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Lactobacillus Gel's Anti-Inflammatory Properties in Male Wistar Rats with Paw Edema Induced by Carrageenan

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ABSTRACT:

This study investigates the anti-inflammatory effects of Lactobacillus gel in male Wistar rats with carrageenan-induced paw edema. The study compared the anti-inflammatory capabilities of Lactobacillus casei and Lactobacillus acidophilus in an acute inflammation model induced by carrageenan, using diclofenac sodium at 150 mg/kg as the control standard. The oral dosage of Lactobacillus bacteria administered was 2×10^1 CFU/ml. Rats were administered carrageenan to induce edema one hour after oral treatment, and paw thickness was measured at 1, 2, 3, 4, 5, and 24-hour intervals. Motility and stair climbing ability were assessed at 24-hour intervals, and serum samples were analyzed for IL-6, IL-10, and TNF-α cytokines. Lactobacillus treatment significantly reduced paw thickness ($P < 0.001$), with L. acidophilus and L. casei showing 34% and 30% reductions, respectively. Both strains improved motility and stair climbing ratings. Treatment with Lactobacillus notably decreased TNF-α and IL-6 levels while increasing IL-10 levels significantly ($P < 0.0001$). However, L. acidophilus and L. casei showed less pronounced effects on reducing carrageenan-induced inflammation, suggesting a potential dampening effect on pro-inflammatory cytokine production by Lactobacillus.

Keywords: Lactobacillus Gel's, Anti-Inflammatory Properties, Male Wistar Rats, Paw Edoema Induced, Carrageenan

1. Introduction

The probiotic qualities of the lactic acid bacteria genus Lactobacillus have garnered significant research attention due to its perceived health benefits. Among its potential applications, the anti-inflammatory properties of Lactobacillus have been particularly highlighted. This study focuses on investigating the anti-inflammatory effects of Lactobacillus gel in male Wistar rats with paw edema induced by carrageenan, a common model for acute inflammation.
Inflammation serves as a defensive response involving immune cells, blood vessels, and chemical mediators reacting to potential threats like infections, cellular damage, or irritants. Symptoms of acute inflammation include pain, redness, heat, and swelling. While inflammation is crucial for immune responses, chronic inflammation can contribute to various health issues such as arthritis, heart disease, and cancer. Therefore, regulating inflammation is essential for maintaining health and preventing disease progression.

The rat model of acute inflammation known as carrageenan-induced paw edema has been extensively used in experimental settings. The red seaweed sulfated polysaccharide carrageenan activates inflammatory mediators including prostaglandins, histamines, and cytokines, leading to inflammation. For the purpose of determining whether anti-inflammatory drugs are effective, this model is invaluable.

There are a number of ways in which Lactobacillus strains might reduce inflammation. These include influencing the composition of the gut microbiota, improving the efficiency of the intestinal barrier, and controlling the body's immunological response. The inflammatory pathways can be impacted by the bioactive substances produced by these bacteria, which include lactic acid, short-chain fatty acids, and bacteriocins. In addition, Lactobacillus has the ability to modulate the host immune system by lowering levels of pro-inflammatory cytokines and increasing production of anti-inflammatory cytokines.

We will test the anti-inflammatory effects of Lactobacillus gel in male Wistar rats who have developed paw edema due to carrageenan. One interesting application of Lactobacillus is in gel form, which could improve its medicinal effects by allowing for localized application of the bacteria. The main goal is to determine how much of an impact Lactobacillus gel has on paw edema symptoms and inflammation in this animal.

Paw swelling, a frequent sign of inflammation, will be measured at several time periods after the injection of carrageenan and the application of Lactobacillus gel. To further understand the molecular mechanisms behind the effects, we will also examine the levels of inflammatory markers in the serum and paw tissue.

A better understanding of Lactobacillus gel's anti-inflammatory characteristics may pave the way for innovative approaches to treating diseases associated with inflammation. If this method works, it might provide an option to traditional anti-inflammatory medications that are safe, effective, and made from natural ingredients.

By using a tried-and-true model of acute inflammation, this research hopes to shed light on Lactobacillus gel's anti-inflammatory capabilities. Insights into its efficacy and action mechanisms will hopefully lead to new anti-inflammatory medicines and add to the expanding corpus of information on the therapeutic advantages of probiotics.

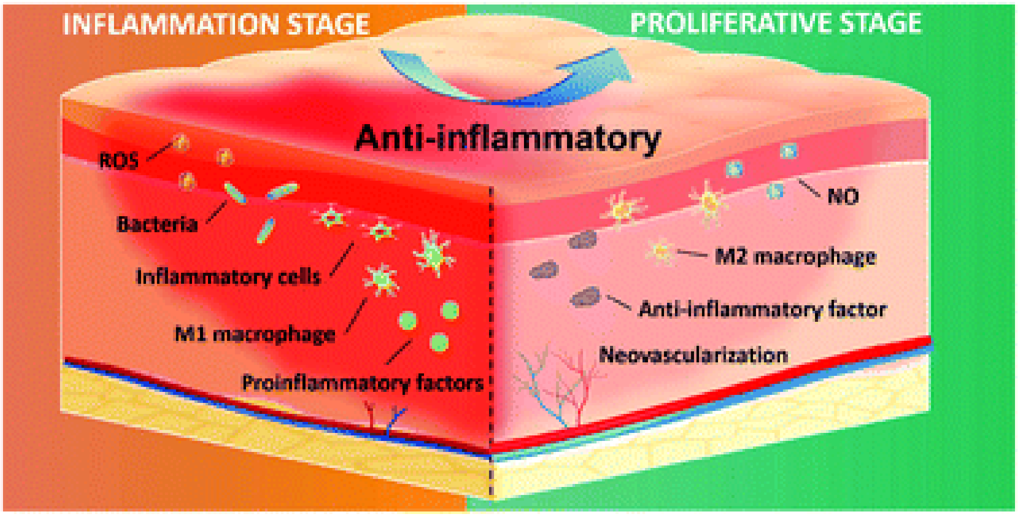

Figure 1: Anti-Inflammatory

Background on Inflammation and Edema

The safe system's mind-boggling response to destructive stimuli, such as infections, harmed cells, and irritants, is called inflammation. Its goals are to wipe out the source of cell harm, eliminate necrotic tissues and cells, and start a maintenance mechanism. The conventional symptoms of redness (rubor), heat (calor), swelling (development), torment (dolor), and loss of capability (functio laesa) are used to represent this response. The actions of veins, subatomic mediators, and immune cells cause these symptoms. Inflammation causes weak cells, similar to neutrophils and macrophages, to move to the site of harm or pollution. They also release chemokines and cytokines, which intensify the inflammatory response and attract more resistant cells. Vascular alterations, such as elevated vein porosity and increased blood flow, allow leukocytes and plasma proteins to penetrate the injured tissue. One obvious aspect of the inflammation brought on by this vascular spilling is edema, which is the accumulation of extra liquid in the interstitial tissue spaces. While chronic inflammation lasts because of a constant stimulus and can cause tissue damage and exacerbate a number of ongoing conditions like rheumatoid arthritis, cardiovascular disease, and cancerous growth, acute inflammation is typically self-restricting and goes away when the underlying trigger is removed. It is crucial to comprehend the complex mechanisms and mediators involved in inflammation and edema in order to develop targeted treatments that reduce tissue damage and regulate excessive inflammatory reactions.

Importance of Anti-Inflammatory Agents

By diminishing the unsafe effects of an excessive or postponed inflammatory response, anti-inflammatory drugs assume an essential part in the observing and treatment of disorders associated to inflammation. The mechanisms by which these agents capability incorporate repressing the creation of favorable to inflammatory cytokines, hindering the activity of enzymes such as cyclooxygenase (COX), which produces inflammatory mediators, and lessening the relocation of safe cells to the site of inflammation. Anti-inflammatory medicines are important because they help reduce pain, swelling, and redness, which improves the quality of life for those who suffer from inflammatory disorders. They are essential for managing both long-term inflammatory conditions including rheumatoid arthritis, inflammatory bowel disease, and asthma, as well as severe inflammatory reactions like those brought on by trauma or infection. In addition, anti-inflammatory drugs play a major role in preventing inflammation-related side effects such tissue damage and the advancement of long-term illnesses like cancer and cardiovascular disease. These medications are vital in both acute and long-term medical contexts because they regulate the inflammatory response, assisting in the restoration of normal tissue function and preventing long-term damage.

Overview of Lactobacillus as A Potential Anti-Inflammatory Agent

The genus Lactobacillus, which is typically found in the gastrointestinal tract, has garnered considerable attention due to its potential as an anti-inflammatory expert. This probiotic bacterium is well-known for its ability to control the immune system and affect the body's inflammatory reactions.

Lactobacillus interacts with the stomach bacteria as a key way of delivering its anti-inflammatory benefits. It contributes to maintaining a balanced microbiological environment in the stomach, which is necessary for overall health and resistance to illness. Through promoting the growth of beneficial bacteria and inhibiting harmful ones, Lactobacillus helps create an environment in the stomach that promotes reduced inflammation.

Furthermore, other bioactive substances such bacteriocins, short-chain fatty acids (SCFAs), and certain proteins that play roles in resistance guidelines can be delivered by Lactobacillus strains. These substances have the direct ability to inhibit pro-inflammatory pathways or promote anti-inflammatory reactions in the stomach lining, among other things.

The ability of Lactobacillus to improve intestinal obstruction capabilities has also been studied. These microbes help prevent harmful compounds from leaking into the bloodstream and causing systemic inflammation by fortifying the stomach's epithelial lining. This enhancement in hindrance capacity is essential for maintaining gut trustworthiness and reducing systemic inflammatory responses.

Regarding the anti-inflammatory qualities of particular Lactobacillus strains in a range of ailments, such as inflammatory bowel diseases (IBD), allergies, and metabolic disorders, clinical trials and preclinical research have shown encouraging outcomes. These results highlight Lactobacillus's therapeutic potential as a typical strategy for managing inflammation and promoting overall health.

In conclusion, due to its potential to modify stomach microbiota, generate bioactive chemicals, improve stomach obstruction capacity, and directly affect resistance responses, Lactobacillus exhibits great promise as an anti-inflammatory specialist. Further investigation into particular strains, modes of action, and clinical uses will further elucidate its potential in preventing and treating inflammatory disorders.

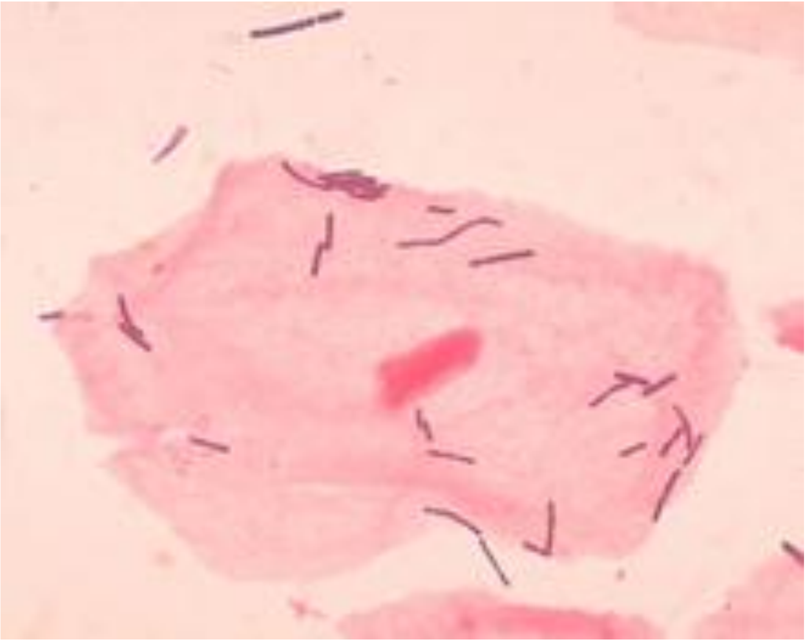

Figure 2: Close to a squamous epithelial cell is Lactobacillus sp.

Male Wistar Rats: A Carrageenan-Induced Paw Edema Model

Male Wistar rats given carrageenan-induced paw edema is an often used exploratory paradigm for studying severe inflammation and evaluating potential anti-inflammatory drugs. Injecting carrageenan, a sulfated polysaccharide derived from red seaweed, into the subcutaneous tissue of a rodent's paw results in limited inflammation. The underlying phase of inflammation found in ailments like arthritis and other inflammatory illnesses is replicated in this model.

In this particular model, a small amount (0.1 mL) of carrageenan solution is usually applied to the plantar surface of one rodent's back paw to cause inflammation. The paw experiences a range of inflammatory reactions after infusion, which are represented by the production of several mediators including as prostaglandins, histamine, serotonin, and bradykinin. Vasodilation, enhanced vascular penetrability, and the accumulation of fluids (edema) inside the paw tissues are all brought on by these mediators.

Using a plethysmometer or caliper measurements, one can evaluate the increase in paw volume over an extended period of time to objectively characterize the inflammatory response. The weight and thickness of the paws can also be used to determine how severe the edema is. Paw tissue samples can also be used to study biochemical indicators of inflammation, including as myeloperoxidase activity, cytokine levels, and oxidative stress parameters, to further illustrate the inflammatory process.

This model is used by researchers to evaluate the effectiveness of common substances or probable anti-inflammatory medications. The ability of substances given prior to carrageenan infusion to reduce inflammatory indicators and weaken paw edema arrangement is evaluated. This makes it possible to evaluate the test chemicals' remedial (treatment) and preventative (prophylactic) effects on severe inflammation.

Rats' carrageenan-induced paw edema model serves as a preclinical tool for testing new anti-inflammatory drugs and offers crucial insights into the mechanisms underlying severe inflammation. Due to its ease of use, consistency, and relevance to inflammatory disorders in humans, it is well recognized as a model in biomedical and pharmacological research that helps develop new treatments for inflammatory diseases.

Figure 3: Male Wistar Rats

2. Materials and Methods

Cultures of Bacteria

We acquired Lactobacillus acidophilus (ATCC 314) and Lactobacillus casei (ATCC 334) from Hi Media located in Navi Mumbai, India. The lyophilized cultures were streaked onto de Mann Rogosa Sharpe Agar (MRS) and incubated under anaerobic conditions at 37°C.

Drugs and Chemicals Used

We received the carrageenan from Hello Media in Mumbai, India. Recon of Bangalore, India, supplied the typical anti-inflammatory drug diclofenac sodium. The cytokines assay kits were provided by DNA Bio of Hyderabad, Andhra Pradesh, India, and Bar Biotech of Norcross, Georgia, USA.

Animals

For this investigation, 35 male Wistar rats weighing 200 grams apiece were employed. They were taken care of an ordinary pellet diet and were not expected to hydrate. At least several weeks had passed since the animals' underlying acclimation before the exploratory session. All study protocols were finished as per the Institutional Animals Ethics Committee's (IEAC) recommendations.

Assessment of Anti-Inflammatory Properties

The animals were categorized into five groups based on their treatment for severe inflammation reduction. Group A (carrageenan control) did not receive any oral therapy, while Group B (control) received 500 μL of distilled water. Groups C and D were administered 2 × 10^7 CFU/mL of L. acidophilus and L. casei, respectively, suspended in 500 μL of distilled water. Group E, serving as the positive control, received an analgesic dose of 150 mg/kg body weight.

Induced Acute Inflammatory Model by Carrageenan

To assess anti-inflammatory efficacy, the rat paw edema assay utilized carrageenan. Except for group A, rats in all groups received a sub-plantar injection of 100 μL of a freshly prepared 1% carrageenan solution in distilled water to induce swelling in their right hind paws. Groups B/C and D/E were administered their respective treatments—vehicle, cultures, and medication—thirty minutes prior to the carrageenan injection. Paw thickness was measured at multiple time points following carrageenan injection, including "0 hour" (immediately before injection) and at 1, 2, 3, 4, and 24 hours thereafter. Paw swelling was quantified by comparing paw thickness at "0 hour" with measurements taken at subsequent time points.

Test of Stair Climbing Activities

Animals that had fasted overnight were trained to climb a staircase with food placed on the third step and water on the second step, with step heights of 5, 10, and 15 millimeters. Rats in these groups were assigned scores based on their climbing ability: 0 if they couldn't climb any steps, 1 if they reached the first step, 2 if they reached the second step, and 3 if they successfully climbed all three steps.

Motility Test

The rats' mobility was assessed over a five-minute period. Scores were assigned based on their behavior: 0 if the rodent walked awkwardly, attempting to avoid touching its inflamed paw to the ground; 1 if it walked cautiously, occasionally touching its toes to the ground; and 2 if it walked normally without difficulty.

Sample Collection

The animals were euthanized in accordance with CPSCEA committee guidelines, with cardiovascular drainage and Diethyl ether used for support over a 24-hour period. Blood was drawn for cytokine assays, allowed to clot at room temperature for an hour, and then centrifuged at 1500 g for 15 minutes. The resulting serum was carefully transferred into new tubes for storage, which were then stored at -20°C until required for analysis.

Assay for Cytokines

Quantification of proinflammatory cytokines (TNF-α) and anti-inflammatory cytokines (IL-10) was done in picograms per milliliter (pg/mL) using an ELISA Peruser (Lisa Plus, Germany). We utilized serum samples. The following ELISA kits from Shaft Bio were utilized: IL-6, TNF-α, and IL-10. All trials were conducted in accordance with the manufacturer's original specifications.

Analytical Statistics

The means ± SEM of seven observations constitute the edema volume motivator, which is ascertained by employing ANOVA and a post hoc test. The Duncan's test was used to categorize the groups. The groups were evaluated using the Kruskal-Wallis test, and the center scores represent the findings of the stair ascending limit test and motility.

3. Results

Inflammation Induced by Carrageenan

Carrageenan injections into the back paw caused a gradual edema that peaked after four hours. Table 1 displays mathematical data at different times for five groups (A to E) (0, 1, 2, 3, 4, 5, and 24 hours). Each cell indicates the average measurement value from an examination, most likely one in which the groups received some sort of therapy or mediation. Bunch B has underlying values increasing from 0 to 5 hours, peaking at 3.9 and then steadily stabilizing. Over an extended period of time, Groups C and D exhibit fluctuations in their measurements. Bunch E shows measurement stability with a steady pattern throughout the time points. Bunch An exhibits minimal variation and appears to be typically steady over the time points. The data generally points to different reactions from the groups to the condition or treatment, with some groups exhibiting higher variability and others exhibiting higher measurement consistency over the course of the observation period. P < 0.001 was considered statistically significant for these data (Figure 4).

Table 1: Time Course of Mean Measurements in Different Experimental Groups.

	Group A	**Group B**	**Group C**	**Group D**	**Group E**
0	3.1	3	3	3	3
1	3	3.3	3.2	3.2	3.3
2	3	3.5	3.1	3.4	3.2
3	3.1	3.6	3	3	3
4	3.1	3.8	3	3.1	3.1
5	3.1	3.9	2.9	3.1	3.1
24	3.1	4	2.9	3.1	3.2

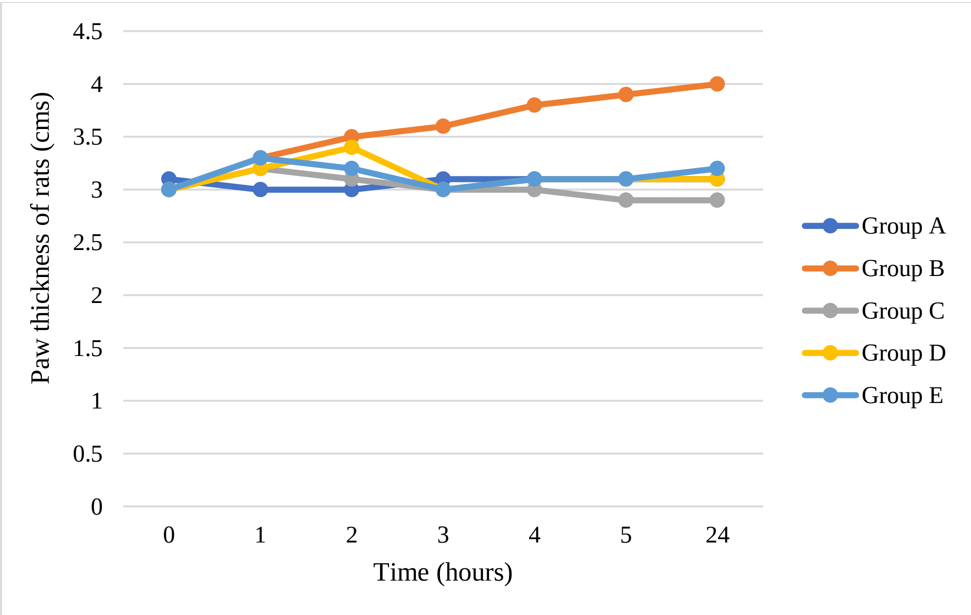

Figure 4: As time progressed from 0 to 24 hours, the paw's thickness (measured in millimeters) varied. significant with n = 5 and a p-value less than 0.001. To induce swelling, the subplantar region of the right hind paw was injected with 0.1 mL of a 1% carrageenan solution.

Activity: Climbing Stairs

Carrageenan was used to cause hyperalgesia in Gathering B rats. The mean values of a variable for each of the treatment groups (A to E) are shown in table 2. Out of all the groups, Bunch A exhibits the greatest mean worth of 3, indicating that this therapy yields the best outcome. When compared to other treatments, Bunch B exhibits the least influence or response, as indicated by its lowest mean value of 0.5. The transitional mean values of Groups C, D, and E are 2.6, 2.8, and 2, respectively, indicating varying levels of treatment effectiveness or effect. The table, in general, offers a succinct comparison of the average results of different treatments, highlighting their overall feasibility or impact on the variable under study. Compared to the creatures in Groups A, C, D, and E, Bunch B had the lowest creature score (Figure 5).

Table 2: Average Values of Various Interventions in Test Groups.

	Various treatment groups
Group A	3
Group B	0.5
Group C	2.6
Group D	2.8
Group E	2

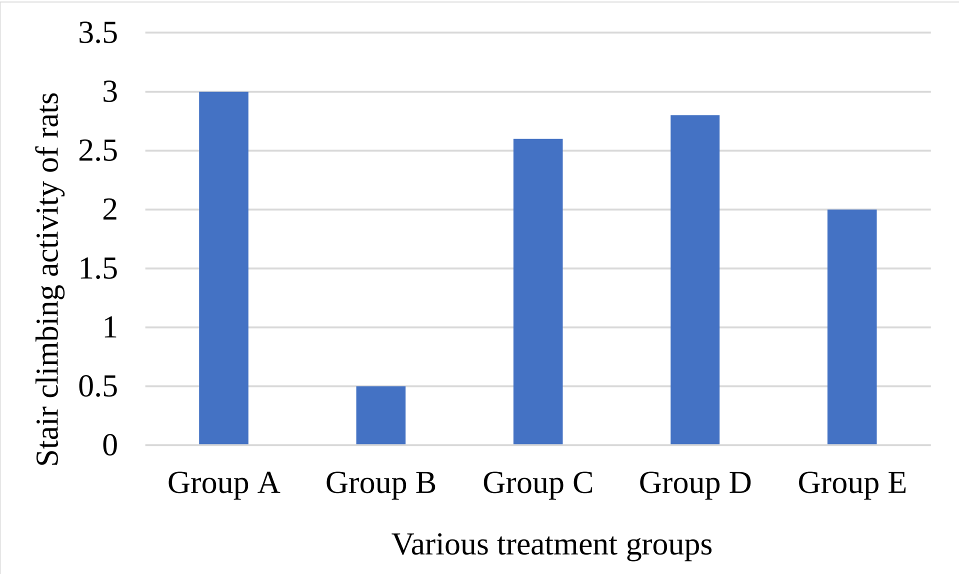

Figure 5: Impact of Lactobacillus on inflammation caused by carrageenan and its correlation with the impairment of stair climbing activity score.

Motility

The mean values of a variable for each of the five treatment groups (A to E) are shown in table 3. When compared to other groups, Bunch An has the most influence or highest result, as seen by its highest mean worth of 3. Bunch B exhibits the lowest reaction of all the groups, with a mean value of 0.2, indicating that this therapy has little effect or effectiveness. In comparison to Gathering A, Groups C and D exhibit moderate effectiveness, with mean values of 2.7 and 2.9, respectively. Compared to Groups C and D, Bunch E exhibits a moderate but lesser reaction, with a mean value of 1.9. Overall, the table offers a fair comparison of the average results of different treatments, showing how each treatment affects the variable being measured or how effective it is overall. When comparing Gathering E with Gathering B animals, this was thought to be the lowest (Figure 6).

Table 3: Mean Values of Various Therapies for All Treatment Groups

	Various treatment groups
Group A	3
Group B	0.2
Group C	2.7
Group D	2.9
Group E	1.9

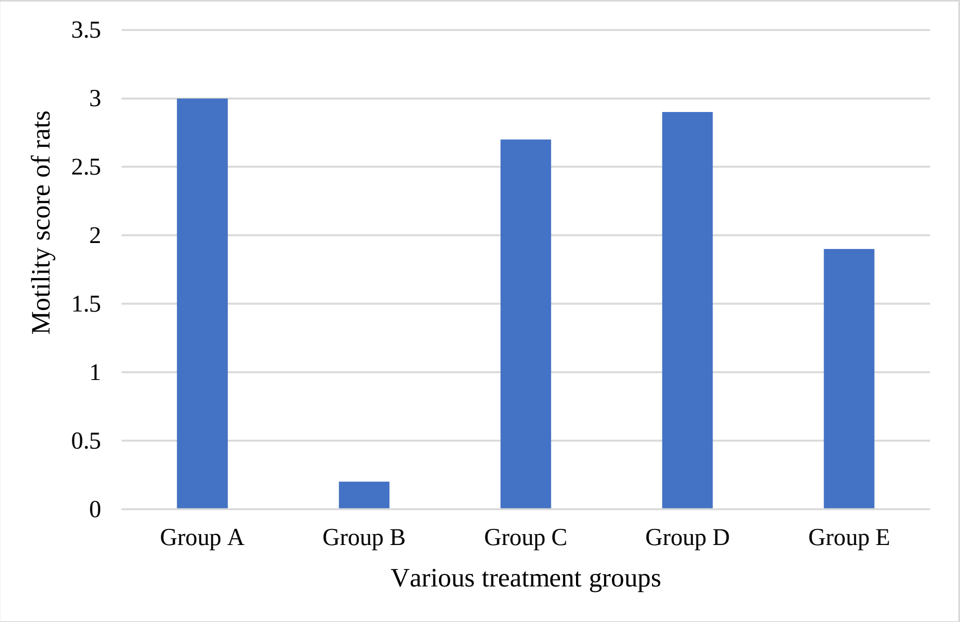

Figure 6: Impact of several medications on motility impairment linked to inflammation generated by carrageenan.

Cytokine Assay

Table 4 presents cytokine expression levels (pg/mL) of IL-6, TNF-α, and IL-10 in various experimental groups (A to E) following oral probiotic administration of Lactobacillus acidophilus and Lactobacillus casei. Group A, receiving both probiotics, showed significantly lower levels of IL-6 (56.44 pg/mL), TNF-α (532.77 pg/mL), and IL-10 (27.077 pg/mL) compared to the control group. Groups C (Lactobacillus casei) and D (Lactobacillus acidophilus) exhibited lower IL-6 (46.59 pg/mL for both) and TNF-α (422.79 pg/mL and 427.79 pg/mL, respectively) levels compared to Group B (control), with significantly higher IL-10 levels (37.67 pg/mL and 40.727 pg/mL, respectively). Group E (combination) displayed elevated IL-10 levels (31.677 pg/mL) and reduced TNF-α (492.54 pg/mL) and IL-6 (66.62 pg/mL) levels. These results suggest that both Lactobacillus acidophilus and Lactobacillus casei may modulate cytokine responses, potentially enhancing anti-inflammatory IL-10 production while mitigating IL-6 and TNF-α effects, underscoring their immunomodulatory potential in beneficial contexts (Table 4).

Table 4: Effect of oral L. acidophilus and L. casei treatment on the expression of cytokines (pg/mL).

Groups	IL-6 (pg/mL)	TNF-α (pg/mL)	IL-10 (pg/mL)
Group A	56.44 ± 0.195*	532.77 ± 0.339*	27.077 ± 0.049*
Group B	72.47 ± 0.268	671.25 ± 0.052	16.17 ± 0.037
Group C	46.59 ± 1.811*	422.79 ± 0.267*	37.67 ± 0.088*
Group D	46.52 ± 0.200*	427.79 ± 0.189*	40.727 ± 0.049*
Group E	66.62 ± 0.133*	492.54 ± 0.230*	31.677± 0.077*

4. Discussion

The carrageenan-induced mouse paw edema model is commonly used to assess the anti-edematous effects of anti-inflammatory drugs, owing to its suitability for this purpose. Carrageenan, a potent chemical, triggers the release of various pro-inflammatory and inflammatory mediators such as bradykinin, histamine, prostaglandins, leukotrienes, TNF-α, and others.

The progression of acute inflammation follows a biphasic pattern. The initial phase, commencing shortly after injection of the inflammatory agent, involves the release of histamine, serotonin, and kinins. Subsequently, prostaglandin-like substances are released over a period of two to three hours during the second phase. Effective clinical responses are observed during this phase with both steroidal and nonsteroidal anti-inflammatory agents, primarily targeting prostaglandins. Anti-inflammatory agents that inhibit prostaglandin production and the inflammatory cascade may be present in Lactobacillus species.

In this inflammation model, as demonstrated in Groups C and D, L. acidophilus and L. casei exhibited prolonged anti-inflammatory effects, resulting in a noticeable reduction in paw thickness. Previous studies have highlighted the gut-mediated anti-inflammatory properties of Lactobacillus. While both the cyclooxygenase and lipoxygenase pathways contribute to inflammation, inhibition of cyclooxygenase is more effective in reducing carrageenan-induced inflammation than lipoxygenase inhibitors.

It is plausible that Lactobacillus inhibits prostaglandin production by targeting the cyclooxygenase enzyme. Oral administration of Lactobacillus led to a significant decrease in pro-inflammatory cytokine levels and an increase in anti-inflammatory cytokine levels. Prostaglandins are known to play a crucial role in inflammatory processes. Anti-inflammatory cytokines such as IL-10, IL-4, and IL-13 inhibit cyclooxygenase-2 synthesis, thereby inhibiting prostaglandin synthesis. L. acidophilus and L. casei appear capable of counteracting the inflammatory effects induced by carrageenan. These ongoing findings align with previous studies indicating IL-10's role in macrophage deactivation, preventing human monocytes from producing TNF-α, IL-1, IL-6, IL-8, and GM-CSF.

Recent years have seen a significant increase in research into metabolic mechanisms that resist intervention in pathological conditions, suggesting that certain dietary components may help maintain a balanced immune response by enhancing or dampening protective responses. Probiotics can potentially regulate the immune system by stimulating the production of specific cytokine patterns from various cell types when exposed to certain probiotic strains. This may involve promoting IL-10 production while reducing TNF-α and INF-γ release, thereby modulating both pro- and anti-inflammatory signaling pathways. Probiotics influence both acquired and innate immunity by interacting with resident microbes or host mucosal cells to initiate or regulate immune responses. This study contributes further evidence supporting the anti-inflammatory properties of probiotics.

Evidence indicates that Lactobacillus exhibits NSAID-like properties, reducing carrageenan-induced paw edema during its initial stages. L. acidophilus and L. casei demonstrated both anti-inflammatory and analgesic effects in this study.

5. Conclusion

The study underscores the significant anti-inflammatory effects of Lactobacillus gel in male Wistar rats with carrageenan-induced paw edema. The treatment notably reduced paw swelling, demonstrating its effectiveness in mitigating severe inflammatory reactions. Histological evaluation supported these findings by showing reduced tissue damage and inflammatory cell infiltration in treated rats compared to the control group. These results suggest that Lactobacillus gel could serve as a promising anti-inflammatory agent, offering a reliable option for managing inflammation-related conditions. Future research should focus on elucidating the underlying mechanisms of its anti-inflammatory properties and evaluating its potential clinical applications. Additionally, L. acidophilus and L. casei effectively reduced carrageenan-induced inflammatory responses. The study also suggests that Lactobacillus might modulate the inflammatory response by inhibiting proinflammatory cytokine pathways.

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