DOI: 10.7860/JCDR/2025/81705.22108

Original Article

Pharmacology Section

Evaluation of Dulaglutide in Acute and Subacute Inflammation Models of Male Wistar Rats: An Experimental Study

AARTI GULABRAO BHOSALE[1], NAYANA KAMALNAYAN HASHILKAR[2], SUNITA Y PATIL[3]

ABSTRACT

Introduction: Dulaglutide, a Glucagon-Like Peptide-Receptor Agonist (GLP-1 RA) commonly used for the treatment of Type 2 Diabetes Mellitus (T2DM), is known for its glycaemic and cardiovascular benefits. However, its anti-inflammatory effects remain uncertain.

Aim: The present study aimed to assess dulaglutide's anti-inflammatory potential in acute and subacute inflammatory models using male rats of Wistar strain.

Materials and Methods: The present experimental study included healthy adult male Wistar rats that received treatment with either dulaglutide or aspirin (as a benchmark) and subjected to carrageenan-induced paw oedema (acute) or foreign body-induced granuloma (subacute). Paw oedema volume, granuloma weight, inflammatory cytokine levels in the serum (IL-1β, CRP, TNF-α), and histopathological changes were evaluated.

Results: A total of 36 healthy adult male Wistar rats were used in this study. The acute model, dulaglutide did not significantly reduce paw oedema compared to the control, while aspirin significantly reduced oedema at 2, 4, and 5 hr ($p<0.05$). In the subacute model, dulaglutide failed to reduce granuloma weight or significantly alter serum inflammatory markers. Histopathological examination revealed abundant granulation tissue, fibroblasts, and collagen in the dulaglutide-treated group, similar to that in the control. In contrast, aspirin-treated rats showed reduced granulation tissue, fibroblasts, and collagen.

Conclusion: Dulaglutide showed no significant independent anti-inflammatory effects in both acute and subacute animal models of inflammation. Thus, GLP-1 receptor agonists like dulaglutide may exert beneficial effects on inflammation associated with metabolic diseases; however, their direct anti-inflammatory actions appear to be limited. Further research is required to explore dulaglutide's role in inflammation and its broader therapeutic implications in inflammatory diseases.

Keywords: Anti-inflammatory agents, Diabetes mellitus, Glucagon-like peptide-1 receptor agonists, Granuloma

INTRODUCTION

Insulin resistance and persistent hyperglycaemia attributed to impaired insulin secretion and compromised function are characteristics of T2DM, which is related to reduced life expectancy attributed to the elevated risk of cardiovascular diseases, neuropathy, renal disease, and other complications [1,2]. The pathophysiology of T2DM involves insulin resistance, β-cell dysfunction, and abnormal glucose metabolism in various organs [3]. Glucolipotoxicity, oxidative stress, and chronic inflammation are additional contributing factors [4].

The close link between T2DM and low-grade chronic inflammation is well-established. Inflammation contributes to the pathogenesis and progression of T2DM, leading to several complications. It weakens immune defences and worsens insulin resistance, complicating disease management [5,6]. It contributes to resistance to insulin and dysfunction of β-cell by disrupting insulin signalling pathways, upregulating pro-inflammatory cytokines, and interfering with β-cell function of pancreas, leading to declined insulin discharge, further exacerbating hyperglycaemia [7]. Pro-inflammatory cytokines namely Interleukin (IL) IL-6, IL-1β, and Tumour Necrosis Factor-alpha (TNF-α) are markedly increased even in children and adolescents, while anti-inflammatory cytokines like adiponectin are decreased. This shows that inflammation has a prominent role in β-cell impairment, even in younger populations where complications from other diseases are minimal [8].

Oxidative stress contributes significantly to insulin resistance, dyslipidaemia and β-cell dysfunction [9]. T2DM is a multifaceted disorder beyond hyperglycaemia, with exosomes being key regulators of intercellular communication and immune responses in T2DM [10]. The interplay among β-cell dysfunction, insulin resistance, oxidative stress, and inflammation contributes to disease progression. Deciphering these complex mechanisms is a key to developing robust management strategies and potential new treatments.

Several therapeutic approaches including supplementation of the diet with anti-inflammatory compounds and antioxidants, such as vitamin D and other micronutrients [11,12], lifestyle modifications, pharmacological interventions, such as metformin and thiazolidinediones, and novel anti-inflammatory agents [13], which include small molecules and monoclonal antibodies targeting inflammatory pathways, have been explored [14]. Promoting mitochondrial biogenesis is promising for insulin resistance reversal and improving β-cell function of pancreas [15]. The use of macrophage membranes to capture inflammatory stimuli and block the inflammation cascade is a promising strategy [16]. By addressing both inflammation and metabolic dysfunctions, these strategies ensure comprehensive and effective management. However, the development of novel anti-inflammatory agents specifically designed for T2DM management is an emerging field.

The GLP-1 RAs improve control over blood sugar levels, and they exhibit notable anti-inflammatory effects in T2DM [17]. They downregulate inflammatory macrophage activation molecule and cytokine levels. They upregulate anti-inflammatory adiponectin and adipokines and downregulate pro inflammatory molecules such as Cluster of Differentiation 163 (CD163), TNF-α, IL-1β and IL-6 [18]. Also, GLP-1 and its analogues inhibit endothelial inflammatory reactions induced by various factors and protect the endothelium from inflammation and ischaemia-reperfusion injury [19].

GLP-1 RAs show pleiotropic effects on different tissues and cellular components of inflammation, with well-recorded anti-inflammatory actions in chronic inflammatory diseases such as neurodegenerative disorders, atherosclerosis, diabetic nephropathy, asthma, non-alcoholic steatohepatitis, and psoriasis [20-22]. They counteract the inflammatory components of T2DM pathophysiology, which impair beta cell function and insulin action.

Dulaglutide, a GLP-1 RA, regulates blood glucose levels and exhibits anti-inflammatory effects. It stimulates insulin secretion and reduces glucagon levels. It alters intestinal floral composition after 48 weeks of administration [23]. Dulaglutide's anti-inflammatory effects extend beyond glycaemic control; it improves multiple cardiovascular risk factors, including body weight, lipid profiles such as High Density Lipoproteins (HDL)-C, triglycerides, and non-HDL-C levels, and Glycated Haemoglobin (HbA1c) levels. These concurrent treatments of the patients with Sodium Glucose Cotransporter 2 (SGLT 2) inhibitors amplifiy the effects [24]. After 12 weeks of treatment, dulaglutide reduces the thickness of Epicardial Adipose Tissue (EAT) by 20%, which is significant considering that EAT is a modifiable cardiometabolic risk factor [25]. Dulaglutide, similar to its other GLP-1 RAs counterparts, exerts both direct and indirect effects on immune function, contributing to therapeutic benefits beyond glycaemic control [26]. However, it is unclear whether their anti-inflammatory properties are independent of their glucose-lowering effects. This study evaluates the anti-inflammatory activity of a GLP-1 RA, dulaglutide, independent of its hypoglycaemic effect, in managing inflammation in models of inflammation (acute and subacute) in male Wistar rats. This is a part of a larger study that evaluates the independent anti-inflammatory effects of lixisenatide [27] and dulaglutide. The studies on the two drugs are independent of each other, and this paper presents only the results with dulaglutide.

MATERIALS AND METHODS

The present experimental study on male Wistar rats, was conducted over a year from January 2017 to December 2017 at the department of Pharmacology of JN Medical College, Belagavi, Karnataka, India. The Institutional Animal Ethics Committee approved the study (CAH-JNMC: Reg.No 627/02/a/CPCSEA). The animals were housed, experimented on, and sacrificed humanely in accordance with guidelines of the Committee for Control and Supervision of Experiments on Animals (CCSEA).

Inclusion and Exclusion criteria: The study included adult healthy male Wistar rats weighing between 160 and 200 grams (180±20 g). Only animals that were clinically healthy, active, and free from any signs of disease or injury were selected for experimentation. Female rats (including those that were pregnant or lactating), animals with visible signs of illness, injury, or behavioural abnormalities, those with congenital or acquired diseases, underweight or overweight rats outside the specified weight range, and any animals that had been previously used in other experiments or had received prior pharmacological treatment were excluded from the study.

Sample size selection: A total of 36 healthy adult male Wistar rats were used in this study. The animals were divided into two sets: acute and subacute inflammation models. Each set comprised three groups with six rats per group (n=6), with a total of six groups. This group size was chosen based on established protocols in similar pharmacological and anti-inflammatory studies [28,29] ensuring sufficient statistical power to detect significant differences while adhering to ethical guidelines that advocate for the minimal use of animals. The design allows for effective comparison among control, standard, and test treatment group within both acute and subacute models.

Study Procedure

Acute model (carrageenan-induced rat paw oedema): For this model, 18 animals categorised into three groups (n=6) were subjected to overnight fasting with water ad libitum. All the drugs were administered through appropriate routes after converting them into clinically corresponding doses [Table/Fig-1] [30]. The control group received 0.5 mL of 1% gum acacia suspension orally, while the treatment groups were administered clinically equivalent doses of either aspirin (200 mg/kg body weight of rat, equivalent to 2222 mg of clinical dose) [31] in 1% gum acacia, orally or dulaglutide (0.15 mg/kg body weight of rat, equivalent to 1.5 mg of clinical dose) [32], subcutaneously. Thirty minutes post-aspirin and two days post-dulaglutide treatment, 0.05 mL of carrageenan (1%) in normal saline was injected into subplantar area of left hind paw [Table/Fig-2]. The malleolus of the leg was marked to ensure consistent dipping. Volume of paw oedema in millilitres was quantified using a digital plethysmograph via the water displacement method [Table/Fig-3] at 0 (immediately post-carrageenan injection), 0.5, 1, 2, 3, 4, and 5 h. The difference between the volumes at zero and subsequent measurements were calculated [33].

Model	S. no.	Groups	Drug administered	Dose	No. of animals
Acute model	I	Control (Vehicle only)	1% gum acacia administered with distilled water	10 mL/kg p/o	6
	II	Standard Control	Aspirin	200 mg/kg p/o [32]	6
	III	Treatment	Dulaglutide	0.15 mg/kg s/c [33]	6
Subacute model	IV	Control (Vehicle only)	Distill water with 1% gum acacia	10 mL/kg p/o	6
	V	Standard control	Aspirin	200 mg/kg p/o	6
	VI	Treatment	Dulaglutide	0.15 mg/kg s/c	6

[Table/Fig-1]: Details of the drugs, dose and administration, and animals used.

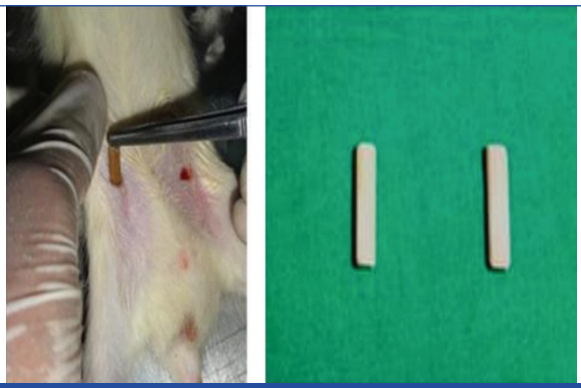
[Table/Fig-2]: Induction of acute paw oedema in rats using carrageenan. Acute inflammation was induced by sub-plantar injection of 0.05 mL of 1% carrageenan solution (prepared in normal saline) into the hind paw of rats.

Subacute model (granuloma induced by foreign body): Animals were categorised into groups of three (n=18, 6 per group). The hair in the axillary and groin regions was trimmed. A pair of 10 mg each sterile cotton pellets [Table/Fig-4] and a pair of sterile grass-piths (25×2 mm) [Table/Fig-5] was randomly implanted subcutaneously through a tiny incision, under thiopental sodium anaesthesia [Table/Fig-5]. After recovering from anaesthesia, the wounds were sutured and the animals were confined individually.

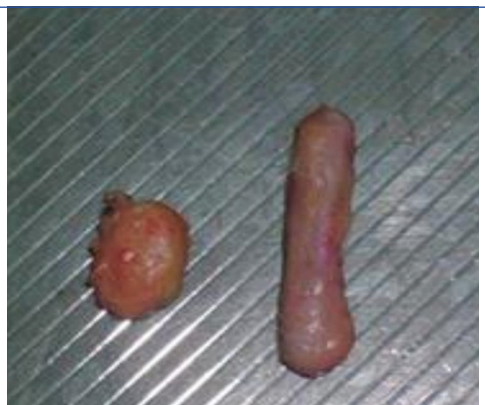
On the implantation day, treatment was initiated and repeated every 24 hour in the control and aspirin group for 10 days; dulaglutide was administered every two days. On day 11, 5 mL blood was obtained through cardiac puncture for estimation of inflammatory cytokines. Rats were euthanised using an overdose of thiopentone anaesthesia, and the cotton pellets and grass piths were collected [Table/Fig-6]. The pellets, devoid of superfluous tissue, were desiccated overnight in the incubator at 60ºC to ascertain their dry weight. The difference between the recorded weights and the cotton pellet's initial weight (10 mg) was calculated as net granuloma formation. The mean of

[Table/Fig-3]: Measurement of rat paw oedema in an acute inflammation model using a digital plethysmometer. Paw volume was measured using a digital plethysmometer to assess the extent of carrageenan-induced oedema in the hind paw of rats.

[Table/Fig-4]: Cotton pellet used as a foreign body in the subacute inflammation model in rats. Sterile cotton pellets (weighing 10 mg) were implanted subcutaneously in the groin region of rats to induce granuloma formation and assess subacute inflammatory response.



[Table/Fig-5]: Implantation of grass pith as a foreign body in a subacute inflammation model. Grass pith rods were implanted subcutaneously in rats to induce granuloma formation as part of a subacute inflammation study.



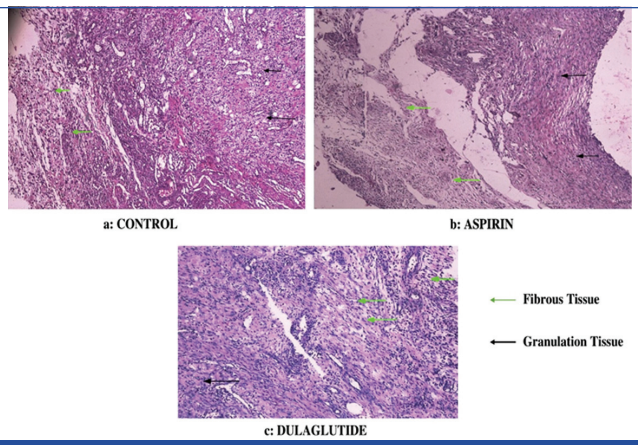
[Table/Fig-6]: Cotton pellet and grass pith surrounded by granulation tissue in a subacute inflammation model. Subcutaneously implanted foreign bodies were surrounded by granulation tissue in rats, representing the subacute inflammatory response.

granuloma's dry weight for different groups was determined and represented as mg per 100 g of body weight.

The granuloma dry weight inhibition as percentage was computed as follows [34,35]:

$$Percentage\ inhibition\ of\ granuloma\ dry\ weight = \left[1 - \frac{Dry\ weight\ of\ granuloma\ in\ treated\ group}{Dry\ weight\ of\ granuloma\ in\ control\ group}\right] \times 100$$

In 10% formalin the grass piths were preserved until use; they were processed and sectioned for staining using Haematoxylin and Eosin (H&E). Each group's granulation tissue was microscopically examined [Table/Fig-7] [34]. The blood collected prior to the sacrifice of the rats was centrifuged, and amounts of markers of inflammation, TNF-α, C-Reactive Proteins (CRP), and IL-1β in the resultant serum were quantified using Enzyme linked immunosorbent assay. (ELISA)



[Table/Fig-7]: Photomicrographs of grass pith implants surrounded by granulation tissue in the subacute inflammation model (H&E staining, 10× magnification). Abundant granulation tissue, inflammatory cell infiltration, and fibrous tissue were observed in the control group (a) and dulaglutide-treated group [27] (c); A marked reduction in granulation tissue, fibrous tissue, and inflammatory cells was noted in the aspirin-treated group (b).

STATISTICAL ANALYSIS

All data are expressed using mean±SEM and were analysed using One-way Analysis of Variance (ANOVA). The results were then analysed using Dunnett's test. Analysis of aspirin and dulaglutide groups was done by using One-way ANOVA and post-hoc Bonferroni's test. The analysis was performed using GraphPad prism, and the criterion for statistical significance was set at $p \leq 0.05$.

RESULTS

Acute model: Significant reduction in volume of paw Oedema of animals in the aspirin treatment group was observed at 2, 4, and 5 h when compared to that in the control ($p<0.05$, one-way ANOVA followed by Dunnett's post-hoc test; [Table/Fig-8]). However, there was no significant reduction in volume of paw oedema of animals in the dulaglutide treatment group compared to that in the vehicle treatment group [Table/Fig-8].

Time after carrageenan injection	Paw oedema in mL (Mean±SD)			ANOVA result p-value
	Control	Aspirin	Dulaglutide	
½ h	0.001±0.113	0.033±0.071	0.08±0.098	0.781
1 h	0.015±0.105	-0.121±0.086	0.04±0.171	0.142
2 h	0.053±0.1	-0.183±0.120*	0.08±0.269	0.003
3 h	0±0.247	-0.165±0.096	0.07±0.073	0.159
4 h	0.028±0.198	-0.175±0.137*	-0.00±0.098	0.008
5 h	0.025±0.201	-0.156±0.145*	-0.03±0.098	0.020

[Table/Fig-8]: Effect of various treatments on carrageenan-induced paw oedema. n=6 in each group, data analysed using one-way ANOVA followed by Dunnett's post-hoc test for comparison with control group: *p≤0.05. SD: Standard deviation

Post-hoc analysis using Bonferroni's test indicated that there was no considerable decrease in oedema of animals in the dulaglutide group in contrast with vehicle group [Table/Fig-9]. The dulaglutide and aspirin group's oedema, however, only showed a difference that was statistically significant at two and three hour [Table/Fig-9].

Time after carrageenan injection	Paw oedema in mL (Mean±SD)		ANOVA result	
	Aspirin	Dulaglutide	F 5,10	p-value
½ h	0.03±0.05	0.08±0.10	1.461	0.50
1 h	-0.12±0.07	0.04±0.17	0.9124	0.36
2 h	-0.18±0.10	0.08±0.27	1.314	0.04*
3 h	-0.16±0.07	0.07±0.00	0.7142	0.03*
4 h	-0.17±0.12	0.00±0.10	1.258	0.07
5 h	-0.15±0.12	-0.03±0.10	1.051	0.38

[Table/Fig-9]: Effect of dulaglutide on carrageenan-induced paw oedema in comparison to the aspirin group.
n=6 in each group. Post-hoc analysis using Bonferroni's Test: *p< 0.05. SD: Standard deviation

Subacute inflammation model: Post-hoc analysis using Dunnett's test indicated that the mean dry weight of the 10-day-old granuloma (expressed as mg per 100 g of body weight) was found to be significantly (p<0.001) lower in aspirin treatment group compared to the control group [Table/Fig-10]. However, post-hoc analysis using Bonferroni's test revealed that dulaglutide treatment resulted in a significantly higher granuloma dry weight compared to that in the aspirin treatment [Table/Fig-11], indicating dulaglutide was less effective than aspirin.

S. no.	Drug treatment	Mean granuloma dry weight mg/100 g body weight (Mean±SD)	Percentage inhibition	p-value
1.	Control	37.25±7.24	-	-
2.	Aspirin	21.58±6.15*	42.07%	0.0009
3.	Dulaglutide	35.25±4.94	12.97%	0.799

[Table/Fig-10]: Effect of treatments on granuloma dry weight.
n=6 in each group. ANOVA: F3,20 = 9.980, p<0.001. Post-hoc analysis by Dunnett's test: *p<0.001. p-values represent comparisons vs. control group. SD: Standard deviation

S. no.	Drug treatment	Mean granuloma dry weight mg/100 g body weight (Mean±SD)
1.	Aspirin	21.58±6.15
2.	Dulaglutide	35.25±4.94*

[Table/Fig-11]: Effect of dulaglutide on granuloma dry weight compared to that in the aspirin group.
n=6 in each group. ANOVA: F2,15 = 2.955, p=0.0048, Post-hoc analysis using Bonferroni's test *p<0.01 compared to aspirin group. SD: Standard deviation

The impact of dulaglutide on serum inflammatory markers such as IL-1β, CRP, and TNF-α, was examined. The levels of these indicators did not significantly differ amongst the control and treatment groups [Table/Fig-12].

Histopathological investigations were used to further assess dulaglutide's impact on inflammation. The H&E stained sections of granulation tissue obtained from the grass piths, examined under 10× magnification, indicated significantly less granulation tissue, fibroblasts, and collagen in aspirin group, compared to that in control group. However, there was no noticeable reduction in fibroblast count, collagen and granulation tissue in dulaglutide treatment [Table/Fig-7].

DISCUSSION

In the present study, the anti-inflammatory activity of dulaglutide, an anti-diabetic drug, was evaluated in acute and subacute inflammatory models of male Wistar rats. In the acute model, dulaglutide failed to show a considerable reduction in volume of paw oedema in contrast with vehicle group, while aspirin significantly reduced paw oedema. The results were similar in the subacute model, with dulaglutide not inducing a substantial decrease in weight of granuloma compared to that in aspirin-treated group. Furthermore, dulaglutide did not significantly affect the measures of inflammatory markers (TNF-α, CRP, and IL-1β). Histopathological analysis revealed abundant granulation tissue, fibroblasts, and collagen in the dulaglutide-treated group; marked reduction in granulation tissue, fibroblasts, and collagen was observed in the aspirin-treated group. No independent anti-inflammatory activity was observed with dulaglutide treatment, in both acute and subacute models of inflammation.

Some antidiabetic medications exhibit holistic effects in managing T2DM, including anti-inflammatory properties. These medications positively impact various aspects of T2DM management and associated complications. The most widely used first-line therapeutic, metformin significantly reduces the proinflammatory cytokine levels (IL-6, IL-1β, and IL-17) while increasing the measures of anti-inflammatory cytokines like IL-37 in T2DM patients [36]. In a mouse model of Lipopolysaccharide (LPS) induced cytokine storm, oral and intraperitoneal metformin administration significantly reduced IL-1, IL-6, and TNF-α levels [37]. Similarly, in diabetic db/db mice, metformin decreased the pro inflammatory cytokine levels in both tissue and blood; oxalate enhanced these anti-inflammatory effects [38].

Dipeptidyl Peptidase 4 inhibitors (DPP-4), SGLT2 inhibitors, and GLP-1 RAs show promising cardiovascular outcomes and decrease mortality in high-risk T2DM patients. Among the various therapeutics, GLP-1 RAs show promising anti-inflammatory effects across various chronic inflammatory diseases, such as atherosclerosis, type 1 and 2 diabetes, diabetic nephropathy, non-alcoholic steatohepatitis, neurodegenerative disorders, psoriasis, and asthma [39]. Their anti-inflammatory properties could have implications beyond metabolic diseases, with potential applications in managing complications associated with viral infections, such as Coronavirus Disease 19 (COVID-19) and asthma [40,41].

The GLP-1 RAs show anti-inflammatory effects in diabetic animal models. The pleiotropic effects of GLP-1 RAs were not limited to glycaemic control; they offered potential benefits in cardiovascular health, kidney function, and respiratory wellness [42,43]. This suggests that the observed anti-inflammatory properties of dulaglutide and the other candidate GLP-1 RAs could be a class effect. Until recently, understanding of the specific cell types and pathways that contributed to these effects remained limited. The brain GLP-1 receptor is the key to anti-inflammatory properties of these agonists in Toll-like receptor and sepsis-mediated inflammation [26]. This finding provides valuable insights for understanding the mechanism of action of the GLP-1 RAs.

The GLP-1 RA, dulaglutide exhibited significant anti-diabetic and weight-loss effects in multiple studies. Dulaglutide showed sustained glycaemic efficacy, improvements in Major Adverse Cardiovascular Event (MACE) outcomes, and also favourable effects on body weight in patients with T2DM [44]. Additionally, dulaglutide treatment reduces the levels of HbA1c and Body Mass Index (BMI) [25,45]. Both dulaglutide and liraglutide ameliorate atherosclerosis development in animal models and reduce cardiovascular risk in T2DM patients [46,47]. They markedly

S. no.	Drug treatment	Serum levels (Mean±SD)					
		TNF-α (pg/mL)	p-value	IL-1β (pg/mL)	p-value	CRP (ng/mL)	p-value
1	Control	4.74±6.88	-	3634±2776.2	-	11.45±3.84	-
2	Aspirin	24.71±13.63	0.060	1622.41±1729	0.062	14.99±4.29	0.461
3	Dulaglutide	22.12±17.77	0.074	3437.21±3311.9	0.739	10.75±7.86	0.965

[Table/Fig-12]: Effect of various treatments on serum inflammatory markers.
n=6 in each group. Data were analysed using One-way ANOVA followed by Dunnett's post-hoc test; p-values represent comparisons vs. control group. SD: Standard deviation

suppress the expression of inflammatory factors in LPS-induced atherosclerosis and promote the polarisation of M1 macrophages toward the M2 phenotype, improving the function of co-cultured endothelial cells [20]. However, there is a notable difference in the intervention duration; liraglutide shows significant effects after 24 hour but dulaglutide requires 72 hour to exhibit similar levels of effect. In an LPS-induced acute lung injury model in mice, dulaglutide significantly alleviated lung injury, decreased pro inflammatory cytokine expression, and inhibited neutrophil and macrophage infiltration in lung tissues [48]. It also showed protective effects against inflammation and apoptosis. It downregulated the expression of NOD, LRR and Pyrin domain-containing protein 3 (NLRP3) and Phosphorylated Signal Transducer and Activator of Transcription 3 (P-STAT3) [48].

Despite the promising anti-inflammatory effects observed when using GLP-1 RAs, there are some contraindications to their use. These include the adverse gastrointestinal effects such as vomiting, nausea, and diarrhoea [49]. They have been linked to an increased frequency of acute pancreatitis [50]. This has led to the Food and Drug Administration (FDA) announcing potential safety concerns for twelve of the GLP-1 RAs in the market [51]. Even with respect to cardiovascular benefits, there are contradictory indications. They help reduce cardiovascular disease risk in people with T2DM. However, their influence on the Wnt/β-catenin pathway raises potential concerns regarding an increase in the risk of colorectal cancer [52].

Dulaglutide is promising in managing diabetes and its complications; however, mild pancreatic changes in animal models are reported. In Zucker diabetic fatty rats, dulaglutide treatment potentially leads to an increase in the activity of pancreatic amylase and mild alterations in ductal epithelium [53]. However, a long-term study in cynomolgus monkeys shows no evidence of pancreatitis or preneoplastic changes in the exocrine pancreas [54]. An instance of morbilliform drug eruption related to dulaglutide has been recorded, suggesting potential for adverse skin reactions [46]. Severe vaginal bleeding after a second dose of dulaglutide was reported in a perimenopausal woman [55]. Acute pancreatitis was reported in a patient using dulaglutide, emphasising the importance of monitoring pancreatic enzyme levels in patients taking this medication [56]. These reports highlight the need to further study the long-term implications of using these receptor agonists, including dulaglutide, before considering them for anti-inflammatory applications.

The lack of anti-inflammatory activity of dulaglutide in the animal models of inflammation is a key finding. The present study provides important insights into the anti-inflammatory activity of dulaglutide or the lack thereof and highlights the need for further research to understand its activity in different models of inflammation. Caution is advised when interpreting the results as the anti-inflammatory activity of dulaglutide could vary with the model of inflammation.

Limitation(s)

Despite presenting some key findings, the study has some limitations. These include the use of a single dose of dulaglutide and the lack of comparison with other anti-inflammatory drugs. In addition, a larger sample size monitored over a longer period of time could yield more insights. It is also important to fully understand the anti-inflammatory activity of dulaglutide in a few additional models of inflammation, preferably those that accurately represent the chronic inflammatory conditions well-established in T2DM.

CONCLUSION(S)

The present study finding add evidence to the possible lack of independent anti-inflammatory activity of dulaglutide. While the anti-inflammatory effects of dulaglutide as part of its positive influence in T2DM is evident, its potential independent anti-inflammatory activity and the complete understanding of its mechanisms of action remains limited. Elucidating the relationship between GLP-1 RAs, inflammation, and T2DM management would enable better understanding of their mechanisms of action and possible broader implications in diabetes care. Specifically, the additive anti-inflammatory effects of dulaglutide may contribute to its overall therapeutic benefit in T2DM management. Deciphering the molecular mechanisms that drive the anti-inflammatory effects of dulaglutide, particularly focusing on its impact on inflammatory markers, oxidative stress, and signalling pathways such as STAT3 and NLRP3, is a key future direction. It is also important to compare the independent anti-inflammatory effects of dulaglutide with that of other similar candidates in different inflammation models to determine if the efficacy or mechanism of action differs significantly. The potential synergistic effects of dulaglutide and other anti-inflammatory agents or antidiabetic drugs in managing inflammation-related complications in metabolic disorders are another potential direction. The long-term positive influences of dulaglutide in patients with T2DM with respect to inflammation and its impact on other co-morbidities such as fatty liver, kidney disorders, and cardiovascular outcomes and on other metabolic syndrome is an interesting direction to pursue.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India.
2. Professor, Department of Pharmacology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India.
3. Professor, Department of Pathology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Aarti Gulabrao Bhosale,
Assistant Professor, Department of Pharmacology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi, Karnataka, India.
E-mail: draartibhosale.mbbs@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 08, 2025
- Manual Googling: Aug 12, 2025
- iThenticate Software: Sep 20, 2025 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 30, 2025**
Date of Peer Review: **Jul 15, 2025**
Date of Acceptance: **Sep 22, 2025**
Date of Publishing: **Dec 01, 2025**