthis* alone. These results align with those of previous studies³⁹. These NPs improve drug delivery and increase the bioavailability of phytoconstituents adsorbed on them because of their small size, large surface area, and high adsorption of bioactive phytochemicals from *Citrullus colocynthis*⁴⁰.

Molecular examination revealed that *glutaraldehyde* exposure significantly upregulated TNF- α , IL-1b, NFkb 1, and ptgs2 mRNA expression, and downregulated TGFBI, these results are consistent with those of⁴¹. This leads to the increase in immune cells (serotonin, histamine, and prostaglandin) therefore, the ability of *glutaraldehyde* to induce dermatitis.

Citrullus colocynthis extract alone downregulated TNF- α , IL1b, NFkb 1, and ptgs2 gene expression and upregulated TGFBI mRNA expression. These results align with those of previous studies^{42,43}. *Citrullus colocynthis* inhibits the activity of Cox2 and the production of prostaglandins thus reducing inflammation and pain⁴⁴.

C. colocynthis- ZnONPs downregulated TNF- α , IL1b, NFkb 1, and ptgs2 gene expression and upregulated TGFBI (anti-inflammatory mediator) to a greater extent than did *Citrullus colocynthis* only, indicating that *C. colocynthis*- ZnONPs are more effective and more protective.

ZnONPs significantly upregulated TGFBI mRNA expression, and these results align with those of previous studies⁴⁵ and downregulated TNF- α , IL1b, NFkb 1, and ptgs2 gene expression through nuclear factor- κ B (NF- κ B) pathway inhibition⁴⁶, and the inhibition of the degranulation of mast cells⁴⁷. Which prevents the release of serotonin and histamine. Our results revealed that the anti-inflammatory impact of the ZnONP group was greater than that of the *C. C*-ZnONPs group, which has a much more potent anti-inflammatory effect than the *C. colocynthis* -ZnONPs, which acts through different pathways (prostaglandin and kinin-like pathways), and these findings need further study.

Conclusions

Local application of natural products loaded with nanoparticles (*Citrullus colocynthis*-ZnONPs) can mitigate *glutaraldehyde*-induced dermatitis by decreasing inflammatory markers and oxidative stress.

Data availability

All the research data will be available on request from the corresponding author.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M.A.I.

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