*Article*

# Vildagliptin attenuates carrageenan-induced air pouch inflammation in rats via modulation of COX-2/ PGF-2α and NF-κB signaling cascade

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**Abstract:**

The carrageenan-induced-air pouch is a particularly good model for evaluating the relationship between inflammation and its related vital mediators. Vildagliptin is an active dipeptidyl peptidase-4 (DPP-4) inhibitor, which is known to possess an anti-hyperglycemic efficacy. The present study was established to investigate the effect of vildagliptin on the carrageenan-induced air pouch model of inflammation. Four groups of rats, each containing eight rats, were used. The experiment was performed over six days. Starting from the first day of the experiment, an air pouch was established on alternate days in the four groups by injecting 20 ml of sterile air subcutaneously into the rat intracapsular area. On the last day of the experiment, rats in the third and fourth groups received vildagliptin 5, and 10 mg/kg, respectively, orally half an hour before carrageenan was given. The second group received indomethacin (10 mg/kg) half an hour before carrageenan was given. Three hours later, the air pouch was opened and the entire exudate of each animal was harvested to assess myeloperoxidase (MPO) & superoxide dismutase (SOD) activities, tumor necrosis factor-alpha (TNF-α), nuclear factor kappa-B (NF-κB), cyclooxygenase 2(COX-2), prostaglandin F2-alpha (PGF-2α), interleukin 10 (IL-10) levels. Vildagliptin 5 mg/kg, 10 mg/Kg, and indomethacin significantly suppressed the NF-κB signaling pathway, reduced TNF-α, MPO, COX-2, PGF2-α levels, while enhancing that of IL-10, and SOD

activity. The findings of this study revealed that vildagliptin has an inhibitory effect on inflammation in carrageenan-mediated air pouch in rats by inhibiting COX-2/PGF2-α activity and suppressing the NF-kB signaling pathway.

*Keywords: Inflammation; carrageenan; vildagliptin; indomethacin.*

## 1. Introduction:

Inflammation is a common component that is linked to the host's response to damage and infection. Numerous disorders such as diabetes, atherosclerosis, and rheumatoid arthritis, are reported to be attributed to excessive inflammation **[1]**. These events would be associated with the production of many critical inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and prostaglandin F2-alpha (PGF-2 α) which is known to be a vasoactive cyclooxygenase-catalyzed prostaglandin, and has been reported to be involved in the control of complex pathophysiological processes, the most crucial of which is inflammation **[2].** Additionally, the inflammatory responses are thought to be triggered by a surge in reactive oxygen species (ROS) release **[3],** and adhesion molecules as well **[4]**.

It's interesting to note that overexpression of dipeptidyl peptidase 4 (DPP-4) has been implicated in oxidative stress, inflammation, and apoptosis **[5,6]**. DPP-4 is a cell surface aminopeptidase that was first discovered as a T cell differentiation antigen (CD26) **[7],** controls inflammation either enzymatically via the breakdown of immune-regulatory peptides or through its soluble form, which interacts with immune cells directly **[8].** DPP-4 is found in a variety of tissues, including the lung, spleen, pancreas, kidney, liver, and intestinal cells. As well, the existence of DPP-4 is also associated with monocytes, natural killer cells, macrophages, and epithelial and endothelial cells **[9]**. DPP-4 seems to be involved in the interaction between innate and adaptive immunity, affecting the immune system and certain tissue functions **[10]**. The importance of DPP4 inhibitors has greatly increased in the scientific and medical communities **[11].** Vildagliptin is an active DPP-4 inhibitor; that binds the DPP-4 catalytic site, prolonging the action of incretins **[12].** Vildagliptin is known to be applied as a solo or combined therapy in the treatment of type 2 diabetes mellitus.

Indeed, exaggeration in an oxidative stress state and the activation of nuclear factor kappa-B (NF-κB) signaling are always suggested to be associated with inflammation progress **[13, 14]**. Besides, it was found that activation of (TNF-α) may be induced by an increase in the production of DPP-4 **[15]**. The NF-κB signaling pathway is considered an important regulator responsible for the transcription of TNF-α and is also implicated in the expression of cyclooxygenase-2 (COX-2), contributing to the activation of further inflammatory cascades **[16, 17].** Indeed**,** TNF-α is considered one of the mediators that are generated by activated macrophages and monocytes and leads to a rise in vascular endothelial permeability **[18]**. The current study was intended to explore the effect of vildagliptin on acute inflammation in a carrageenan-induced air pouch model in rats; by investigating its effect on COX-2, PGF-2α, the NF-κB signaling cascade, as well as studying its effect on superoxide dismutase (SOD) activity.

## 2. Materials and Methods

### 2.1. Drugs and chemicals

Carrageenan, Indomethacin, and vildagliptin were obtained from Sigma (St. Louis, MO). All other chemicals were of the finest analytical grade.

### 2.2. Animals

Male Wister albino rats were acquired from Nile Co. for pharmaceutical and chemical industries (Egypt), and housed in plastic cages with wood shave bedding in the animal care unit. The animals were kept in well-ventilated cages at room temperature (28-30) and under controlled light cycles (12 h light/12 h dark). They were fed a standard pellet chow diet and allowed free access to tap water. Animals were kept for at least two weeks before the experiment for acclimatization. The Ethical Committee of the Faculty of Egyptian Russian University, ERUFP-PO-23-004 confirmed the study protocol.

### 2.3. Experimental design:

In this study, a carrageenan-induced air pouch was established according to the previous study **[19]**, rats were randomly divided into four groups of eight rats each. The experiment was performed over six days. Starting from the first day of the experiment, an air pouch was established on alternate days. Upon anaesthetization of rats of four groups via exposure to a compressed gas

mixture of 60:40 $CO_2/O_{2;\ an}$ air-pouch was established by injecting 20 ml of sterile air subcutaneously into the intracapsular area of the back of the rat.

On the last day of the experiment, the first group: received only 5 ml of carrageenan (0.5 %) and was considered a control group. While rats in the third and fourth groups received vildagliptin 5 mg/kg and 10 mg/kg, respectively, orally half an hour before carrageenan was given. Whereas, the second group received indomethacin (10 mg/kg) intraperitoneal (IP) half an hour before carrageenan and was considered a reference group **[20,21, 22].**

Three hours later, rats were anesthetized and 10 ml of lavage solution was injected into each air pouch. Afterward, the air pouch was opened by cutting sagittally across it (~2 inches), and the entire exudate of each animal was harvested to assess MPO and SOD activities, as well as levels of inflammatory indicators including TNF-α, NF-κB, COX-2, and PGF-2 α. Also, anti-inflammatory IL-10 was detected.

### 2.4. Spectrophotometric assay of oxidative stress indicators

Tissue levels of MPO (Cat. No: K744-100, Eurodiagnostico, Madrid, Spain), and SOD (Cat. No.SD2521, Dokki, Giza, Egypt) were detected using commercially available kits according to the manufacturer's instructions, and results for MPO, and SOD were expressed as μmol/min/mg tissue, U/mg protein, respectively.

### 2.5. Enzyme-linked immunosorbent assay (ELISA)

Additionally, tissue levels of NF-κB (Cat. No: SEB824Mu, Cloud Clone -Corp, Katy, Texas, USA), IL-10 (Cat. No. SEA056Ra, Cloud Clone -Corp, Katy, Texas, USA), TNF-α (Cat. No. SEA133Ra, Cloud Clone -Corp, Katy, Texas, USA), COX-2 (Cat No. MBS725633, Mybiosource, Inc Co., San Diego, USA), and PGF-2α (Cat. No: RTES00662, Cusabio, Dublin, Ireland), were detected via using sandwich ELISA immunoassay commercially available kits as instructed by manufacturers and results were expressed as pg/mg protein for TNF-α, IL-10, and PGF-2 α, while that of NF-κB and COX-2 was expressed as ng/mg protein.

### 2.6. Statistical analyses

All data were expressed as mean ± SD. Statistical analyses of differences among groups were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey Kramer test as

a post hoc test. Differences are considered significant at $p < 0.05$. All analyses and graphs were performed and sketched using Graph Pad Prism (ISI® software, USA) version 5 software.

## 3. Results:

### 3.1. Effect of vildagliptin and indomethacin on NF-κB level.

In the present study, co-treatment with vildagliptin 5, and 10 mg/kg, and indomethacin markedly decreased NF-κB by 70, 79, and 73 % respectively, as compared to the carrageenan group **(Table 1)**.

**Table 1: Effect of vildagliptin and indomethacin in carrageenan-induced air pouch in rats.**

| Groups | NF-κB (ng/mg/protein) | TNF-α (pg/mg/protein) | IL-10 (pg/mg/protein) | MPO (µmol/min/mg tissue) |
|---|---|---|---|---|
| **Carrageenan** | **5.95 ± 1.06** | **247.86 ± 33.92** | **59.98±5.82** | **16.831±2.55[a]** |
| **Indomethacin+ Carrageenan** | **1.58 ±0.45[a]** | **103.082 ±19.825[a]** | **171.28± 31.39[a]** | **7.98±1.43[a]** |
| **Vildagliptin (5 mg/kg) + Carrageenan** | **1.80± 0.52[a]** | **147.26 ±28.32[a]** | **155.71±28.53[a]** | **8.40±1.51[a]** |
| **Vildagliptin (10 mg/kg) + Carrageenan** | **1.22±0.211[a]** | **88.76±9.875[a]** | **244.78±42.041[a,b]** | **6.72±1.21[a]** |

Rats received vildagliptin 5, 10 mg/kg orally, and indomethacin 10 mg/kg, i.p. half an hour before carrageenan (0.5%) was given. Carrageenan group as a control group. Indomethacin+ Carrageenan group as a standard group. Data are represented as mean ± SD (**n = 8**). a: Significant difference from the carrageenan group, at $p<0.05$ using ANOVA followed by Tukey–Kramer as a post-hoc test. **NF-κB**: Nuclear factor-κB**, TNF-α**: Tumor necrosis factor- α, **IL-10**: Interlukin-10, **MPO**: Myeloperoxidase.

### 3.2. Effect of vildagliptin and indomethacin on level of TNF-α.

Furthermore, there was a significant reduction in the level of TNF-α in the groups of rats; that were co-treated with vildagliptin 5, 10 mg/kg, and indomethacin by 41, 64, and 58% respectively, as compared to the carrageenan group **(Table 1)**.

### 3.3. Effect of vildagliptin and indomethacin on the anti-inflammatory IL-10.

Meanwhile, co-treatment with vildagliptin 5, and 10 mg/kg, and indomethacin significantly enhanced the level of IL-10 by 3, 2, and one-fold, respectively, compared to the carrageenan group **(Table 1)**.

### 3.4. Effect of vildagliptin and indomethacin on COX-2 level.

Additionally, as compared to the carrageenan group, co-treatment with vildagliptin 5, and 10 mg/kg, and indomethacin significantly suppressed COX-2 levels by 60, 76, and 74%, respectively **(Fig. 1).**

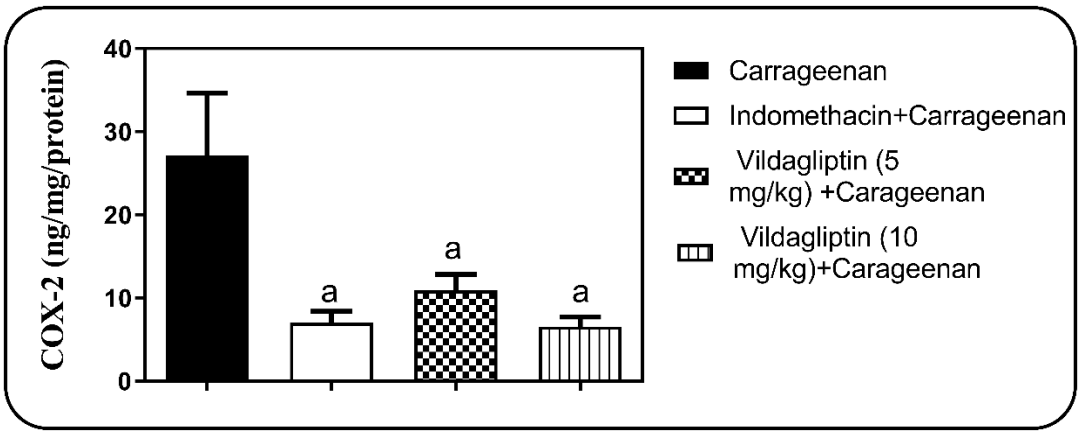


**Fig. 1: Effect of vildagliptin and indomethacin on COX-2 level in carrageenan-induced air pouch in rats.**

Rats received vildagliptin 5, 10 mg/kg orally, and indomethacin 10 mg/kg, i.p. half an hour before carrageenan (0.5%) was given. Carrageenan group as a control group. Indomethacin+ Carrageenan group as a standard group. Data are represented as mean ± SD (n = 8). a: Significant difference from the carrageenan group, at $p<0.05$ using ANOVA followed by Tukey–Kramer as a post-hoc test. COX-2: cyclooxygenase.

### 3.5. Effect of vildagliptin and indomethacin on PGF-2 α level.

**Fig. 2** showed that there was a significant drop in PGF-2 α level in rats co-treated with vildagliptin 5, 10 mg/kg, and indomethacin by 52, 69, and 59 %, respectively, as compared to the carrageenan group.

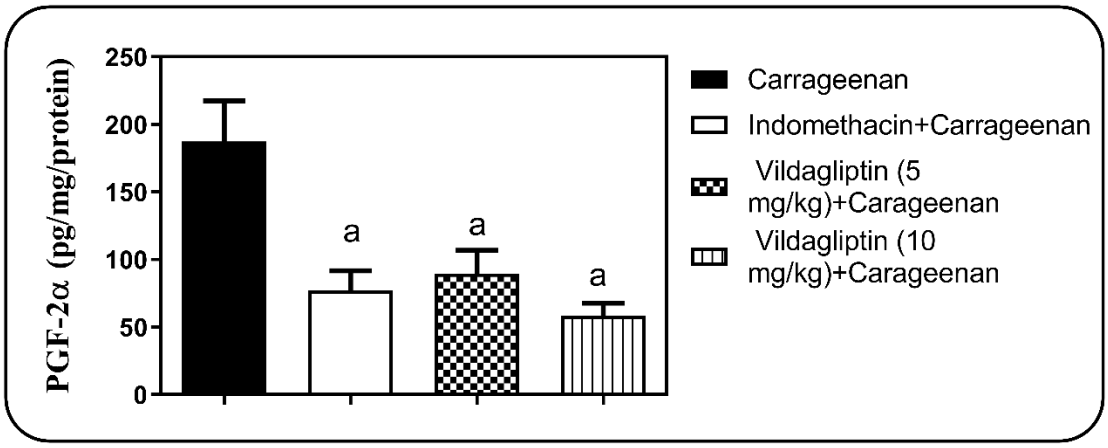


**Fig. 2: Effect of vildagliptin and indomethacin on PGF-2α level in carrageenan-induced air pouch in rats.**

Rats received vildagliptin 5, 10 mg/kg orally, and indomethacin 10 mg/kg, i.p. half an hour before carrageenan (0.5%) was given. Carrageenan group as a control group. Indomethacin+ Carrageenan group as a standard group. Data are represented as mean ± SD (**n = 8**). a: Significant difference from the carrageenan group, at $p<0.05$ using ANOVA followed by Tukey–Kramer as a post-hoc test. **PGF-2 α**: prostaglandin F2-α.

### 3.6. Effect of vildagliptin and indomethacin on MPO.

Besides, co-treatment with vildagliptin 5, 10 mg/kg, and indomethacin significantly reduced MPO activity by 50, 60, and 53%, respectively, as compared to the carrageenan group **(Table 1).**

### 3.7. Effect of vildagliptin and indomethacin on SOD activity.

**Fig. 3** in the current study showed that co-treatment with vildagliptin 5 mg/kg markedly induced SOD levels by 2-fold while that of vildagliptin 10 mg/kg and indomethacin exhibited a significant rise of about 3-fold for both, as compared to the carrageenan group.

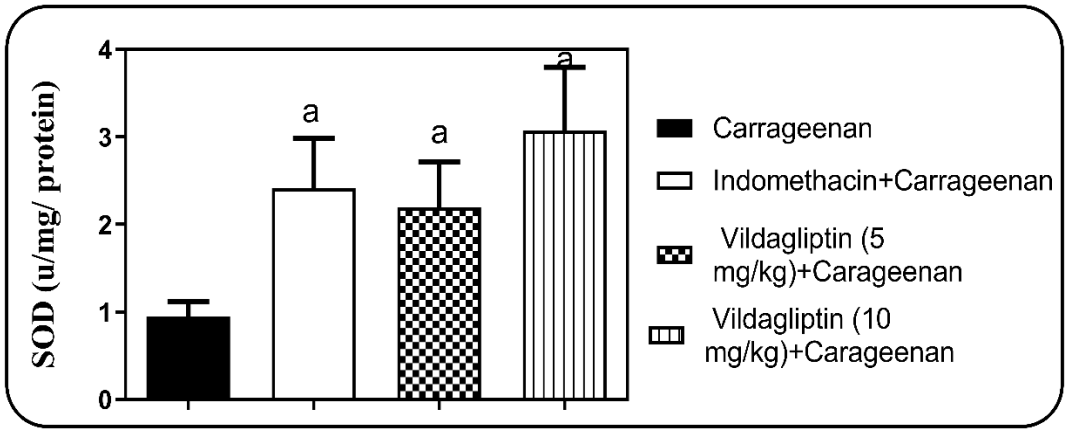


**Fig. 3: Effect of vildagliptin and indomethacin on SOD activity in carrageenan-induced air pouch in rats.**

Rats received vildagliptin 5, 10 mg/kg orally, and indomethacin 10 mg/kg, i.p. half an hour before carrageenan (0.5%) was given. Carrageenan group as a control group. Indomethacin+ Carrageenan group as a standard group. Data are represented as mean ± SD (n = 8). a: Significant difference from the carrageenan group, at $p<0.05$ using ANOVA followed by Tukey–Kramer as a post-hoc test. SOD: superoxide dismutase.

## 4. Discussion

Carrageenan-induced air pouch is a particularly good model for evaluating the relationship between inflammation and its related vital mediators such as cytokines, and prostaglandins **[23]**. The current study was performed to investigate the effect of vildagliptin on inflammation induced by carrageenan in the air pouch of rats while using indomethacin as a standard agent. Other studies showed that upon injection of a carrageenan solution into the rats' air pouch, an inflammatory reaction would occur. This reaction would be expressed mainly by the infiltration of cells, and an increase in exudate, which was reported to be associated with a marked surge in pro-inflammatory mediators, including, cytokines, and prostaglandins **[24]**. The results of the current study demonstrated this initiated inflammatory response upon injection of carrageenan into rats' air pouches.

Indeed, a previous study indicated the role of NF-κB in the expression of pro-inflammatory genes such as cytokines, chemokines, and adhesion molecules **[25]**. NF-κB was demonstrated to elicit expression of TNF-α, which is known to be a critical regulatory cytokine, contributing to

inflammation as well [**26**]. The data of the present study demonstrated an elevation in NF-κB and TNF-α in the carrageenan-induced group; which were in accordance with previous work **[27]**. On the other hand, there was a reduction in NF-κB levels in the vildagliptin-treated groups. The reduction of NF-κB level in the vildagliptin-treated groups was in accordance with another study **[28],** which demonstrated that vildagliptin reduced NF-κB in carbon tetrachloride-induced liver fibrosis. The results suggest the anti-inflammatory effect of vildagliptin. Moreover, there was a reduction in TNF-α in the vildagliptin-treated groups. The findings were in accordance with another study **[29]**, which suggested the potential anti-inflammatory effect of vildagliptin.

Additionally, IL-10 has potent anti-inflammatory properties. These features are mostly attributed to the capability of IL-10 to inhibit inflammatory components and their function in initiating immune responses **[30].** The results of the present study demonstrated a reduction in IL-10 levels in the carrageenan group. On the other hand, our study showed an increase in IL-10 in the vildagliptin-treated groups. The detected rise was in line with a previous study **[31]**, which demonstrated the protective effect of vildagliptin in diabetic patients with coronary artery disease via increasing IL 10.

Indeed, it has been reported that neutrophils have a key role in activating NF-κB signaling cascades **[32]**. Expression of MPO was reported mainly in neutrophils and monocytes. Furthermore, it has been demonstrated that MPO is implicated in inflammatory responses upon its secretion from activated neutrophils **[33].** Besides, MPO is reported to be involved in oxidative stress outcomes **[34].** Results of the current study showed a significant enhancement in MPO activity in the carrageenan group. The findings were in line with a previous study **[35].** On the contrary, there was a significant reduction in the vildagliptin-treated groups. The reducing effect associated with vildagliptin was in accordance with another study **[36]**, which revealed the effect of vildagliptin on MPO activity in a model of type 2 diabetes.

Additionally, COX-2 is known to be expressed in response to an inflammatory stimulus **[37].** Other reports demonstrated the contribution of COX-2 to the production of numerous vital prostaglandins. Those prostaglandins were previously suggested to have a role in the mediation of inflammatory reactions **[38].** Besides, a recent study has revealed the participation of DPP4 in the activation of COX-2, clarifying the importance of DPP4 inhibitors **[39].** The present study revealed a rise in COX-2 levels in the carrageenan group. These results were supported by other work **[40].**

Conversely, there was a decrease in COX-2 levels in the vildagliptin-treated groups. The decline was correlated with another study **[41],** which demonstrated the suppressing effect of vildagliptin; which is a DPP-4 inhibitor; on COX 2 in a model of type 2 diabetes, indicating the anti-inflammatory effect of vildagliptin.

Moreover, PGF-2α has been demonstrated to participate in the inflammatory process **[42].** According to an earlier study, PGF-2α can induce an enhancement in the free radical surge, which in turn leads to the peroxidation of lipids **[43].**

Results of the current study demonstrated elevation of PGF2-α level in the carrageenan group. The results were in accordance with other work **[44].** On the contrary, there was a reduction in PGF2-α in the vildagliptin-treated groups; which was in accordance with another study **[45]**, which demonstrated that the role of vildagliptin in the reduction of PGF2-α in a model of type 2 diabetes was inadequately controlled with metformin.

Furthermore, a previous study defined oxidative stress and inflammation as interconnected critical contributors responsible for various disease pathologies. It has been demonstrated that the excessive release of superoxide anions and hydroxyl radicals, has an impact on the stimulation of neutrophil-related immune-related reactions; which end up with the release of additional inflammatory mediators **[46]**. Moreover, an earlier study **[6],** revealed the role of DPP4 in oxidative stress conditions and indicated the beneficial effect of DPP4 inhibition; proposing DPP4 inhibitors as promising agents. Besides, it has been found that the overexpression of SOD has a protective effect **[47].** The current study showed a reduction in SOD in the carrageenan group. These results were in accordance with a previous study **[48]**.

Conversely, there was an increase in SOD activity in the vildagliptin-treated groups. The enhancement in SOD activity was in line with another study **[22]**, which demonstrated the protective effect of vildagliptin on SOD activity in a model of type 1 diabetes; indicating the anti-oxidant effect of vildagliptin.

Notably, our results showed that there was no significant difference between two doses of vildagliptin 5, and 10 mg/kg, or between vildagliptin doses and indomethacin. Collectively, the findings of our study indicated the anti-inflammatory impact of vildagliptin, which proved to share some similarities with indomethacin, suggesting vildagliptin is a potent anti-inflammatory agent.

## 5. Conclusion

The results of the current study proved the beneficial modulatory changes that are linked to vildagliptin and highlighted its role in attenuation of the inflammatory impact of carrageenan, which manifested by suppression of the NF-κB signaling pathway, reduction of TNF-α, MPO, COX-2, and PGF2-α levels, and enhancement induced in the level of anti-inflammatory IL-10. Additionally, vildagliptin showed an anti-oxidant effect manifested by an enhancement of SOD activity. Collectively, all the above-mentioned findings declare the protective anti-inflammatory and anti-oxidant effects of vildagliptin in carrageenan-induced air pouch in rats.

## Conflict of Interest

All authors declare that they have no competing interests.

## 6. References

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