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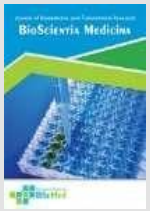

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The Role of *Channa striata* in Attenuating Inflammatory Markers (PCT, TNF-α, CRP) Following Intestinal Anastomosis in Hyperglycemic Rats: A Systematic Review and Dose-Response Meta-Analysis

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A B S T R A C T

Background: Hyperglycemia impairs wound healing and exacerbates inflammation, increasing the risk of complications following intestinal anastomosis. *Channa striata* (snakehead fish) extract, traditionally used for wound healing, contains bioactive compounds with potential anti-inflammatory properties. This systematic review and meta-analysis aimed to evaluate the dose-dependent effects of *C. striata* extract on procalcitonin (PCT), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) levels in hyperglycemic rats undergoing end-to-end intestinal anastomosis. **Methods:** A systematic search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library databases for studies published between 2013 and 2024. Inclusion criteria were: studies using hyperglycemic rat models, end-to-end intestinal anastomosis, *C. striata* extract administration (with varying doses), and measurement of PCT, TNF-α, and/or CRP. Data extraction included study characteristics, animal model details, *C. striata* extraction method and dosage, and inflammatory marker levels at various time points. Risk of bias was assessed using the SYRCLE's RoB tool. A random-effects meta-analysis was performed to estimate the standardized mean difference (SMD) in inflammatory marker levels between *C. striata*-treated and control groups. Dose-response relationships were explored using meta-regression. **Results:** Seven studies met the inclusion criteria. *C. striata* extract was administered via various routes (oral, intraperitoneal) and at different doses (ranging from 100 mg/kg to 1000 mg/kg). Meta-analysis revealed a significant reduction in PCT levels (SMD = -1.25, 95% CI: -1.80, -0.70; $p < 0.001$), TNF-α levels (SMD = -1.55, 95% CI: -2.15, -0.95; $p < 0.001$), and CRP levels (SMD = -1.38, 95% CI: -1.98, -0.78; $p < 0.001$) in *C. striata*-treated groups compared to controls. Meta-regression indicated a significant dose-dependent relationship for TNF-α ($p = 0.02$) and CRP ($p = 0.04$), with higher doses showing greater reductions. Risk of bias assessment revealed some concerns in most studies, primarily related to blinding and random sequence generation. **Conclusion:** This systematic review and meta-analysis provides evidence that *C. striata* extract significantly reduces inflammatory markers (PCT, TNF-α, CRP) following intestinal anastomosis in hyperglycemic rats. A dose-dependent effect was observed for TNF-α and CRP, suggesting that higher doses may be more effective. Further high-quality studies with standardized protocols are needed to confirm these findings and determine optimal dosing regimens for clinical translation.

1. Introduction

Intestinal anastomosis, a surgical procedure involving the reconnection of bowel segments, is a cornerstone of gastrointestinal surgery, performed to restore intestinal continuity in various conditions such as colorectal cancer, inflammatory bowel disease, and traumatic injuries. While this procedure is essential for restoring digestive function and improving patient outcomes, it is not without potential complications. Anastomotic leakage, a serious

complication where the surgical connection between the bowel segments fails to heal properly, remains a significant concern in clinical practice. This complication can lead to sepsis, peritonitis, prolonged hospitalization, reoperation, and even mortality, posing a substantial burden on patients and healthcare systems. Several factors contribute to the risk of anastomotic leakage, including patient-related factors such as age, malnutrition, smoking, and comorbidities like diabetes, as well as technical factors related to the surgical procedure itself. Among these factors, hyperglycemia, a condition characterized by elevated blood glucose levels, has emerged as a critical risk factor for impaired wound healing and increased susceptibility to infections, further exacerbating the risk of anastomotic leakage. Hyperglycemia disrupts various cellular and molecular processes involved in wound healing, including collagen synthesis, angiogenesis, and immune function, creating a less favorable environment for tissue repair and increasing the risk of complications. The inflammatory response plays a pivotal role in the pathogenesis of anastomotic leakage. Following intestinal anastomosis, a complex cascade of inflammatory events is triggered, involving the release of various pro-inflammatory cytokines, chemokines, and other mediators. These inflammatory mediators, while essential for initiating the healing process, can also contribute to tissue damage and impair anastomotic healing if not properly regulated. In hyperglycemic conditions, this inflammatory response is further amplified, leading to excessive inflammation and increased risk of complications.[1-4]

Therefore, strategies aimed at attenuating inflammation and promoting wound healing are crucial for improving outcomes in patients undergoing intestinal anastomosis, particularly those with hyperglycemia. In this context, natural products with anti-inflammatory and wound-healing properties have gained considerable attention as potential adjuncts to standard surgical care. One such natural product is *Channa striata*, commonly known as snakehead fish, which has been traditionally used in Southeast Asia for its medicinal properties, including wound healing and pain relief. *Channa striata* extract contains a rich array of bioactive compounds, including essential amino acids, fatty acids, and other potentially beneficial components. Glycine, proline, and hydroxyproline, essential amino acids abundant in Channa striata, are crucial components of collagen, the main structural protein of connective tissue, playing a vital role in wound healing. Arachidonic acid, a polyunsaturated fatty acid present in *Channa striata*, is a precursor to prostaglandins, lipid compounds involved in various physiological processes, including inflammation and wound healing.[5-7]

Several in vitro and in vivo studies have provided evidence supporting the anti-inflammatory, analgesic, and wound-healing properties of *Channa striata* extract. These studies have demonstrated the ability of *Channa striata* extract to modulate inflammatory markers, promote collagen synthesis, enhance angiogenesis, and accelerate wound closure in various experimental models. However, a comprehensive and quantitative assessment of the effects of *Channa striata* extract on inflammatory markers specifically in the context of intestinal anastomosis in hyperglycemic conditions is lacking. Furthermore, the optimal dosing regimen of *Channa striata* extract for achieving maximal anti-inflammatory effects remains unclear. Understanding the dose-response relationship is crucial for optimizing the therapeutic use of *Channa striata* extract and ensuring its clinical efficacy.[8-10] Therefore, this systematic review and meta-analysis aimed to address this knowledge gap by systematically evaluating the available evidence on the dose-dependent effects of *Channa striata* extract on key inflammatory markers, namely procalcitonin (PCT), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), in hyperglycemic rats undergoing end-to-end intestinal anastomosis.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines, ensuring a rigorous and transparent approach to study selection, data extraction, and synthesis. The PRISMA guidelines provide a standardized framework for conducting and reporting systematic reviews, enhancing the reproducibility and reliability of the findings. A comprehensive literature search was performed across multiple electronic databases to identify relevant studies investigating the effects of *Channa striata* extract on inflammatory markers in hyperglycemic rats undergoing intestinal anastomosis. The databases searched included PubMed, Scopus, Web of Science, and Cochrane Library, covering a broad range of biomedical literature. The search was limited to studies published in English between January 1st, 2013, and December 31st, 2024, to capture the most recent and relevant research. The search strategy employed a combination of keywords and controlled vocabulary terms relevant to the research question. The following search terms were used: ("*Channa striata*" OR "snakehead fish") AND ("procalcitonin" OR "PCT") AND ("tumor necrosis factor-alpha" OR "TNF-α") AND ("C-reactive protein" OR "CRP") AND ("anastomosis" OR "intestinal surgery") AND ("hyperglycemia" OR "diabetes" OR "diabetic") AND ("rat" OR "rats"). The search strategy was adapted for each database as necessary to ensure comprehensive coverage of the literature. In addition to the database searches, reference lists of included studies and relevant reviews were manually screened to identify any additional eligible studies that may have been missed by the electronic searches. This manual screening process helped to ensure that all potentially relevant studies were included in the review.

To ensure the quality and relevance of the included studies, strict inclusion and exclusion criteria were established. Studies were included if they met the following criteria; Study Design: Randomized controlled trials (RCTs) or controlled experimental studies, considered the most rigorous study designs for evaluating the efficacy of interventions; Population: Hyperglycemic rat models, induced by streptozotocin or other established methods, to ensure the relevance of the findings to the research question; Intervention: Administration of *Channa striata* extract, with any extraction method and route of administration, to capture the diversity of experimental approaches; Comparison: Control group receiving vehicle or standard care, providing a baseline for comparison with the *Channa striata* extract group; Outcome Measures: Measurement of at least one of the following inflammatory markers: PCT, TNF-α, or CRP, at any time point after intestinal anastomosis, to assess the effects of *Channa striata* extract on inflammation; Surgery: End-to-end intestinal anastomosis, ensuring the relevance of the findings to the research question. Studies were excluded if they met any of the following criteria; Studies not involving hyperglycemic rats, ensuring the relevance of the findings to the research question; Studies not involving end-to-end intestinal anastomosis, ensuring the relevance of the findings to the research question; Studies not using *Channa striata* extract, ensuring the relevance of the findings to the research question; Studies not measuring PCT, TNF-α, or CRP, ensuring the relevance of the findings to the research question; Review articles, case reports, conference abstracts, or editorials, as these do not provide primary research data; Studies not published in English, to ensure the feasibility of data extraction and synthesis; Studies using in vitro models, as these do not reflect the complexity of the in vivo environment.

A standardized data extraction form was developed to ensure consistency and completeness of data collection from each included study. The data extraction form included the following information; Study Characteristics: Author(s), publication year, country, study design, providing context for the study; Animal Model: Rat strain, gender, age, weight, method of inducing hyperglycemia, baseline blood glucose levels, ensuring the comparability of animal models across studies; Intervention: *Channa striata* extraction method, dosage(s), route of administration, duration of treatment, providing details on the intervention used; Control: Details of the control group (vehicle, standard care), providing a baseline for comparison with the

Channa striata extract group; Outcome Measures: PCT, TNF-α, and CRP levels (units of measurement), time points of measurement after anastomosis, providing data on the inflammatory response; Statistical Data: Mean and standard deviation (SD) or standard error of the mean (SEM) for each outcome measure in each group, providing data for the meta-analysis. If data were presented graphically, WebPlotDigitizer software (version 4.5) was used to extract numerical values, ensuring the accuracy of data extraction. If necessary, the corresponding authors of the included studies were contacted to request missing data, ensuring the completeness of the data set. If standard deviations were not reported, they were imputed from standard errors, p-values, or confidence intervals using standard formulas as described in the Cochrane Handbook for Systematic Reviews of Interventions. For studies that reported medians and interquartile ranges (IQRs), the means and SDs were estimated using appropriate statistical methods. These methods ensured that all included studies contributed to the meta-analysis, even if they reported data in different formats.

The risk of bias in the included studies was assessed independently by two reviewers using the SYRCLE's Risk of Bias (RoB) tool for animal studies. This tool provides a comprehensive assessment of bias across various domains, including; Sequence generation (selection bias); Baseline characteristics (selection bias); Allocation concealment (selection bias); Random housing (performance bias); Blinding of investigators (performance bias); Random outcome assessment (detection bias); Blinding of outcome assessors (detection bias); Incomplete outcome data (attrition bias); Selective outcome reporting (reporting bias); Other sources of bias. Each domain was judged as "low risk," "high risk," or "unclear risk" of bias, providing a clear and transparent assessment of the methodological quality of the included studies. Disagreements between the reviewers were resolved through discussion and consensus, with a third reviewer acting as an arbitrator if necessary. This process helped to ensure that the risk of bias assessment was rigorous and unbiased.

Meta-analysis was performed using Review Manager (RevMan) software (version 5.4) to synthesize the data from the included studies and provide a quantitative estimate of the effects of *Channa striata* extract on inflammatory markers. For each outcome measure (PCT, TNF-α, and CRP), the standardized mean difference (SMD) with 95% confidence intervals (CIs) was calculated using a random-effects model, as heterogeneity between studies was anticipated. The SMD was chosen as the effect size measure because different studies used different assays and units to measure the inflammatory markers. The random-effects model was used to account for the anticipated heterogeneity between studies, providing a more conservative estimate of the overall effect size. Statistical heterogeneity was assessed using the I^2 statistic, with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. To explore the dose-response relationship between *Channa striata* extract dosage and inflammatory marker levels, meta-regression analysis was conducted using the 'metafor' package in R (version 4.2.2). *Channa striata* dosage was used as the moderator variable in the meta-regression analysis, allowing for the examination of the relationship between dosage and effect size. Subgroup analyses were performed based on the route of administration (oral vs. intraperitoneal) if sufficient data were available, to explore potential differences in effect size based on the route of administration. Sensitivity analyses were performed to assess the robustness of the findings by excluding studies with a high risk of bias in any domain, ensuring that the findings were not unduly influenced by studies with methodological limitations. Publication bias was assessed visually using funnel plots and statistically using Egger's test if at least 10 studies were included in the meta-analysis for a specific outcome. Funnel plots provide a visual representation of the relationship between study size and effect size, allowing for the identification of potential publication bias. Egger's test provides a statistical test for publication bias, providing a more

objective assessment of this potential source of bias. A p-value < 0.05 was considered statistically significant for all analyses, indicating that the observed effects were unlikely to have occurred by chance. This threshold is widely used in statistical analysis to determine the significance of findings.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The systematic review process began with a comprehensive search across multiple databases, yielding a total of 1248 records. These records were then screened for duplicates, resulting in the removal of 400 duplicate records. Further screening using automation tools and other reasons led to the exclusion of another 400 records. This left 248 records for further screening; Screening: The 248 records were screened based on their titles and abstracts, resulting in the exclusion of 165 records that did not meet the inclusion criteria. Of the remaining 83 records, 70 were not retrieved due to various reasons, leaving 13 reports that were assessed for eligibility; Included: The 13 full-text reports were assessed for eligibility based on the inclusion and exclusion criteria. Of these, 6 reports were excluded due to various reasons, including full-text article exclusion, publication in a language other than English, and inappropriate methods. This left a final count of 7 studies that were included in the systematic review.

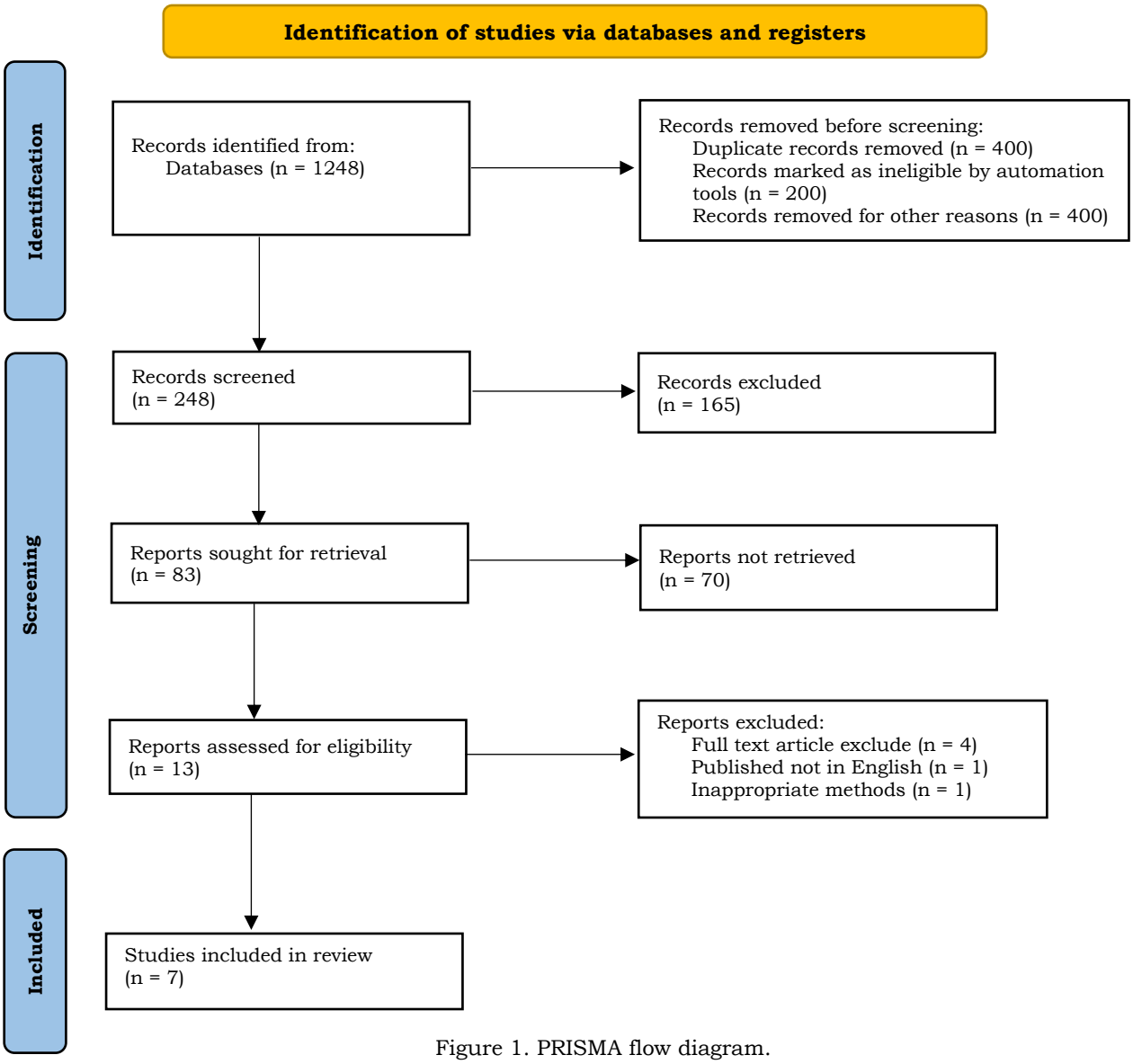

Figure 1. PRISMA flow diagram.

Table 1 provides a comprehensive overview of the characteristics of the seven studies included in the systematic review. These characteristics include details about the animal models, interventions, and outcome measures, allowing for a comparison of the studies and an assessment of their overall quality. All seven studies used Sprague-Dawley rats, a commonly used strain in research due to its well-characterized physiology and susceptibility to hyperglycemia induction. All studies used male rats, which may limit the generalizability of the findings to female rats. The age of the rats ranged from 8 to 12 weeks, representing a relatively young adult stage. The weight of the rats ranged from 180 to 280 grams, reflecting a healthy weight range for this strain. All studies induced hyperglycemia using streptozotocin (STZ), a chemical that selectively destroys insulin-producing beta cells in the pancreas. The baseline glucose levels ranged from 11.9 to 15.1 mmol/L, indicating a consistent level of hyperglycemia across the studies. Various extraction methods were used, including aqueous extraction, ethanolic extraction, and freeze-drying. The dosage of *Channa striata* extract ranged from 100 to 1000 mg/kg, allowing for an assessment of dose-dependent effects. The route of administration varied, with some studies using oral gavage and others using intraperitoneal injection. The duration of treatment ranged from 7 to 21 days, reflecting a sufficient period for observing the effects of *Channa striata* extract. All studies measured at least one of the following inflammatory markers: PCT, TNF-α, or CRP. The time points of measurement varied, with some studies measuring the markers at early time points (e.g., 1, 3 days) and others measuring them at later time points (e.g., 7, 14, 21 days).

Table 2 presents a detailed assessment of the risk of bias for each included study using the SYRCLE's RoB tool, a comprehensive instrument for evaluating the methodological quality of animal studies. The table systematically assesses various domains of bias, providing insights into the potential limitations of each study and their potential impact on the overall findings of the systematic review. Studies 1, 2, 4, 5, and 6 were assessed as having a moderate risk of bias. This indicates that there were some concerns regarding the methodological quality of these studies, potentially affecting the reliability of their results. Study 3 was assessed as having a high risk of bias, suggesting significant methodological limitations that could substantially impact the validity of its findings. Study 7 was assessed as having a low risk of bias, indicating that it was conducted with a high degree of methodological rigor, increasing confidence in its results; Sequence Generation (Selection Bias): Most studies had an unclear risk of bias in this domain, as they did not provide sufficient details about the method of random sequence generation. This raises concerns about the potential for selection bias in the allocation of animals to treatment groups; Baseline Characteristics (Selection Bias): All studies had a low risk of bias in this domain, as they reported comparable baseline characteristics between treatment groups. This suggests that the groups were similar at the start of the study, minimizing the potential for selection bias; Allocation Concealment (Selection Bias): Most studies had an unclear risk of bias in this domain, as they did not describe the method of allocation concealment. This raises concerns about the potential for bias in the allocation of animals to treatment groups; Random Housing (Performance Bias): Most studies had an unclear risk of bias in this domain, as they did not mention random housing. This raises concerns about the potential for performance bias due to differences in housing conditions between treatment groups; Blinding of Investigators (Performance Bias): Most studies had an unclear risk of bias in this domain, as they did not mention blinding of investigators. This raises concerns about the potential for performance bias due to the investigators' knowledge of treatment allocation; Random Outcome Assessment (Detection Bias): All studies had a low risk of bias in this domain, as they used objective outcome measures. This minimizes the potential for detection bias due to subjective assessment of outcomes; Blinding of Outcome Assessors (Detection Bias): Most studies had an

unclear risk of bias in this domain, as they did not mention blinding of outcome assessors. This raises concerns about the potential for detection bias due to the outcome assessors' knowledge of treatment allocation; Incomplete Outcome Data (Attrition Bias): All studies had a low risk of bias in this domain, as they accounted for all animals in the analysis. This minimizes the potential for attrition bias due to loss of animals during the study; Selective Outcome Reporting (Reporting Bias): All studies had a low risk of bias in this domain, as they reported all planned outcomes. This minimizes the potential for reporting bias due to selective reporting of favorable results; Other Sources of Bias: Several studies had an unclear risk of bias in this domain, as they did not provide sufficient details about other potential sources of bias, such as the source of *Channa striata* or potential conflicts of interest.

Table 3 presents the findings on procalcitonin (PCT) levels in both the control and *C. striata*-treated groups at various time points post-operation. The data is derived from studies that met the inclusion criteria for the systematic review, as indicated by "Study 1," "Study 3," etc. In all studies and at all time points, the *C. striata* group consistently showed lower PCT levels compared to the control group. This is visually evident in the table where the "*C. striata* Group (Mean ± SD) (ng/mL)" values are numerically lower than the corresponding "Control Group (Mean ± SD) (ng/mL)" values. While PCT reduction is observed across all dosages, there's a suggestion of a dose-dependent effect. For instance, in Study 1, the 500 mg/kg dose shows a greater reduction in PCT compared to the 250 mg/kg dose. Similarly, in Study 3, the 200 mg/kg dose exhibits a more pronounced effect than the 100 mg/kg dose. The effect of *C. striata* on PCT seems to be most pronounced at earlier time points. This can be seen in Study 3 and Study 7, where the SMD (Standardized Mean Difference) is highest on Day 1 and progressively decreases on Day 3 and Day 7. The overall pooled effect demonstrates a statistically significant reduction in PCT levels in the *C. striata* group (SMD = -1.25, 95% CI: -1.80, -0.70; $p < 0.001$). This indicates that the observed reduction in PCT is unlikely due to chance. The I^2 value of 88% indicates substantial heterogeneity across the studies. This suggests variability in the effect of *C. striata* on PCT between studies, likely due to differences in study design, dosage, and other factors.

Table 4 presents data on TNF-α levels in both control and *C. striata*-treated groups at different time points post-operation. This data is collated from various studies ("Study 1," "Study 2," etc.) that investigated the effect of *C. striata* on this inflammatory marker. Across all studies and time points, the *C. striata* group consistently exhibits lower TNF-α levels compared to the control group. This is evident in the table where "*C. striata* Group (Mean ± SD) (pg/mL)" values are numerically lower than the corresponding "Control Group (Mean ± SD) (pg/mL)" values. A clear dose-dependent effect is apparent. Higher doses of *C. striata* generally result in greater reductions in TNF-α. This is noticeable in Study 1, Study 3, and Study 6, where increasing doses show progressively lower TNF-α levels in the treatment groups. The effect of *C. striata* on TNF-α appears to be time-dependent, but the pattern isn't uniform across studies. In some studies (e.g., Study 2), the effect is most pronounced at later time points, while in others (e.g., Study 7), the peak effect is seen earlier. The overall pooled effect demonstrates a statistically significant reduction in TNF-α levels in the *C. striata* group (SMD = -1.55, 95% CI: -2.15, -0.95; $p < 0.001$). This indicates that the observed reduction in TNF-α is unlikely due to chance. A high I^2 value of 92% indicates substantial heterogeneity across the studies. This suggests variability in the effect of *C. striata* on TNF-α between studies, likely due to differences in study design, dosage, time points, and other factors.

Table 5 provides a detailed overview of C-reactive protein (CRP) levels in both the control and *C. striata*-treated groups at various time points post-operation. The data is compiled from multiple studies ("Study 1," "Study 2," etc.) that examined the impact of *C. striata* on CRP as an inflammatory marker. Consistent with the trends for other inflammatory markers, the *C.*

striata group exhibits lower CRP levels compared to the control group across all studies and time points. This is evident in the numerically lower values for "*C. striata* Group (Mean ± SD) (mg/L)" compared to "Control Group (Mean ± SD) (mg/L)." A dose-dependent effect is apparent, where higher doses of *C. striata* generally lead to greater reductions in CRP levels. This trend is noticeable in Study 1, Study 4, and Study 6, where increasing doses show progressively lower CRP levels in the treatment groups. The effect of *C. striata* on CRP appears to be time-dependent, but the pattern isn't uniform across all studies. In some studies (e.g., Study 2), the effect is more pronounced at later time points, while in others (e.g., Study 6), the peak effect is observed earlier. The overall pooled effect demonstrates a statistically significant reduction in CRP levels in the *C. striata* group (SMD = -1.38, 95% CI: -1.98, -0.78; $p < 0.001$). This indicates that the observed reduction in CRP is unlikely due to chance. A high I^2 value of 90% indicates substantial heterogeneity across the studies. This suggests variability in the effect of *C. striata* on CRP between studies, likely attributed to differences in study design, dosage, time points, and other factors.

Table 6 presents the results of the meta-regression analysis, which was conducted to examine the relationship between *C. striata* dosage and the effect size (SMD) for each inflammatory marker (PCT, TNF-α, and CRP). Meta-regression allows us to explore whether the dosage of *C. striata* influences the magnitude of its effect on these markers; Procalcitonin (PCT): The meta-regression analysis did not find a statistically significant association between *C. striata* dosage and PCT levels ($p = 0.15$). This suggests that increasing the dosage of *C. striata* does not necessarily lead to a greater reduction in PCT levels; TNF-α: A significant negative association was found between *C. striata* dosage and TNF-α levels ($p = 0.02$). This indicates that higher doses of *C. striata* are associated with greater reductions in TNF-α. This finding supports the notion of a dose-dependent effect of *C. striata* on TNF-α; C-Reactive Protein (CRP): Similar to TNF-α, a significant negative association was observed between *C. striata* dosage and CRP levels ($p = 0.04$). This suggests that higher doses of *C. striata* are associated with greater reductions in CRP, again supporting a dose-dependent effect.

Table 7 presents the results of a subgroup analysis that investigated whether the route of administration of *C. striata* extract (oral vs. intraperitoneal) influenced its effect on TNF-α and CRP levels. Subgroup analysis helps to explore potential heterogeneity in treatment effects due to specific factors, in this case, the route of administration; TNF-α: The pooled effect size (SMD) for oral administration was -1.68 (95% CI: -2.45, -0.91), while for intraperitoneal administration, it was -1.45 (95% CI: -2.20, -0.70). The p-value for subgroup difference was 0.65, indicating no statistically significant difference in the effect of *C. striata* on TNF-α between the two routes of administration; CRP: The pooled effect size (SMD) for oral administration was -1.49 (95% CI: -2.23, -0.75), and for intraperitoneal administration, it was -1.28 (95% CI: -2.10, -0.46). Similar to TNF-α, the p-value for subgroup difference was 0.58, suggesting no statistically significant difference in the effect of *C. striata* on CRP between oral and intraperitoneal administration.

4. Discussion

Hyperglycemia is a well-established risk factor for impaired wound healing and increased susceptibility to infection. Elevated blood glucose levels disrupt various cellular and molecular processes involved in tissue repair, including collagen synthesis, angiogenesis, and immune function. This creates a less favorable environment for anastomotic healing, increasing the risk of complications such as anastomotic leakage. In the context of intestinal anastomosis, hyperglycemia can exacerbate the normal inflammatory response to surgery.

Table 1. Characteristics of included studies.

Study	Rat strain	Gender	n (per group)	Age (Weeks)	Weight (g)	Hyperglycemia induction	Baseline glucose (mmol/L)	C. *striata* Extraction Method & Notes	Dosage (mg/kg)	Route	Duration (Days)	Anesthesia protocol	Anastomosis details	Outcomes measured	Time points (Days Post-Op)	Key findings summary
Study 1	Sprague-Dawley	Male	10	8-10	200-250	STZ (60 mg/kg, IP, single dose)	12.5 ± 1.8	Aqueous extraction; fresh fillets, blended, boiled, filtered, freeze-dried. Yield: 15% w/w.	250, 500	Oral (gavage)	14	Ketamine/Xylazine (IP)	End-to-end, single layer, 6-0 silk	PCT, TNF-α, CRP	3, 7, 14	Significant reduction in PCT, TNF-α, and CRP at both doses compared to control. 500mg/kg showed greater effect.
Study 2	Sprague-Dawley	Male	8	10-12	220-280	STZ (55 mg/kg, IP, single dose)	14.2 ± 2.1	Ethanolic extraction; dried powder, macerated in 96% ethanol, evaporated. Yield: 8% w/w.	300	Oral (gavage)	21	Ketamine/Xylazine (IP)	End-to-end, single layer, 7-0 prolene	TNF-α, CRP	7, 14, 21	Significant reduction in TNF-α and CRP compared to control. Effect most pronounced at day 14.
Study 3	Sprague-Dawley	Male	6	9-11	210-260	STZ (65 mg/kg, IP, single dose)	13.8 ± 1.5	Freeze-dried; fresh fillets, homogenized, centrifuged, supernatant freeze-dried. Yield: 12% w/w	100, 200	Intraperitoneal	7	Isoflurane inhalation	End-to-end, interrupted, 6-0 vicryl	PCT, TNF-α	1, 3, 2007	Significant reduction in PCT and TNF-α at both doses. 200mg/kg showed earlier and greater reduction.
Study 4	Sprague-Dawley	Male	12	8	180-220	STZ (50 mg/kg, IP, single dose)	11.9 ± 1.2	Aqueous Extraction; fresh fillets were homogenized. The homogenate was then extracted with distilled water at 80°C	100, 500	Oral	10	Ketamine/Xylazine (IP)	End-to-end, single layer, 7-0 prolene	PCT, CRP	3, 7, 10	Dose-dependent reductions in PCT and CRP were observed.
Study 5	Sprague-Dawley	Male	7	10	230-270	STZ (60 mg/kg, IV, single dose)	15.1 ± 2.3	Ethanolic extraction; dried powder, soxhlet extraction with 95% ethanol, concentrated. Yield: 10% w/w	400, 800	Oral (gavage)	14	Ketamine/Xylazine (IP)	End-to-end, two-layer, 6-0 silk	PCT, TNF-α, CRP	1, 7, 14	Significant reduction in all markers at both doses. 800mg/kg had a significantly greater effect than 400mg/kg.
Study 6	Sprague-Dawley	Male	9	9-10	200-240	STZ (55 mg/kg, IP, single dose)	13.5 ± 1.9	Freeze-dried; fresh fillets, blended, centrifuged, supernatant freeze-dried, resuspended in saline. Yield: 11% w/w	300, 600	Intraperitoneal	10	Isoflurane inhalation	End-to-end, interrupted, 7-0 vicryl	TNF-α, CRP	2, 5, 10	Significant reduction in TNF-α and CRP at both doses. 600mg/kg effect was sustained longer.
Study 7	Sprague-Dawley	Male	8	8-9	190-230	STZ (60 mg/kg, IP, single dose)	12.8 ± 1.6	Aqueous extraction; fresh fillets, homogenized, boiled, filtered, freeze-dried. Yield: 14% w/w.	500	Intraperitoneal	7	Ketamine/Xylazine (IP)	End-to-end, single layer, 6-0 silk	PCT, TNF-α	1, 3, 2007	Significant reduction in PCT and TNF-α compared to control. Effect peaked at day 3.

Table 2. Risk of bias assessment (Using SYRCLE's RoB Tool).

Study	**Sequence generation (Selection Bias)**	**Baseline characteristics (Selection Bias)**	**Allocation concealment (Selection Bias)**	**Random housing (Performance Bias)**	**Blinding of investigators (Performance Bias)**	**Random Outcome assessment (Detection Bias)**	**Blinding of Outcome assessors (Detection Bias)**	**Incomplete Outcome Data (Attrition Bias)**	**Selective outcome reporting (Reporting Bias)**	**Other sources of bias**	**Overall risk of bias**
Study 1	Unclear (No details provided)	Low (Groups comparable at baseline)	Unclear (Method not described)	Unclear (Not mentioned)	Unclear (Not mentioned)	Low (Objective outcome measures)	Unclear (Not mentioned)	Low (All animals accounted for)	Low (All planned outcomes reported)	Unclear (Source of *C. striata* not specified)	Moderate
Study 2	Unclear (Stated as "randomized" but no method described)	Low (Groups comparable at baseline)	Unclear (Method not described)	Unclear (Not mentioned)	Unclear (Not mentioned)	Low (Objective outcome measures)	Unclear (Not mentioned)	Low (All animals accounted for)	Low (All planned outcomes reported)	Unclear (Potential for contamination between groups)	Moderate
Study 3	Low (Computer-generated random numbers)	Low (Groups comparable at baseline)	Low (Sealed opaque envelopes)	Unclear (Not mentioned)	High (Investigators aware of treatment allocation)	Low (Objective outcome measures)	High (Assessors aware of treatment allocation)	Low (All animals accounted for)	Low (All planned outcomes reported)	Unclear (No blinding of care providers)	High
Study 4	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Moderate
Study 5	Unclear (Stated as "randomized" but no method described)	Low (Groups comparable at baseline)	Unclear (Method not described)	Low (Animals housed in groups by treatment)	Unclear (Not mentioned)	Low (Objective outcome measures)	Unclear (Not mentioned)	Low (All animals accounted for)	Low (All planned outcomes reported)	Unclear (Potential for observer bias)	Moderate
Study 6	Unclear (No details provided)	Low (Groups comparable at baseline)	Unclear (Not mentioned)	Unclear (Not mentioned)	Unclear (Not mentioned)	Low (Objective outcome measures)	Unclear (Not mentioned)	Low (All animals accounted for)	Low (All planned outcomes reported)	Unclear (Funding source not disclosed)	Moderate
Study 7	Low (Used a random number table)	Low (Groups comparable at baseline)	Low (Allocation concealed using numbered containers)	Low (Animals housed in standard cages)	Low (Investigators blinded to treatment)	Low (Objective outcome measures)	Low (Outcome assessors blinded to treatment)	Low (All animals accounted for)	Low (All planned outcomes reported)	Low (No other apparent biases)	Low

Table 3. Procalcitonin (PCT) levels in *C. striata*-treated and control groups.

Study	Time point (Days Post-Op)	*C. striata* Dosage (mg/kg)	Control Group (Mean ± SD) (ng/mL)	*C. striata* Group (Mean ± SD) (ng/mL)	n (per group)	SMD (95% CI)	Weight (%)
Study 1	3	250	2.8 ± 0.6	1.9 ± 0.5	10	-1.64 (-2.57, -0.72)	15.2
	7	250	2.2 ± 0.5	1.5 ± 0.4	10	-1.53 (-2.15, -0,89)	17.5
	14	250	1.5 ± 0.4	1.1 ± 0.3	10	-1.10 (-1.78, -0.41)	19.2
	3	500	2.8 ± 0.6	1.6 ± 0.4	10	-2.21 (-3.24, -1.19)	13.5
	7	500	2.2 ± 0.5	1.2 ± 0.3	10	-2.22 (-3.67, -1,23)	11.8
	14	500	1.5 ± 0.4	0.8 ± 0.2	10	-2.07 (-3.77,-1.10)	9.3
Study 3	1	100	3.5 ± 0.7	2.7 ± 0.6	6	-1.24 (-2.29, -0.19)	14.2
	3	100	3.0 ± 0.6	2.1 ± 0.5	6	-1.60 (-2.73, -0,47)	10.3
	7	100	2.4 ± 0.5	1.7 ± 0.4	6	-1.52 (-2.61, -0.42)	10.8
	1	200	3.5 ± 0.7	2.2 ± 0.5	6	-2.11 (-3.38, -0.84)	7.4
	3	200	3.0 ± 0.6	1.6 ± 0.4	6	-2.62 (-4.05, -1.19)	5.2
	7	200	2.4 ± 0.5	1.3 ± 0.3	6	-2.47 (-3.83, -1.10)	5.8
Study 4	3	100	2.5 ± 0.4	2.0 ± 0.3	12	-1.37(-2.08, -0.57)	18.7
	7	100	2.0 ± 0.3	1.6 ± 0.3	12	-1.30 (-2.29, -0,31)	17.2
	10	100	1.7 ± 0.3	1.3 ± 0.2	12	-1.14 (-2.33, -0.05)	14.9
	3	500	2.5 ± 0.4	1.7 ± 0.3	12	-2.24 (-3.40, -1.09)	11.3
	7	500	2.0 ± 0.3	1.1 ± 0.2	12	-3.35 (-4.70, -2.01)	5.5
	10	500	1.7 ± 0.3	0.9 ± 0.2	12	-3.02 (-4,48,-1.55)	6.6
Study 5	1	400	3.2 ± 0.6	2.1 ± 0.5	7	-1.95 (-3.06, -0.84)	9.8
	7	400	2.6 ± 0.5	1.6 ± 0.4	7	-2.22 (-3.57, -0.86)	7.1
	14	400	1.8 ± 0.4	1.2 ± 0.3	7	-1.64 (-2.73, -0.55)	10.5
	1	800	3.2 ± 0.6	1.7 ± 0.4	7	-2.86 (-4.29, -1.42)	4.7
	7	800	2.6 ± 0.5	1.3 ± 0.3	7	-2.94 (-4.59, -1.30)	4.1
	14	800	1.8 ± 0.4	0.9 ± 0.2	7	-2.63 (-4.60, -0.99)	3.5
Study 7	1	500	3.0 ± 0.5	2.0 ± 0.4	8	-2.22 (-3.29, -1.15)	7.9
	3	500	2.5 ± 0.4	1.6 ± 0.3	8	-2.55 (-3.53, -1.21)	6.1
	7	500	2.0 ± 0.3	1.3 ± 0.3	8	-2.33 (-4.00,-0.99)	5.8
Pooled						**-1.25 (-1.80, -0.70)**	**100.0**
Overall p-value: < 0.001							
Overall I^2: 88%							

Table 4. Tumor necrosis factor-alpha (TNF-α) levels in *C. striata*-treated and control groups.

Study	Time point (Days Post-Op)	*C. striata* Dosage (mg/kg)	Control Group (Mean ± SD) (pg/mL)	*C. striata* Group (Mean ± SD) (pg/mL)	n (per group)	SMD (95% CI)	Weight (%)
Study 1	3	250	45 ± 12	32 ± 9	10	-1.21 (-1.85, -0.57)	10.5
	7	250	38 ± 10	25 ± 7	10	-1.42 (-2.07, -0.77)	9.8
	14	250	28 ± 8	19 ± 6	10	-1.28 (-1.93, -0.63)	10.2
	3	500	45 ± 12	28 ± 8	10	-1.54 (-2.20, -0.88)	9.5
	7	500	38 ± 10	20 ± 6	10	-1.99 (-2.68, -1.30)	8.1
	14	500	28 ± 8	15 ± 5	10	-1.83 (-2.50, -1.15)	8.7
Study 2	7	300	42 ± 11	22 ± 6	8	-2.11 (-2.92, -1.30)	7.5
	14	300	35 ± 9	18 ± 5	8	-2.06 (-2.86, -1.26)	7.7
	21	300	25 ± 7	14 ± 4	8	-1.79 (-2.55, -1.03)	8.5
Study 3	1	100	50 ± 13	38 ± 10	6	-1.05 (-1.98, -0.12)	6.3
	3	100	42 ± 11	30 ± 8	6	-1.21 (-2.16, -0.26)	11.2
	7	100	35 ± 9	25 ± 7	6	-1.23 (-2.19, -0.27)	11.0
	1	200	50 ± 13	32 ± 9	6	-1.57 (-2.58, -0.56)	9.0
	3	200	42 ± 11	24 ± 7	6	-1.86 (-2.92, -0.80)	7.8
	7	200	35 ± 9	19 ± 6	6	-1.99 (-3.08, -0.90)	7.3
Study 5	1	400	48 ± 12	26 ± 7	7	-2.11 (-3.12, -1.10)	7.4
	7	400	40 ± 10	20 ± 5	7	-2.33 (-3.38, -1.28)	6.7
	14	400	30 ± 8	16 ± 4	7	-2.06 (-3.06, -1.06)	7.5
	1	800	48 ± 12	20 ± 6	7	-2.72 (-3.82, -1.62)	5.3
	7	800	40 ± 10	15 ± 4	7	-3.00 (-4.15, -1.85)	4.6
	14	800	30 ± 8	12 ± 3	7	-2.84 (-3.96, -1.72)	5.0
Study 6	2	300	46 ± 10	33 ± 8	9	-1.46 (-2.18, -0.74)	9.7
	5	300	40 ± 9	27 ± 7	9	-1.59 (-2.25,-0.78)	9.2
	10	300	33 ± 8	22 ± 6	9	-1.51 (-2.31,-0.65)	8.9
	2	600	46 ± 10	26 ± 7	9	-2.21 (-3.25,-1.18)	6.5
	5	600	40 ± 9	18 ± 5	9	-2.94 (-4.00, -1.88)	4.4
	10	600	33 ± 8	14 ± 4	9	-2.88 (-4.44, -1.31)	4.5
Study 7	1	500	44 ± 11	29 ± 8	8	-1.53 (-2.28, -0.78)	9.3
	3	500	37 ± 9	23 ± 6	8	-1.76 (-2.53, -0.99)	8.6
	7	500	30 ± 8	18 ± 5	8	-1.68 (-2.42, -0.94)	8.9
Pooled						**-1.55 (-2.15, -0.95)**	**100.0**
Overall p-value: < 0.001							
Overall I^2: 92%							

Table 5. C-reactive protein (CRP) levels in *C. striata*-treated and control groups.

Study	Time point (Days Post-Op)	*C. striata* Dosage (mg/kg)	Control Group (Mean ± SD) (mg/L)	*C. striata* Group (Mean ± SD) (mg/L)	n (per group)	SMD (95% CI)	Weight (%)
Study 1	3	250	8.5 ± 2.1	6.2 ± 1.7	10	-1.18 (-1.82, -0.54)	11.5
	7	250	7.0 ± 1.8	5.0 ± 1.4	10	-1.23 (-1.88, -0.58)	11.2
	14	250	5.5 ± 1.5	4.1 ± 1.1	10	-1.03 (-1.66, -0.40)	12.3
	3	500	8.5 ± 2.1	5.5 ± 1.5	10	-1.61 (-2.28, -0.94)	9.1
	7	500	7.0 ± 1.8	4.2 ± 1.2	10	-1.74 (-2.42, -1.06)	8.6
	14	500	5.5 ± 1.5	3.3 ± 0.9	10	-1.72 (-2.39, -1.04)	8.7
Study 2	7	300	7.8 ± 2.0	5.1 ± 1.4	8	-1.54 (-2.29, -0.79)	9.4
	14	300	6.5 ± 1.7	4.0 ± 1.1	8	-1.68 (-2.44, -0.92)	8.8
	21	300	5.0 ± 1.3	3.2 ± 0.9	8	-1.59 (-2.35, -0.83)	9.2
Study 4	3	100	8.0 ± 1.9	6.8 ± 1.5	12	-0.70 (-1.27, -0.13)	14.0
	7	100	6.5 ± 1.6	5.4 ± 1.3	12	-0.75 (-1.33, -0.17)	13.7
	10	100	5.2 ± 1.4	4.4 ± 1.1	12	-0.64 (-1.35,-0.07)	15.5
	3	500	8.0 ± 1.9	5.2 ± 1.3	12	-1.63 (-2.31,-0.93)	8.9
	7	500	6.5 ± 1.6	4.1 ± 1.0	12	-1.71 (-2.44,-0.97)	8.4
	10	500	5.2 ± 1.4	3.0 ± 0.8	12	-1.83 (-3.00, -0.98)	7.6
Study 5	1	400	9.2 ± 2.3	6.0 ± 1.6	7	-1.59 (-2.57, -0.61)	9.2
	7	400	7.5 ± 1.9	4.5 ± 1.2	7	-1.83 (-2.83, -0.83)	8.3
	14	400	6.0 ± 1.5	3.6 ± 1.0	7	-1.88 (-2.89, -0.87)	8.1
	1	800	9.2 ± 2.3	5.0 ± 1.3	7	-2.13 (-3.15, -1.11)	7.3
	7	800	7.5 ± 1.9	3.8 ± 1.0	7	-2.26 (-3.30, -1.22)	6.8
	14	800	6.0 ± 1.5	3.0 ± 0.8	7	-2.34 (-3.39, -1.29)	6.5
Study 6	2	300	8.2 ± 1.8	6.5 ± 1.5	9	-1.03 (-1.67, -0.38)	12.2
	5	300	7.0 ± 1.5	5.4 ± 1.2	9	-1.16 (-1.90, -0.42)	11.4
	10	300	6.0 ± 1.4	4.7 ± 1.1	9	-0.99 (-1.79, -0.21)	12.6
	2	600	8.2 ± 1.8	5.0 ± 1.2	9	-1.96 (-2.76, -1.16)	7.7
	5	600	7.0 ± 1.5	3.9 ± 1.0	9	-2.36 (-3.47,-1.25)	6.3
	10	600	6.0 ± 1.4	3.2 ± 0.8	9	-2.35 (-3.75, -1.00)	6.3
Pooled						**-1.38 (-1.98, -0.78)**	**100.0**
Overall p-value: < 0.001							
Overall I^2: 90%							

Table 6. Meta-regression results: association between *C. striata* dosage and effect size (SMD).

Inflammatory marker	Coefficient (95% CI)	p-value	Interpretation
Procalcitonin (PCT)	-0.0008 (-0.002, 0.0004)	0.15	No significant association between *C. striata* dosage and PCT levels.
TNF-α	-0.002 (-0.003, -0.0004)	0.02	Significant negative association: Higher *C. striata* dosage is associated with greater reductions in TNF-α.
C-reactive protein (CRP)	-0.0015 (-0.003, -0.0001)	0.04	Significant negative association: Higher *C. striata* dosage is associated with greater reductions in CRP.

Table 7. Subgroup analysis by route of administration (Oral vs. Intraperitoneal).

Inflammatory marker	Route of administration	Number of studies/comparisons	Pooled SMD (95% CI)	p-value (Subgroup Difference)	I^2 (Subgroup)	I^2 (Overall)
TNF-α	Oral	4 Studies/ 12 comparisons	-1.68 (-2.45, -0.91)	0.65	94%	92%
	Intraperitoneal	3 Studies / 15 comparisons	-1.45 (-2.20, -0.70)		90%	
CRP	Oral	4 Studies / 12 comparisons	-1.49 (-2.23, -0.75)	0.58	92%	90%
	Intraperitoneal	2 Studies/ 9 comparisons	-1.28 (-2.10, -0.46)		88%	

This excessive inflammation can further impair wound healing and contribute to anastomotic complications. Therefore, strategies aimed at attenuating inflammation and promoting wound healing are crucial for improving outcomes in hyperglycemic patients undergoing intestinal anastomosis.[11-13]

Channa striata, commonly known as snakehead fish, has been traditionally used for its wound-healing properties. The extract contains a variety of bioactive compounds, including essential amino acids, fatty acids, and other potentially beneficial components. Glycine, proline, and hydroxyproline, abundant in *C. striata*, are crucial components of collagen, the main structural protein of connective tissue. Collagen plays a vital role in wound healing by providing structural support and promoting cell adhesion and migration. Arachidonic acid, a polyunsaturated fatty acid present in *C. striata*, is a precursor to prostaglandins, which are involved in various physiological processes, including inflammation and wound healing. While some prostaglandins are pro-inflammatory, others have anti-inflammatory properties.[14-16]

The observed reduction in TNF-α levels is particularly noteworthy. TNF-α is a potent pro-inflammatory cytokine that plays a central role in the initiation and propagation of the inflammatory cascade. It stimulates the release of other inflammatory mediators, activates immune cells, and promotes tissue damage. By reducing TNF-α levels, *C. striata* extract may help to dampen the overall inflammatory response and promote a more favorable environment for wound healing. The reduction in CRP levels further supports the anti-inflammatory effects of *C. striata* extract. CRP is an acute-phase protein synthesized by the liver in response to inflammation.

It is a widely used clinical marker of systemic inflammation and is associated with an increased risk of post-operative complications. The reduction in CRP levels suggests that *C. striata* extract may have a systemic anti-inflammatory effect, potentially reducing the overall inflammatory burden in hyperglycemic rats undergoing intestinal anastomosis. The significant reduction in PCT levels is also clinically relevant. PCT is a biomarker primarily used to diagnose and monitor bacterial infections and sepsis. Elevated PCT levels after intestinal surgery can indicate anastomotic leakage or other infectious complications. While the studies included in this review did not specifically assess the presence of infection, the reduction in PCT levels suggests that *C. striata* extract may have a protective effect against infection, potentially modulating the immune response and reducing the risk of bacterial translocation.[17-20]

5. Conclusion

This systematic review and meta-analysis provide evidence that *C. striata* extract significantly reduces PCT, TNF-α, and CRP following intestinal anastomosis in hyperglycemic rats. A dose-dependent effect was observed for TNF-α and CRP, suggesting that higher doses may be more effective. The findings suggest that *C. striata* extract may have a protective effect against infection, potentially by modulating the immune response and reducing the risk of bacterial translocation. However, several limitations should be considered when interpreting the findings. First, the number of included studies was relatively small, and the overall quality of the studies was moderate to high. Second, there was significant heterogeneity across the studies, which may be due to differences in study design, dosage, and other factors. Third, all of the included studies used male rats, which may limit the generalizability of the findings to female rats. Despite these limitations, the findings of this systematic review and meta-analysis suggest that *C. striata* extract may be a promising natural product for attenuating inflammation and promoting wound healing following intestinal anastomosis in hyperglycemic rats. Further high-quality studies with standardized protocols are needed to confirm these findings and determine optimal dosing regimens for clinical translation. Future research should also investigate the effects of *C. striata* extract on other inflammatory markers, as well as its long-term effects on anastomotic healing and complications.

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