

Original Research Article

Polypeptide-K from bitter melon (*Momordica charantia*) seeds attenuates carrageenan-induced inflammation in streptozotocin-diabetic Sprague–Dawley rats

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Abstract

Purpose: To investigate the anti-inflammatory activity of orally administered Polypeptide-K (PPK) in streptozotocin (STZ)-induced diabetic Sprague–Dawley rats using the paw edema model.

Methods: A total of 42 male rats were randomly assigned into 7 groups (n = 6 each). Group 1 was the inflammation group; group 2 was induced with diabetes; groups 3, 4, 5, 6, and 7 were induced with diabetes and treated with distilled water, indomethacin (10 mg/kg), and PPK at 50, 150, and 300 mg/kg, respectively. A plethysmometer was used to measure paw volume every hour for 5 h. Three hours after intraperitoneal carrageenan induction, peritoneal exudate was analyzed for Evans blue extravasation, nitrite (NO surrogate), total cyclooxygenase (COX) activity, and prostaglandin E2 (PGE2) levels.

Results: In the paw edema model, PPK at 300 mg/kg significantly reduced edema at 5 h, achieving 78 % inhibition compared to indomethacin (81 %). In the peritonitis model, 300 mg/kg PPK significantly reduced Evans blue leakage, nitrite, and PGE2 (p < 0.05), while COX activity showed no significant change.

Conclusion: Polypeptide-K (PPK) significantly suppressed NO and PGE2-associated pathways, reducing acute inflammatory reactions in diabetic rats.

Keywords: Carrageenan, Diabetes, *Momordica charantia*, Paw edema, Polypeptide-K

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INTRODUCTION

Diabetes mellitus contributes to delayed tissue repair and microvascular problems leading to persistent low-grade inflammation [1]. Inflammation in animal models is induced with carrageenan because it induces a well-characterized, time-dependent edema and exudative response in acute inflammation

models, which is mediated by histamine/serotonin in the early phase and prostanoids and nitric oxide (NO) in the later phase [2,3].

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and diclofenac are used to treat inflammatory episodes. However, they exhibit negative effects on the kidneys and

gastrointestinal tract when used repeatedly [4]. As a result, there is ongoing interest in anti-inflammatory drugs derived from plants acting through various metabolic pathways [5]. Bitter melon, or *Momordica charantia*, is a popular food and traditional medicine [6].

Contemporary reviews have demonstrated the presence of multiple bioactive compounds such as triterpenoids, polysaccharides, and proteins/peptides with hypoglycaemic and immunomodulatory activities [7]. An isolated bioactive protein from *M. charantia* seeds called polypeptide-K (PPK) has garnered interest due to its antimicrobial [8], anti-diabetic [9,10], and anti-hyperlipidemic properties [11]. A retrospective clinical investigation has demonstrated the efficacy of PPK [12]. Polypeptide-K (PPK) in bread decreased glucose surge in healthy people [10].

Few studies have examined the direct anti-inflammatory effects of PPK in standardized experimental models, despite its well-established advantages [13]. This study therefore investigated the anti-inflammatory activity of orally administered Polypeptide-K (PPK) in streptozotocin (STZ)-induced diabetic Sprague-Dawley rats using the paw edema model, and explored mechanistic biomarkers (nitrite/NO, COX activity, and PGE2) relevant to the inflammatory cascade.

EXPERIMENTAL

Materials

Chemicals and reagents. PPK (Magna Bio-Laboratories, Malaysia) and indomethacin (Sigma Co. Ltd, Malaysia) were used as test and reference compounds. Streptozotocin (STZ), carrageenan, Evans blue dye, and assay kits for COX activity and PGE2 were obtained from Sigma Co. Ltd, Malaysia.

Animals

Male Sprague-Dawley rats weighing between 200 and 300 g were kept in cages with six rats per cage. The animals were placed under standard conditions (23 ± 2 °C and 12 h light-dark cycle), and allowed to acclimatize for two weeks with unrestricted access to food and water. Ethical approval was obtained from the Animal Care and Use Committee, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (IACUC; approval no: UPM/FPSK/PADS/BR-UUH/0038), and complied with the internationally accepted guide for the care and use of laboratory animals [14].

Induction of diabetes

After an 18-h fast, diabetes was induced in groups 3 – 7 using freshly prepared single STZ injection (60 mg/kg, i.p.; Sigma Co. Ltd, Malaysia). Fasting blood glucose was measured after 24 h, and rats with glucose > 16 mmol/L were considered diabetic [15].

Groups and treatment

For each model, rats were equally randomized into seven groups ($n = 6$). Group 1 was non-diabetic and induced with carrageenan (Sigma Co. Ltd, Malaysia; non-diabetic + carrageenan), group 2 was STZ-induced and given distilled water, group 3 was induced with STZ (diabetic only, no carrageenan), groups 4 – 7 were induced with STZ, and treated with the vehicle (as control), indomethacin (10 mg/kg), and PPK (50, 150, or 300 mg/kg) respectively. Treatments were administered orally by gavage. Doses of PPK administered were based on previous studies [7,16,17] following induction of diabetes as established in previous study [18].

Evaluation of parameters/indices

Paw volume

The right hind paw received subcutaneous injection of carrageenan (0.1 mL of 1% w/v) 30 min after treatment. Paw volume was recorded at baseline and every hour for 5 h using a plethysmometer. Edema was calculated as the change from baseline, and percentage inhibition at 5 h was calculated relative to the vehicle [19].

Peritoneal vascular permeability

About 60 min after dosing, Evans blue (10 mg/kg, i.v.) was administered followed by intraperitoneal carrageenan (0.3 mL of 1% w/v). After 3 h, the rats were euthanized and peritoneal cavities were lavaged with normal saline. Supernatants were used for Evans blue quantification at 630 nm and nitrite (Griess), COX activity, and PGE2 levels were measured following standard kit instructions [20,21].

Statistical analysis

Data were analyzed using GraphPad Prism (var 8.4.3; USA). Values were presented as mean $\pm$ standard error of the mean (SD; $n = 6$), and compared using analysis of variance (ANOVA) with Tukey post hoc test. $P < 0.05$ was considered statistically significant.

RESULTS

Carrageenan-induced paw edema (time course and dose response)

Polypeptide-K (PPK) at 300 mg/kg significantly reduced paw edema compared to negative control and other doses of PPK ($p < 0.05$) at 2 h and a more significant reduction at 5 h ($p < 0.05$; Table 1).

Percent paw edema inhibition

Indomethacin (10 mg/kg) produced strong anti-edematous activity, with reduced paw swelling over time corresponding to 81 % inhibition compared to the vehicle. Furthermore, PPK reduced paw edema dose-dependently, with the strongest suppression observed at 300 mg/kg. At 5 h, PPK 300 mg/kg reduced edema to 0.158 ± 0.133 mL, corresponding to 78 % inhibition, closely comparable to indomethacin (Table 2).

Carrageenan-induced peritoneal vascular permeability (Evans blue extravasation)

Elevated Evans blue dye leakage in the negative control group indicated that carrageenan-induced

peritonitis increased microvascular permeability (Evans blue extravasation), while indomethacin inhibited dye extravasation by 49.1 % (Table 3).

Inflammatory mediators in peritoneal exudate

COX activity

Total COX activity in the peritoneal exudate did not differ significantly across groups (Table 4), although numerically lower mean values were observed for indomethacin and PPK 300 mg/kg compared with the vehicle.

Levels of prostaglandin E2 (PGE2)

Treatment with polypeptide-K significantly reduced levels of PGE2 in a dose-dependent manner comparable to indomethacin ($p > 0.05$; Table 5).

Levels of Nitrite (NO surrogate)

Treatment with polypeptide-K significantly reduced levels of NO in a dose-dependent manner comparable to indomethacin ($p > 0.05$; Table 6).

Table 1: Change in paw edema volume (mL) following carrageenan administration

Group	1 h	2 h	3 h	4 h	5 h
Inflammation	0.301 ± 0.020^{ax}	0.393 ± 0.023^{bx}	0.500 ± 0.024^{bx}	0.530 ± 0.031^{cx}	0.680 ± 0.041^{by}
Diabetic	0	0	0	0	0
Negative control	0.208 ± 0.020^{ax}	0.385 ± 0.040^{bx}	0.530 ± 0.028^{by}	0.650 ± 0.030^{cy}	0.720 ± 0.030^{bz}
Indomethacin 10 mg/kg	0.318 ± 0.021^{ax}	0.325 ± 0.042^{bx}	0.252 ± 0.062^{ax}	0.168 ± 0.054^{ax}	0.133 ± 0.103^{ax}
PPK (50 mg/kg)	0.310 ± 0.026^{ax}	0.155 ± 0.052^{ax}	0.187 ± 0.086^{ax}	0.338 ± 0.110^{abx}	0.713 ± 0.130^{bx}
PPK (150 mg/kg)	0.433 ± 0.036^{ax}	0.640 ± 0.073^{cy}	0.565 ± 0.068^{bxy}	0.445 ± 0.130^{bcx}	0.532 ± 0.171^{bxy}
PPK (300 mg/kg)	0.442 ± 0.027^{ax}	0.212 ± 0.054^{ax}	0.332 ± 0.080^{ax}	0.368 ± 0.087^{abx}	0.158 ± 0.133^{ax}

Values are presented as mean $\pm$ SEM (n = 6). Baseline (0 h) = 0 for all groups. $^{abc}P < 0.05$ across dosing groups (column), $^{xyz}p < 0.05$ across time intervals (rows)

Table 2: Percentage of paw edema inhibition at 5 h compared to vehicle

Group	Inhibition (%)
Positive control	81.0
PPK 50	0.9
PPK 150	26.0
PPK 300	78.0

Table 3: Evans blue dye leakage in carrageenan-induced peritoneal vascular permeability

Group	Dye leakage (μ g/rat)	Inhibition (%)
Inflammation	20.48 ± 1.56^{bc}	-
Diabetes	11.73 ± 1.72^a	-
Indomethacin 10 mg/kg	12.66 ± 4.18^{ab}	49.10
Negative control	24.87 ± 1.30^{bc}	-
PPK 50 mg/kg	21.51 ± 1.90^{bc}	13.51
PPK 150 mg/kg	15.84 ± 2.76^b	36.30
PPK 300 mg/kg	11.84 ± 0.93^a	52.39

Values are presented as mean $\pm$ SEM (n = 6 in each group). Vehicle group = STZ-diabetic + distilled water, $^{ab}P < 0.05$ across groups

Table 4: Total COX activity in peritoneal exudate after carrageenan challenge

Group	COX activity (U/mL)
Inflammation	10.040±4.358
Diabetes	7.352±3.051
Indomethacin 10 mg/kg	3.432±1.303
Negative control	10.920±5.595
PPK 50 mg/kg	11.370±2.956
PPK 150 mg/kg	9.629±6.123
PPK 300 mg/kg	4.937±1.649

Values are presented as mean ± SEM (n = 6 in each group). Vehicle group = STZ-diabetic + distilled water

Table 5: PGE2 levels in peritoneal exudate after carrageenan challenge

Group	PGE2 (pg/mL)	Inhibition (%)
Inflammation	156.90±14.90 ^{bc}	
Diabetes	137.00±19.38 ^b	
Indomethacin 10 mg/kg	85.72±17.15 ^a	55.70
Negative control	193.50±7.79 ^c	
PPK 50 mg/kg	149.10±24.51 ^b	22.95
PPK 150 mg/kg	145.90±20.34 ^b	24.60
PPK 300 mg/kg	88.49±22.74 ^a	54.27

Values are presented in mean ± SEM (n = 6 in each group), ^{abc}p < 0.05 across groups

Table 6: Nitrite levels (NO surrogate) in peritoneal exudate after carrageenan challenge

Group	Nitrite (μmol/g)	Inhibition (%)
Inflammation	18.55±4.15 ^b	
Diabetes	14.69±3.93 ^{ab}	
Indomethacin 10 mg/kg	8.24±1.74 ^a	73.71
Negative control	31.35±5.44 ^c	
PPK 50 mg/kg	13.46±1.93 ^a	57.07
PPK 150 mg/kg	13.18±1.45 ^a	57.96
PPK 300 mg/kg	10.56±0.98 ^a	66.32

Values are mean ± SEM (n = 6 in each group), ^{abc}p < 0.05 across groups

DISCUSSION

This study demonstrated that orally administered PPK modulated acute inflammatory responses in STZ-diabetic rats across two complementary carrageenan models, which include paw edema (tissue swelling) and peritoneal vascular permeability (microvascular leakage). Strongest effects were consistently observed at 300 mg/kg, where PPK produced near indomethacin-level inhibition of paw edema at 5 h and inhibition of Evans blue extravasation along with significant suppression of nitrite and PGE2. Carrageenan-induced inflammation is widely described as biphasic, where early events are driven by vasoactive mediators and later events increasingly reflect leukocyte recruitment and inducible inflammatory pathways, including nitric oxide and prostanoid signaling [22-24].

In the paw edema model, the results showed significant suppression at 5 h, which is most likely the late inflammatory phase, where NO and prostaglandins play important roles in sustaining swelling and vascular alterations [23, 24]. This is further supported by lower levels of PGE2 and nitrite, consistent with molecular patterns

documented in carrageenan inflammation research [25]. Furthermore, results showed convergent evidence that PPK-restricted inflammatory microvascular leakage was associated with decrease in Evans blue extravasation.

Evans blue is frequently utilized as a marker of plasma protein extravasation in permeability models due to its high binding to serum albumin [26]. A useful technique for connecting vascular leakage with inflammatory mediator synthesis in exudates is to use carrageenan-induced peritonitis models that measure Evans blue exudation [27]. In this regard, a dose-related decrease in dye leakage by PPK, which is significant at 300 mg/kg, suggests a protective effect on microvascular permeability corresponding with PGE2 and NO suppression. Furthermore, significant PGE2 reductions with indomethacin and high-dose PPK, total COX activity showed no significant change between the two treated groups, which may be due to several reasons. One such reason is that inflammatory PGE2 generation in the acute model is always more closely linked to inducible COX-2 and terminal PGE synthase regulation

compared to total COX activity, and the assay measures total COX activity rather than COX-2-specific activity. Also, levels of PGE2 modulate upstream signaling, substrate availability, and cellular inflow throughout time; a single sample time point may not reveal prevailing variations in peak enzyme activity. Furthermore, statistical power to identify differences may be diminished by variability in COX activity assessments, as indicated by comparatively large SEM values. Consequently, decreased PGE2 does not conflict with anti-inflammatory effect and is still biologically feasible when total COX activity is maintained [23,25].

Diabetes is linked to increased inflammatory signaling and poor inflammatory resolution, which exacerbates vascular dysfunction and delays recovery. Diabetic microvascular damage and associated complications have been linked to inflammatory processes [28,29]. While acknowledging that acute carrageenan models primarily establish anti-inflammatory signal and mechanism plausibility rather than long-term clinical benefit, this current study revealed the ability of PPK to limit microvascular leakage and reduce NO- and PGE2-associated inflammatory responses, suggesting potential value for inflammatory complications in diabetes.

CONCLUSION

Polypeptide-K (PPK) significantly suppresses NO and PGE2-associated pathways, reducing acute inflammatory reactions in diabetic rats. Future studies should incorporate COX-2 and iNOS expression (Western blot or immunohistochemistry), cytokines (TNF- α , IL-1 β , IL-6), and oxidative stress markers to comprehensively investigate the effect of PPK on vascular signalling, inflammatory cell recruitment, inflammatory mediator induction, or several nodes in the acute inflammatory cascade.

DECLARATIONS

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Ethical approval

All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the Faculty of Medicine and Health Sciences,

Universiti Putra Malaysia (UPM/FPSK/PADS/BR-UUH/0038).

Availability of data and materials

The corresponding author can provide the datasets used and/or analyzed in the current work upon reasonable request.

Conflict of Interest

No conflict of interest is associated with this study.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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