European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: Applied Website:
https://farmclin.com/

Histopathological and Immunohistochemical Characterization of T-Cell Activation Following κ-CGN Treatment in S. typhimurium-Infected Rats

Afrah H. Alshammari[1], Zainab J Mohammed Jawad[1]
[1]Department of Pathology and Poultry Diseases, College of Veterinary Medicine, University of Baghdad. Baghdad. Iraq.
Email: afrah.dishar2307p@covm.uobaghdad.edu.iq
https://orcid.org/0009-0000-1955-4183

ABSTRACT

This study investigates the spatial distribution and activation patterns of $CD4^+$ and $CD8^+$ T lymphocytes as central regulators of adaptive immune responses during Salmonella Typhimurium infection in a rat model. Infection was confirmed through culture on XLD agar. κ-CGN, a widely used food additive with emerging immunomodulatory properties, was characterized FTIR spectroscopy. The primary objective of this work was to evaluate the dual biological role of κ-CGN in modulating pathological alterations in colonic tissue during bacterial infection. The study further aimed to determine the immunological and therapeutic window of low-dose κ-CGN oral administration and assess its potential as a safe modulator of host immune responses. Findings indicate that κ-CGN influences T-cell–mediated immunity, where low concentrations are associated with regulated immune activation and preservation of colonic tissue integrity, suggesting a dose-dependent immunomodulatory effect.

KEYWORDS: κ-CGN, Immunomodulatory, S. Typhimurium, T lymphocytes.

How to Cite: Afrah H. Alshammari, Zainab J Mohammed Jawad, (2026) Histopathological and Immunohistochemical Characterization of T-Cell Activation Following κ-CGN Treatment in S. typhimurium-Infected Rats., European Journal of Clinical Pharmacy, Vol.8, No.1, pp. 2847-2856

INTRODUCTION

κ-carrageenan (κ-CGN) is a naturally occurring sulfated polysaccharide derived from red seaweeds, widely applied in food and cosmetic industries due to its gelling, stabilizing, and thickening properties (Bono et al., 2025; Ghasempour et al., 2025). Its favorable physicochemical features, including high viscosity, thermal reversibility, and biocompatibility, support its safe use as a food additive, with toxicological evidence indicating no significant adverse effects under normal consumption levels (Wang et al., 2023). In addition to its technological value, κ-CGN exhibits notable biological activities such as antibacterial and immunomodulatory effects, enabling its application in biomedical fields including drug delivery and wound healing (Huang et al., 2024; Amin et al., 2020; Jafari et al., 2022; Jaiswal et al., 2019). Importantly, native κ-CGN differs from its degraded form, which is not approved for food use; current evidence supports that native κ-CGN does not induce significant inflammation under physiological conditions (Kimilu et al., 2024). Despite these advantages, limited studies have investigated the immunopathological impact of pre-exposure to κ-CGN during bacterial infections, particularly with Salmonella Typhimurium, a major foodborne pathogen widely used to model chronic enteric inflammation, immune dysregulation, and systemic dissemination (Hanoun and Al-Samrraae, 2019; Huang et al., 2020; Wei et al., 2021; Lamichhane et al., 2024). T lymphocytes, especially $CD4^+$ and $CD8^+$ subsets, play a central role in adaptive immunity, developing in the thymus and differentiating into effector and memory cells essential for immune defense and long-term protection (Obeagu & Obeagu, 2024; Sun et al., 2023).

MATERIALS AND METHODS

Ethics

Approval for this study was granted by the Ethics Committee of University Baghdad (**No. P.G.\666 dated on March 17/2025**), and the research was conducted at the pathology Laboratory, Faculty of Veterinary Medicine, University Baghdad.

Experimental animals

The study was conducted on 20 healthy adults male Wistar albino rats, (200g), and (8-9) weeks of age were procured from a private farm. The rats were maintained at 20 ± 5 ºC with a 12-h light/dark cycle and provided with a standard diet according to **Ahmed and Mohammed (2022) and Abbasa and Jawad (2023).** All the rats were kept under acclimatization for 14 days prior to grouping and initiation of experiment in the animals housing facility of the College of Veterinary Medicine/ Baghdad University.

As shown in Table (1): Experimental groups and treatment. The animals were randomly divided into four groups, each containing 5 animals.

NO.	Treatment
G1:	Negative control (vehicle).
G2:	Positive group rats received an oral challenge with *S. typhimurium* by a single dose.
G3:	κ-CGN **75mg/kg** BW (orally, once daily).
G4:	κ-CGN **(75mg/kg** BW**)** orally, once daily at 30,60 and 100 days preinfected with *S. Typhimurium,* sacrificed after 7 days.

Preparation of κ -carrageenan (κ-CGN).

κ-carrageenan (κ-CGN) was obtained from MedChemExpress and prepared by dissolving the powder in distilled water, followed by magnetic stirring at 60–70 °C for 30 minutes. The acceptable daily intake (ADI) of carrageenan (75 mg/kg) body weight, as reported in previous studies. During the experimental feeding period, the administered gavage dose was continuously adjusted according to variations in the rats' body weight to ensure accurate dosing according to **Sutrisni *et al.* (2019**) and **Shang *et al*. (2025).**

Preparation of Salmonella typhimurium suspension

Salmonella typhimurium was cultured on XLD agar using the streak-plate technique and then cultured at 37°C for 18–24 h, after which the colonies were harvested with a sterile disposable loop, resuspended in phosphate-buffered saline, homogenized by magnetic stirring **(Al–Rubaye and Al-doori, 2023; Nkamkeu *et al*., 2025).**

Animal treatment and sampling

Male Wistar rats were assigned to groups and orally administered G1: distilled water and G3: κ-CGN for 100 days. While, on day 1, G2*: S. typhimurium* infected by stomach tube orally as a single dose. But the G4 received oral administration of κ-CGN was given to rats at 75 mg/kg for different pre-challenge durations at 30,60 and 100 days. After each period the animals were challenged with *S typhimurium* a single dose to induce infection, then euthanized 7 days later. Animals were anesthetized, sacrificed and tissue fixed for histology **(Atshan and Zalzala, 2023; Abdul-Azeez and Mutlag, 2024)** and immunohistochemistry (IHC). **(El-Roghy and Eissa, 2026).**

Histopathology and immunohistochemistry

Colon specimens underwent paraffin embedding, were sliced into 6–7 μm sections, and then stained with hematoxylin and eosin (**Khalaf and Salih, 2023; AL-Kurdy and Kazaal, 2024).** For IHC, sections were stained for CD4+ and $CD8^+$ T-cells, depended on biovision Kit was used **(Aldali, *et al*., 2024; Bilash *et al*., 2026).**

RESULTS AND DISSCUSSION:

Salmonella colonies exhibited characteristic morphology on selective media: small, smooth, red colonies with black centers on XLD agar. As appeared in Fig. (1).

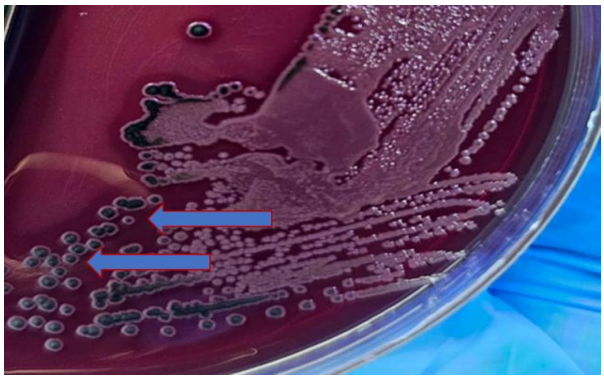


Fig (1): S. Typhimurium colonies on XLD agar.

FTIR analysis identified characteristic absorption bands (400-4000 **cm^{-1}**). confirming the molecular structure of κ-carrageenan.

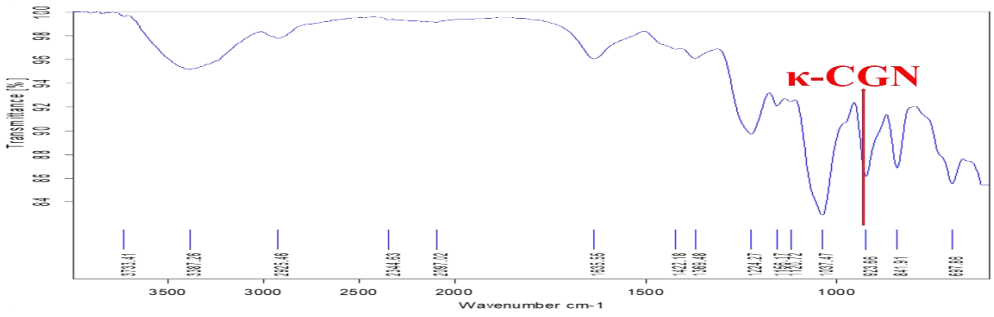


Fig (2) FTIR spectra powder sample of pure κ-CGN.

Table (2). The main characteristic peaks of FTIR analysis.

NO.	Wavenumber (cm^{-1})	Vibrational assignments	functional group
1	3733.41	Free OH stretching	Hydroxyl-unbound group in polysaccharides (Weak)
2	3387.26	Broad OH stretching	hydrogen-bonded hydroxyls in polysaccharides
3	2925.46	CH stretching	Asymmetric stretching of CH_2 &CH_3 groups.
4	1635.55	H–O–H bending, bound water	Absorbed moisture in the sample
5	1224.27	S=O stretching of sulfate ester groups.	($–OSO_3^-$), Strongly present in sulfated polysaccharides.
6	923.66	3,6-Anhydrogalactose	Unique fingerprint for κ -CGN

Histopathology and immunohistochemistry

The main pathological characteristic of the tissue section through 30,60 and 100 days from the pre- and post-infected rat with *S. typhimurium* (10^8 cfu/ml). The histopathological figures of the colon are in Fig. 3,4, 5, 6, 7 and 8. IHC is in Fig. 9,10,11, 12 (A&B) and 13 (A&B). While, the colon tissue in the other groups through 30,60, and 100 days is normal.

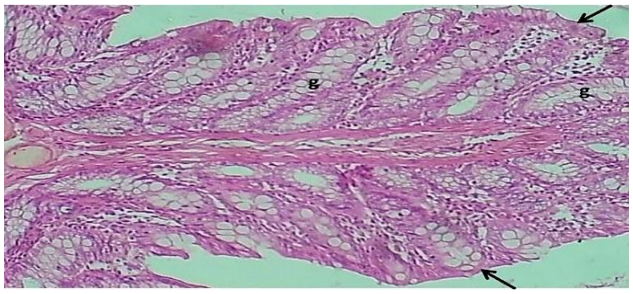


Figure 3: section of colon (Control) shows normal colon mucosal folds with normal tubular glands (g) & normal lining cells (arrows).H&E.100x

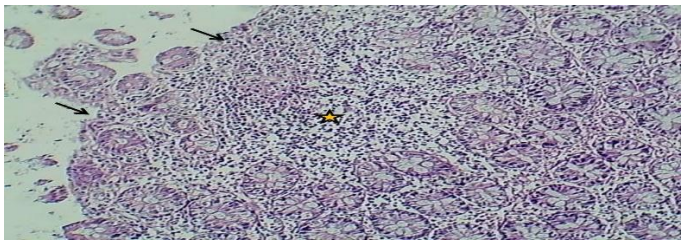


Figure 4: section of colon (G2-30days) shows severe colitis with marked colonic mucosal polyp associated with severe mucosal inflammatory infiltration with edema (Asterisk) and colonic mucosal ulcer (arrows) .H&E.100x

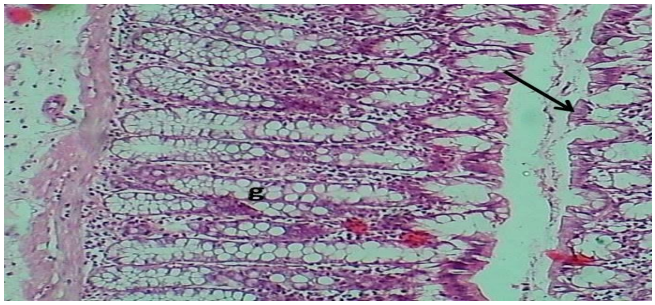


Figure 5: section of colon (G3-30 days) shows normal colon mucosal folds with normal tubular glands (g) and normal lining cells (arrows).H&E.100x

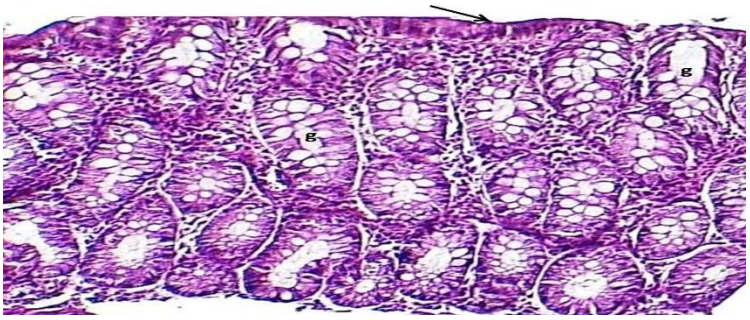


Figure 6: section of colon (G4-30 days) shows normal lining cells (Arrow) and normal tubular glands (g).H&E.100x

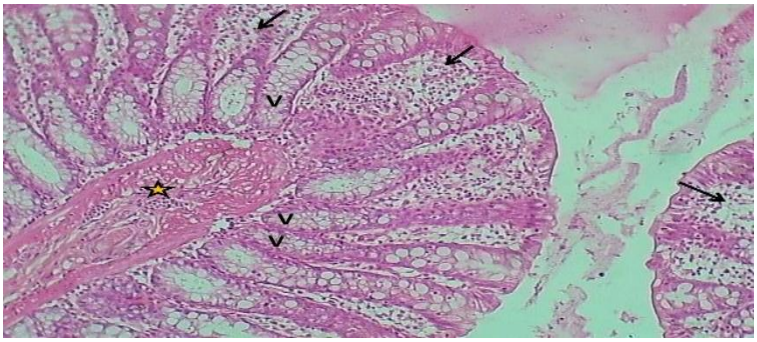


Figure 7: section of colon (G2-60days) shows colitis with marked mucosal thickening associated with inflammatory infiltration with edema within lamina propria (Asterisk), microvascular degeneration of tubular glands goblets cells (V) & submucosal congestion with infiltration of leukocytes .H&E.100x

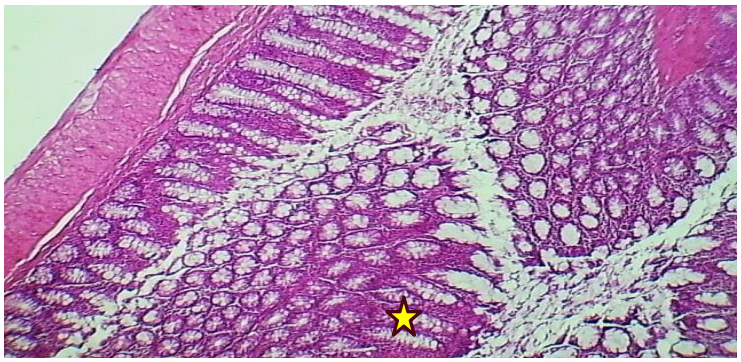


Figure 8: section of colon (G2-100days) shows inflammatory colonic polys with infiltration with edema within lamina propria.H&E.100x

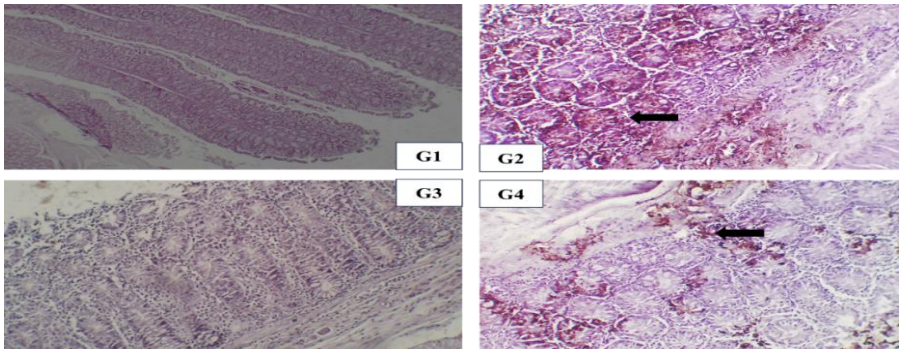


Figure 9: Immunohistochemical staining of colon showing lymphocyte aggregation Blak arrows show CD4+ positive staining (brown) in 30 days.

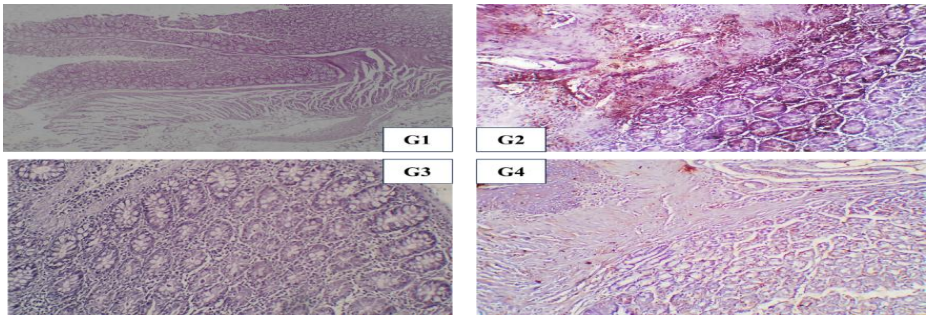


Figure 10: Immunohistochemical staining of colon showing CD8+ lymphocyte aggregation positive staining (brown color) in 30 days.

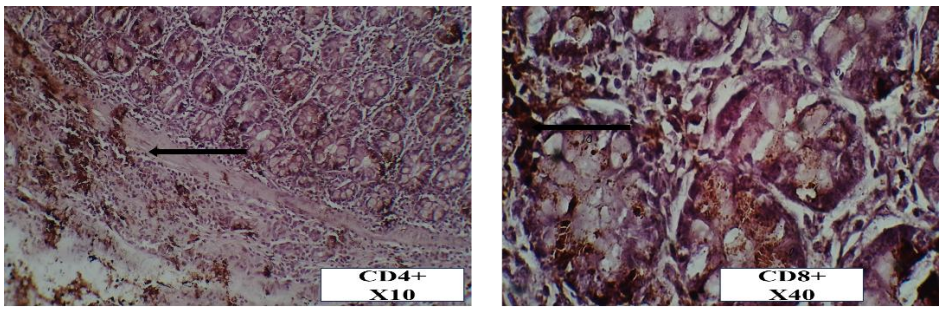


Figure 10: Immunohistochemical staining of colon showing CD4+ and CD8+ lymphocyte aggregation positive staining (brown color) in G2-60 days.

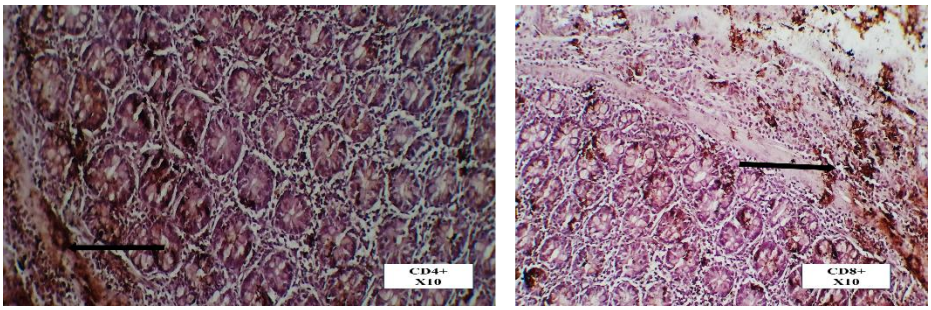


Figure11: Immunohistochemical staining of colon showing CD4+ and CD8+ lymphocyte aggregation positive staining (brown color) in G2-100 days.

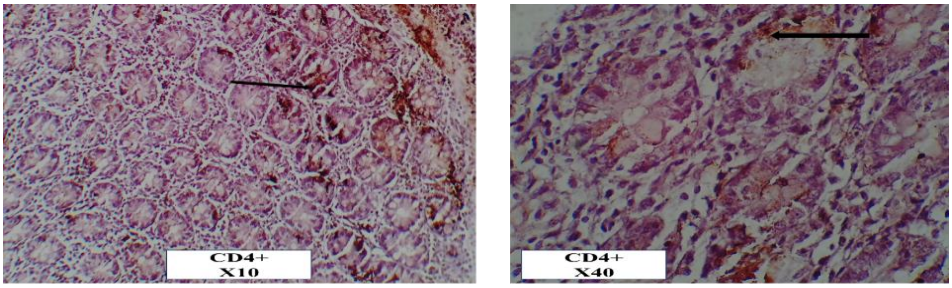


Figure 12 A: Immunohistochemical staining of CD4+ of colon showing lymphocyte aggregation (black arrow), (G4-60 days).

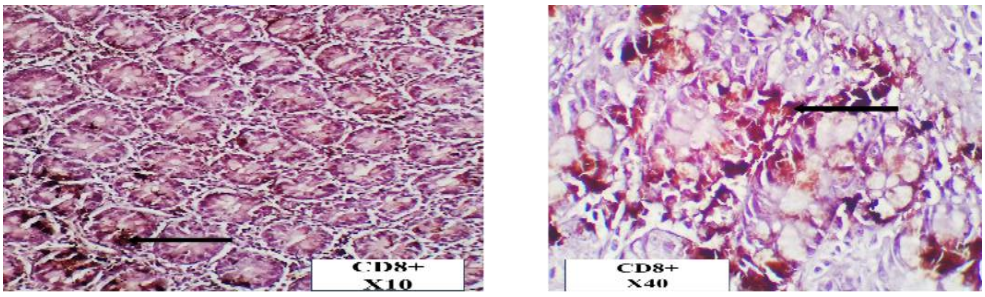


Figure 12 B: Immunohistochemical staining of CD8+ of colon showing lymphocyte aggregation (black arrow) (G4-60 days).

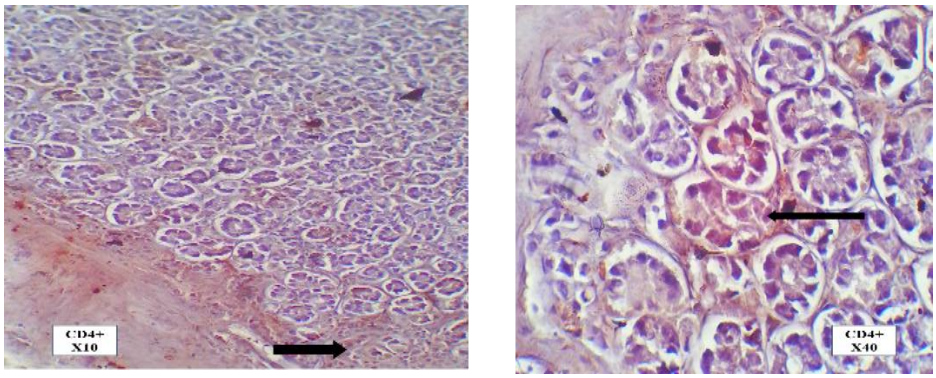


Figure 13 A: Immunohistochemical staining of CD4+ of colon showing lymphocyte aggregation (black arrow) (G5-100 days).

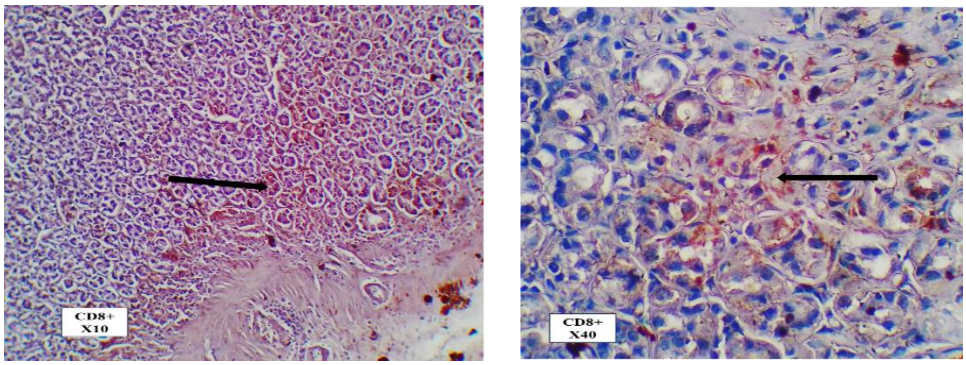
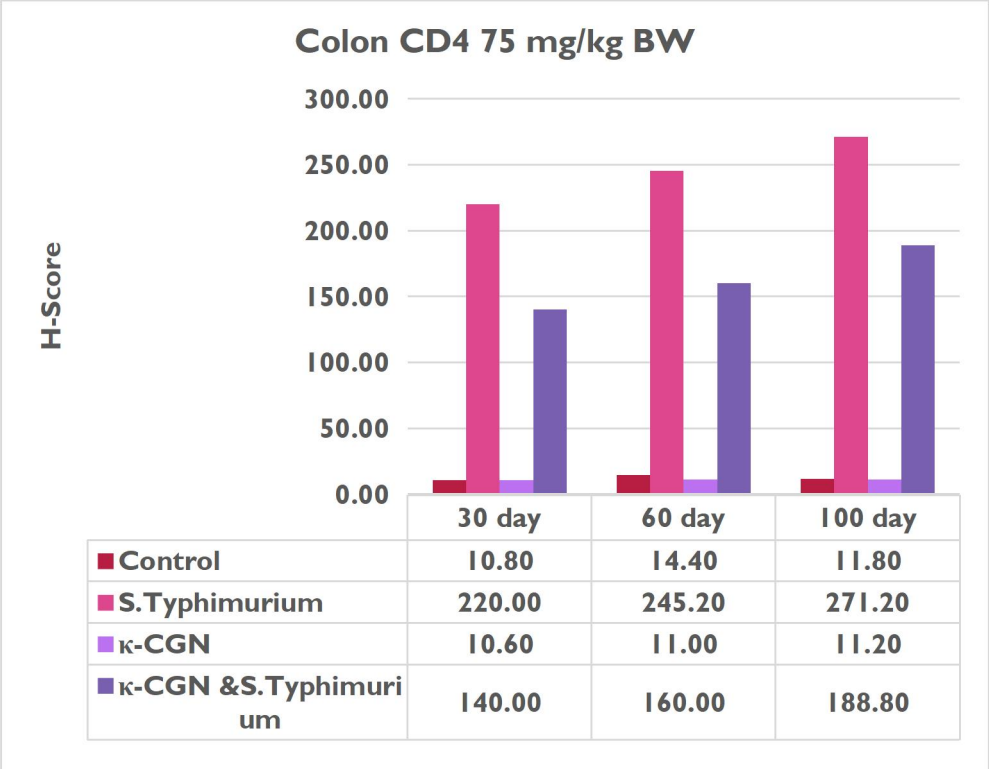


Figure 13B: Immunohistochemical staining of CD8+ of colon showing lymphocyte aggregation (black arrow) (G4-100 days).

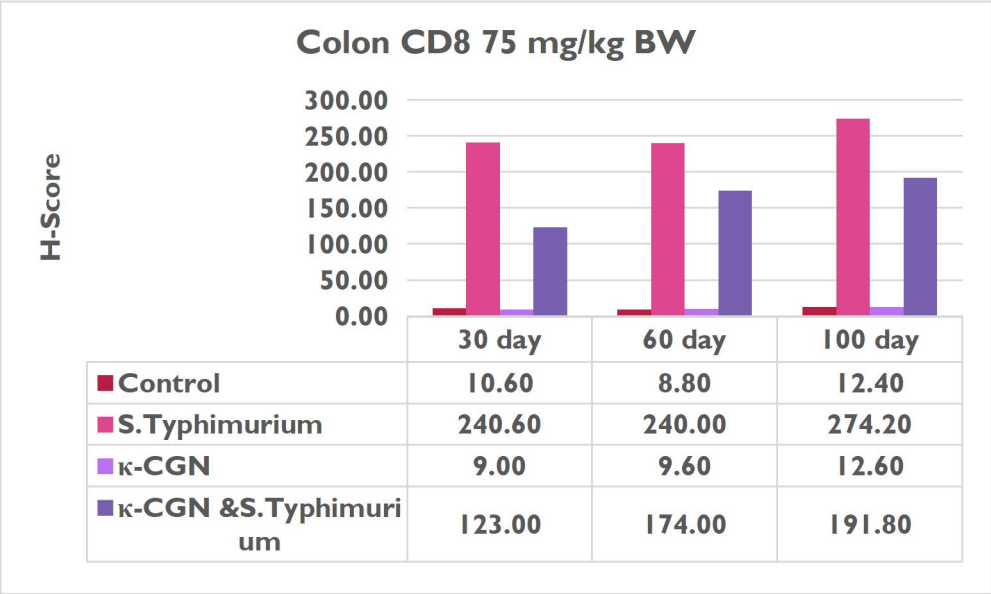
Scoring of marker deposition:

In the rat model, the CD4+ and CD8+ scored remarkably varying degrees of susceptibility to infection. Immunohistochemical staining demonstrated that their CD4+ and CD8+ increased substantially in the infected group with *S. typhimurium* (G2= 271.20 -100days in CD4+ and 274.20 in CD8+) compared to those in the non-infected groups, but the inhibition of *S. typhimurium* colonization by κ-carrageenan is decreased significantly in the G4. On the other hand, the treated group (G3) showed a marked increase in the number of CD4+ and CD8+ positively stained cells compared to the control group, with moderate to strong staining intensity with a statistically significant difference compared to the control group ($p < 0.05$). As appeared in Fig. (14 and 15).



	30 day	60 day	100 day
Control	10.80	14.40	11.80
S.Typhimurium	220.00	245.20	271.20
κ-CGN	10.60	11.00	11.20
κ-CGN &S.Typhimurium	140.00	160.00	188.80

Figure (14) shows results of scoring immunohistochemistry staining on colon tissue specimens (CD4+).



	30 day	60 day	100 day
Control	10.60	8.80	12.40
S.Typhimurium	240.60	240.00	274.20
κ-CGN	9.00	9.60	12.60
κ-CGN &S.Typhimurium	123.00	174.00	191.80

Figure (15) shows results of scoring immunohistochemistry staining on colon tissue specimens (CD8+).

DISCUSSION

Local Iraqi studies and standard reagent/medium datasheets explain the same chemical basis and use these traits as primary differentiating features in routine isolation. The black center observes on XLD is the classical visual marker of Hydrogen sulfide (H_2S) production. Salmonella reduces thiosulfate or similar sulfur compounds via thiosulfate reductase, producing sulfide that reacts with ferric salts (ferric ammonium citrate / ferric citrate) in the medium and precipitates as a black iron sulfide core in colonies. This reaction explains the black-centered, small, round colonies typical of Salmonella on XLD agar our results are in consistent with (Al-Shafee and Abdulwahid, 2024; Marza et al., 2025).

The molecular k-carrageenan is determined via FTIR analysis, and the corresponding spectrum is shown in Fig. (1). The characteristic vibrational absorption bands of pure k-carrageenan membrane at 3733.41, 3387.26, 2925.46, 1635.55,1224.27, 923.66, (cm^{-1}); correspond to O–H stretching (free / Hydrogen-bonded), C–H stretching, atmospheric CO_2 stretching, H–O–H bending (bound water), symmetrical band of COO^- Stretching, C–H bending group of stretching, sulfate stretching of S=O, C–O–C of glycosidic linkage C–O stretching, 3,6-Anhydrogalactose, C–O–S stretching of Gal-4-sulfate, S–O bend skeletal vibrations, our results are in consistent with (Perumal & Selvin, 2020).

The systemic pathological alterations observed in the intestine of rats infected with Salmonella Typhimurium reflect the pathogen's well-documented ability to induce both localized gastrointestinal damage and systemic immune responses. At 30, 60, and 100 days pre- and post-infection, the presence of severe ulcerative colitis characterized by mucosal ulceration, glandular necrosis, and dense inflammatory infiltration is indicative of the acute phase of infection. During this stage, S. Typhimurium actively invades epithelial cells and triggers strong inflammatory signaling pathways, leading to epithelial destruction and disruption of intestinal integrity. Recent studies have shown that bacterial virulence factors stimulate cytokine release and neutrophil recruitment, resulting in extensive mucosal injury and ulcer formation (Han et al., 2024; Cui et al., 2025). The current study investigated the effects of κ-carrageenan on T-cell–mediated immune responses in rats experimentally infected with Salmonella Typhimurium. The findings demonstrate distinct patterns of $CD4^+$ and $CD8^+$ T-cell activation in response to infection and immunomodulatory treatment. Consistent with (Khan et al., 2026) CD4+ T-cells represent a subgroup of lymphocytes vital for immune defense. During Salmonella infection, these cells contribute to enhancing host defense, leading to an elevation in CD4+ T-cell levels. These results imply that κ-carrageenan acts as a supportive immunomodulatory agent, enhancing T-cell–mediated clearance of S. Typhimurium without exacerbating tissue injury. The differential localization of T-cell subsets in the colon underscores the integrated nature of systemic and mucosal immunity. The lamina propria serves as a critical effector site for antigen-experienced T cells. The combined pattern observed in infected and κ-carrageenan-treated rats suggests that the compound supports effective coordination of local and systemic immune responses, optimizing pathogen control while preventing immunopathology Consistent with (Hassan, et al., 2026; Latimer et al., 2025).

CONCLUSION

Overall, κ-CGN shows promise as a therapeutic immunomodulator, capable of reducing pathological damage during bacterial infection while preserving essential immune functions, and κ-carrageenan appears relatively safe under typical exposure conditions, though its safety may vary depending on dose, molecular characteristics, and dietary context.

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