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Original Article

INCREASED SUSCEPTIBILITY TO GASTRIC ULCERATION IN DIABETIC RATS: SYNERGISTIC EFFECT OF QUERCETIN AND PIOGLITAZONE

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ABSTRACT

Objective: This research delves into the potential therapeutic benefits of quercetin, a prominent flavonoid, in addressing diabetes and associated ulcers, emphasizing its synergistic effects with oral hypoglycemic agent, pioglitazone.

Methods: Sprague-Dawley rats received a high-fat diet and 35 mg/kg streptozotocin to mimic human diabetic condition. These rats were exposed to drug (indomethacin) and alcohol induced gastric ulceration, to study the flavonoid's effect alone and in combination with pioglitazone (low doses) in type 2 diabetes enhanced gastric mucosa sensitivity towards ulcerogenic insults. Quercetin and pioglitazone administered alone and in combination over eight-week period. OGTT, antioxidant status was estimated at the end of the study. Ulcer score and index were also determined by using respective standards.

Results: Monotherapy of pioglitazone (low dose) and quercetin exhibited limited effectiveness in increasing insulin sensitivity and ulcer prevention. Blood sample analyses, unveiled elevated antioxidant levels in the combination group compared to monotherapy. Notably, low dose combinations of quercetin and pioglitazone effectively displayed better healing-promoting properties. The combination of low doses of quercetin and pioglitazone demonstrated superior efficacy in ameliorating resistance towards insulin, physiological restoration, and prevention of stomach ulcers in diabetic rats.

Conclusion: The synergistic effects of quercetin and pioglitazone at low doses offers promising avenues for slowing the progression of diabetic gastric ulcers by enhancing antioxidant levels and maintaining physiological balance. Our findings open new possibilities for innovative treatment strategies in the realm of diabetes and related complications.

Keywords: Diabetic ulcers, Insulin resistance, Pioglitazone, Quercetin, Antioxidant levels

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INTRODUCTION

Ulcer formation stems from a discrepancy in the acidic peptic secretions and weakened mucosal resilience, the diabetic condition negatively impacts various gastrointestinal functions. In insulin-dependent diabetic rats, both starvation and stress contribute to cancer genic responses of gastric mucosa [1]. Diabetes amplifies vulnerability of mucosa layer to ulcer-causing factors, predisposing individuals to gastric ulcers. This highlights the complex interplay between diabetes and gastrointestinal well-being, emphasizing the increased likelihood of ulcer development in diabetic states due to compromised mucosal integrity and heightened responsiveness to cancer genic triggers [2]. In diabetic animals, multiple ulcerogens, like ethanol and non-steroidal anti-inflammatory agents caused increase vulnerability of gastric mucosa, i. e increase in susceptibility of gastric mucosa in causing ulceration [3, 4].

Lipid peroxidation is suggested as a crucial factor inulcerogenesis, contributing to acute hemorrhagic ulceration through increased back diffusion of acid [5]. Non-insulin-dependent diabetic (NIDDM) rats display an elevated predisposition to ulceration across studied gastric ulcer models. Despite varied causative factors, the root cause of ulcer genesis is perceived as an imbalance between offensive and defensive factors. Optimal glycemic control and achieving nonglycemic goal, like the antioxidant status as well as lipid levels are imperative in preventing long-lasting diabetes induced comorbid conditions [6]. Diabetic ulcer genesis is mitigated by exogenous supplements of antioxidants that could regularize the gastric motility, impaired duodenal bicarbonate secretion [7, 8].

In streptozotocin-induced diabetic rats, flavonoids like quercetin foster pancreatic islet regeneration, likely enhancing insulin release. Notably, quercetin's antioxidant-scavenging activity delays lipid peroxidation and hinders CuZ-induced LDL oxidation by chelating copper ions [9-11]. The restoration of antioxidant enzymes in diabetic ulcer was due to protective nature of quercetin, a powerful antioxidant [12]. Pioglitazone exhibited gastric ulcer healing in rats by activating PPAR-ɣ receptors and hence stimulating angiogenesis near to the margin of ulcer [13]. Proton pump inhibitors (PPI) are widely meant for treating gastric ulcers but on long term use, they are associated with renal disease, calcium and vitamin B12 deficiencies [14]. Proton pump inhibitors are bound to increase the levels of gastrin via negative feedback [15] and gastrin has been proved to secrete insulin in animal models [16, 17]. So simultaneously usage of PPI with oral hypoglycemics could lead into hypoglycemic episodes when therapy is for a longer duration of time. This study aims to investigate the impact of quercetin and pioglitazone and their low dose combination on gastric mucosa of diabetic rats that were susceptible to ulcerogenic stimuli as well as prevent hypoglycemic episodes

MATERIALS AND METHODS

Drugs and chemicals

Streptozotocin, omeprazole and and absolute ethanol were aquired from Sigma Aldrich Ltd, USA; Quercetin and pioglitazone from Sisco Research Laboratories, India. Analytical grade chemicals were used for the rest of the protocols.

Sprague Dawley rats (150-180g),received from our institutional animal house, wereshelteredinawell-ventilated animal facility, at a regulated temperature of 25°±5 °C and a 12:12 day-night cycle. Experimental methodology along with the protocol was approved by the InstitutionalAnimal Ethics Committee (KCP/IAEC-34/2011-12), in accordance with the standard conditions and guidelines established by the Committee for control and supervision of experiments onanimals (CCSEA). Handling of animals was as per the guidelines of the ethical committee.

Experimental models

Induction of type 2 diabetes in rats through high-fat diet and low-dose streptozotocin treatment

Rats was fed with modified diet for few weeks, then given *i. p* injections of subdiabetagenic dose of streptozotocin i. e 35 mg/kg following an overnight fast. To prevent hypoglycemic mortality, those injected with streptozotocin received a 5% w/v glucose for six hours post dosage of streptozotocin. Diabetic classification relied on non-fasted plasma glucose levels ≥300 mg/dl, assessed from tail vein blood samples using an AccuCheck glucose diagnostic kit [18].

Experimentdesign

Rats were assigned into eight groups (n=08). Group I: Normal Control (untreated, non-diabetic rats), received salineorally. The rats that developed diabetes were split into various groups such as Group II: Negative control (untreated, diabetic rats), Group III: Diabetic rats with low dose Pioglitazone treatment (07 mg/kg) [19], Group IV: Diabetic rats with Quercetin therapy (100 mg/kg) [20]. Diabetic rats with low dose of pioglitazone (07 mg/kg)+Quercetin treatment (50 mg/kg)was considered as Group V. Omeprazole (n=10) and sucralfate (n=10) were used as standard in respective animal model. The therapy commenced prior to diabetes induction and continued for 8 w.

Single and multiple dose studies in rats with diabetes

Single dose study

The study involved segregating animals into five groups, including Group I –Non diabetic rats (Control), Group II-diabetic control rats, group III received quercetin (50 mg/kg), while the fourth group was admin istered pioglitazone (7 mg/kg). Blood sugar levels measured at specified time.

Multiple dose study

In the prolonged multi dose study, oral treatment of the sample was performed daily for ten days. Serum glucose concentration was assessed from tail-tip blood sample son days 1, 3, 7, and 11 post-administrations. Additionally, body weights were recorded on the 10^{th} day for all animals [21].

Oral glucose tolerance test (OGTT)

Post twelve hour fasting state, oraldoseof2.0g/kg glucose was given to rats and blood sugar levels estimated at specified intervals [22].

Recovery from drug-induced gastric ulcers: Investigation of free radical scavenging capabilities

Rats develop gastric ulcers through a five-day regimen of indomethacin administration (5 mg/kg,p. o). After ulcer formation, treatment will be administered for five days, with the control group receiving only the vehicle and omeprazole was used as standard drug. The rats were sacrificed using anaesthetic ether. The stomach was removed; ulcerscore and ulcerindex was determined [23, 24]. Theglandularportion ofthestomach used for the estimation of mucin content [25], total proteins [26] antioxidant factors like superoxide dismutase activity [27], and catalase activity [28].

The number of ulcers was noted and the severity was recorded with the following scores: 0 = no ulcer, 1 = superficial ulcer, 2 = deep ulcers, 3 = perforation.

Evaluation

An ulcer index *U*I is calculated by the formula: $UI=UN+US+UP * 10^{-1}$

UN – Average number of ulcers per animal, US – Average of severity score, UP – percentage of animals with ulcers [29]

Ethanolinducedulcer

Prior to the administration of 90% ethanol (1 ml/200 gm), albino rats underwent a 36-hour fast. The drug was given one hour before ethanol administration. Following ethanol exposure, the animals were sacrificed one hour later, and the stomach was isolated for the determination of the ulcer index. Sucralfate was used as standard drug [30].

Evaluation of antioxidant levels in tissue homogenate

Stomach homogenate preparation

Post conclusion of treatment period, stomachwas homogenizedwith cold 0.1 N perchloric acidand disodium EDTA. Isopropyl homocholine served as an internal standard. The homogenized mixture was then subjected to centrifugation (48 degree centigrade) for 20 min at 10,000 rpm [31].

Quantification of gastric content

The gastric glandularmucouswasmeasured. Excised stomach was soaked for a period of two hours in 0.1%alcian blue. Stomach was cleaned for two times using sucrose (0.25 M). Magnesium chloride (0.5 m) was used to remove the dye and the obtained solution was mixed with diethyl ether. The optical density of the aqueous phase was measured at 605 nm and the concentration (expressedinmg) of dye was calculated by using a standard curve. Finally, the dye's weight was revealed over the weight of the stomach [32].

Quantification oftotalprotein

Protein concentration was measured through Lowry's method, using bovine serum albumin (BSA) as the benchmark standard [33].

Quantification of enzyme activity

A solution comprising of gastric tissue homogenate (100 µl), sodium carbonate (01 ml), NBT (0.4 ml), and EDTA (0.2 ml) was prepared. The resulting supernatant was utilized to assess superoxide dismutaseand catalase activity [34].

StatisticalInterpretation of the data

The information is laid out in the form of mean±standard error of the mean (SEM). Group distinctions were assessed utilizing one-way analysis of variance (ANOVA), succeeded by Tukey's post hoc multiple comparison examination. Statistical significance was determined for P values less than 0.05 [35].

RESULTS

Single as well as repeated dose study of quercetin and pioglitazone in rats

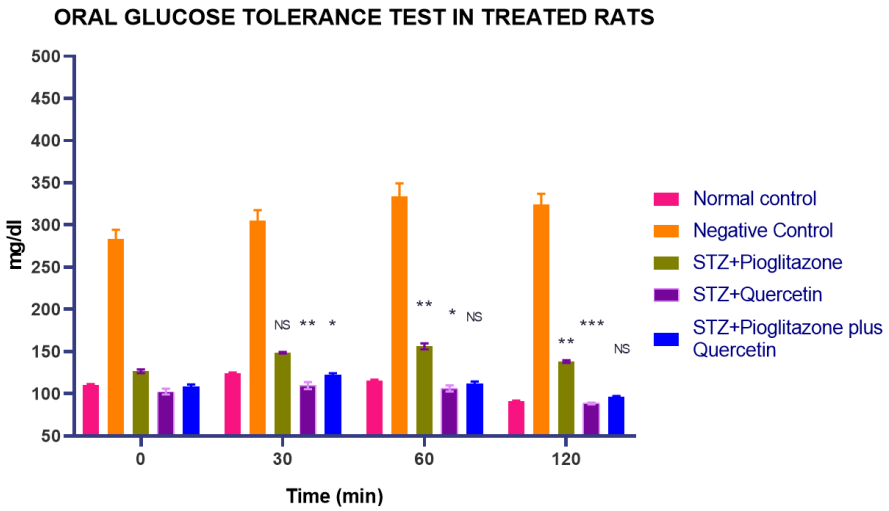
Two weeks, post STZ administration, the rats exhibited elevated blood glucose concentration than control rats. In the single dose study, quercetin and pioglitazone exhibited decline in blood glucose concentration by 26.24 % as well as 08.6 % respectively. Repeated dosage study confirms that the quercetin as well as pioglitazone displaying a remarkable decline in blood concentration of glucose from 38.2 to 42.6 % and 14.23 to 17.86% respectively between 9^{th} and 11^{th} d of treatment. Quercetin being more effective than pioglitazone.

Effect of quercetin,* pioglitazone and their combination *on glucose tolerance in diabeticrats

In glucose tolearance test, we observed a decline of blood glucose concentration was exceptional with quercetin alone treated rats at 2 h post glucose load. The % increase in blood glucose level at 30^{th} min and 60^{th} min was more pronounced in rats treated with pioglitzone than the group treated with quercetin. i. e. quercetin exhibtedmore tolerance towards glucose loadthan pioglitazone. Percentage decrease of blood glucose shown by pioglitzone alone was more pronounced at 2^{nd} h in contrast to quercetin's response. Quercetin (Low dose) as well as pioglitazone (Low dose) when administered together, unveiled a remarkable decline in glucose concentration of blood in comparison with untreated diabetic rats and with group of diabetic rats treated with pioglitazone alone (graph 1).

Effect of quercetin, pioglitazone and quercetin plus pioglitazoneon antioxidant's status

A remarkable short fall of content of super oxide dismutase as well as catalase was observed in post eight week treated diabetic rats and marked comparative response was noticed when matched with control rats. Post eight weeks treatment period, quercetin, pioglitazone and their combination restored the short fall of super oxide dismutase as well as catalase but the combined therapy of quercetin and pioglitazone resulted in a better response (table 1) than when treated alone.



Graph 1: Quercetin alone and in combination with pioglitazone on OGTT in treated rats. All values are represented as mean±SEM, n= 10, ***p<0.001, **p<0.01, *p<0.05, NS = Not significant when all groups were compared with normal control group

Table 1: The influence of quercetin, pioglitazone and their combination on mucin content (µg/gm), total proteins (mg/ml), and SOD (U/mg of protein), CAT (U/mg of protein) observed in indomethacin-induced gastric ulcers model

Parameter	Mucin content (µg/gm)	Total proteins	SOD (U/mg)	CAT (U/mg)
Normal Control	0.55±0.14	18.5±1.7	21.3±1.58	17.3±1.11
Negative Control	0.097±0.022***	8.7±0.83***	9.08±0.74***	4.56±0.66***
Omeprazole	2.24±0.28a***	12.65±0.87a***	10.3±0.49***	7.11±0.91***
Sucralfate	1.42 ±0.49a***	11.75±0.25a***	9.45±0.22***	5.16±0.31***
Pioglitazone (Pio)	0.15±0.022***	14.06±0.80a***	18.9±0.66a**	13.6±0.9a**
Quercetin (QE)	1.24±0.16a***	14.6±0.61a***	16.75±0.92a**	12.05±0.77a***
Pio+QE	1.74±0.13a***	15.9±0.85a*	17.3±0.9a*	14.7±0.84a*

Results are mean±SEM of 6 rats in each group. One-way ANOVA followed by Tuckey's test for multiple compar isons was applied for comparing the parameters with NC and DC groups. The difference was considered to be significant when ***P<0.001, **P<0.01, *P<0.05 when compared to normal control group and aP<0.001, bP<0.01, cP<0.05 when compared to diabetic control group. Pio – Pioglitazone, QE-Quercetin

Assessment of the anti-ulcer activity in ulcer models induced by indomethacin and ethanol

Ethanol-ulcerated rats displayeda remarkable (p<0.001) percentage elevation of ulcerated area in comparison with control group (table 2.1). In contrast, pre-treatment with sucralfate, low dose of pioglitazone (Pio) and Quercetin (QE) and their combination (Pio+QE) manifested a less mucosal injury as witnessed by a significant (p<0.01) decline in percentage of ulcerated area by 81.46%, 19.87%, 41.75 %, and 43.05 %, respectively, comparedF to untreated ethanolulcerated rats. Combination of pioglitazone and quercetin showed a better protective effect than when treated alone. (table 2.1)

Table 2: Effect of quercetin (QE), pioglitazone and their combination on ulcer ındex and ulcer score

Ethanol induced ulcer model

Groups	Ulcer ındex	Ulcer score
Normal Control	1.59±0.12	7.5±0.42
Negative Control	3.04±0.10***	15.1±0.56***
Sucralfate	0.11±0.02a***	2.8±0.70a***
Pioglitazone (Pio)	1.46±0.05a!!!	12.1±1.1***!!!
Quercetin (QE)	0.88±0.05a***!!!	8.8±0.03a!!!
Pio+QE	0.41±0.06a***!!	8.6±0.40a!!!

The Mean±SEM for 6 rats/group underwent one-way ANOVA with Tukey's test. Significance levels: ***P<0.001, **P<0.01, *P<0.05 vs. NC; aP<0.001, bP<0.01, cP<0.05 vs. DC; !!!P<0.001, !!P<0.01, !P<0.05 vs. sucralfate-treated group. Pio – Pioglitazone, QE-Quercetin

Drug (Indomethacin)-ulcerated rats unveileda exceptional (p<0.001) percentage surge of ulcerated area in comparison with control group (table 2.2). In contrary, pre-treatment with a standard drug, omeprazole, low dose of pioglitazone (Pio) and Quercetin (QE) and their combination (Pio+QE) demonstrated a less mucosal injury as observed by a significant (p<0.01) decline in percentage of ulcerated area by 76 %, 18.54 %, 39.33 %, and 52.25 %, respectively, compared to untreated drug induced ulcerated rats. Low dose pioglitazone and quercetin elicited the best protective effect than when treated alone (table 2.2) (fig. 1).

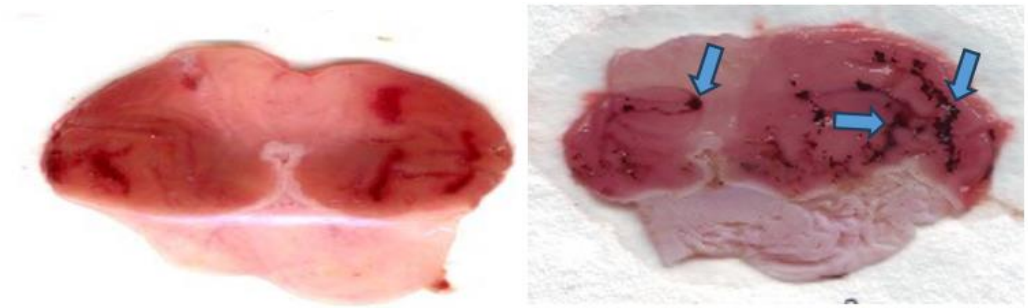
Macroscopic features of gastric ulcers in different groups (Indomethacin and Ethanol Models)

Efect of quercetin (QE) and pioglitazone (Pio) and their combination (QE+Pio) on lesion score records obtained from the histological examination in Indomethacine-induced gastric ulcer in rats.

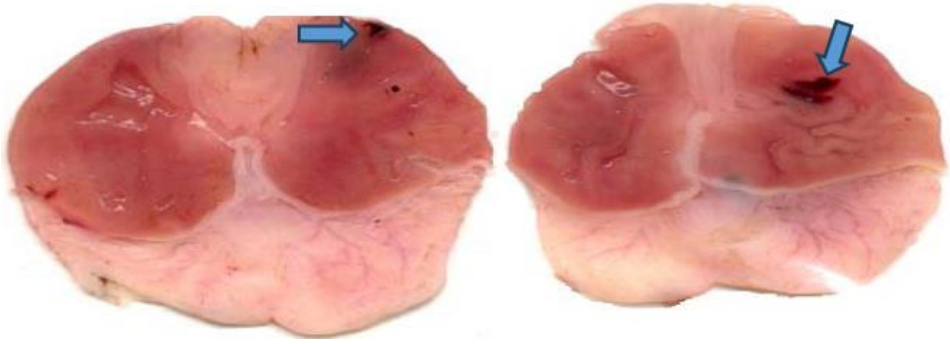
Table 3: Indomethacin induced ulcer model

Groups	Ulcer ındex	Ulcer score
Normal Control	1.62±0.18	10.8±0.70
Negative Control	2.32±0.49***	17.8±0.96***
Omeprazole	0.34±0.08^{a***}	4.3±0.55^{a***}
Pioglitazone (Pio)	1.91±0.05$^{c!!!}$	14.5±0.56$^{c**!!!}$
Quercetin (QE)	1.17±0.07$^{a!!!}$	10.8±0.60$^{a!!!}$
Pio+QE	0.97±0.04$^{a!!}$	8.5±0.61$^{a!!!}$

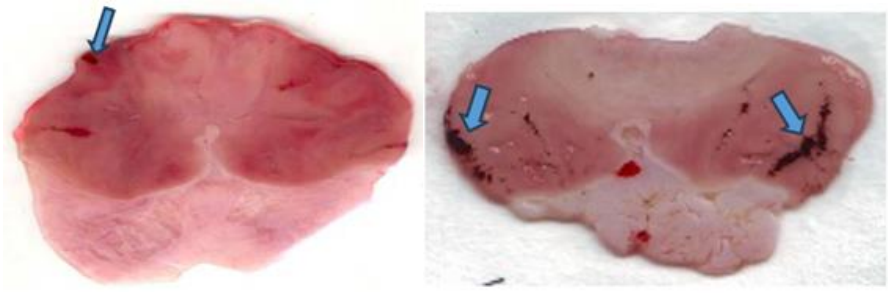
The Mean±SEM for 6 rats/group underwent one-way ANOVA with Tukey's test. Significance levels: ***P<0.001, **P<0.01, *P<0.05 vs. NC; ^{a}P<0.001, ^{b}P<0.01, ^{c}P<0.05 vs. DC; !!!P<0.001, !!P<0.01, !P<0.05 vs. omeprazole-treated group. Pio – Pioglitazone, QE-Quercetin



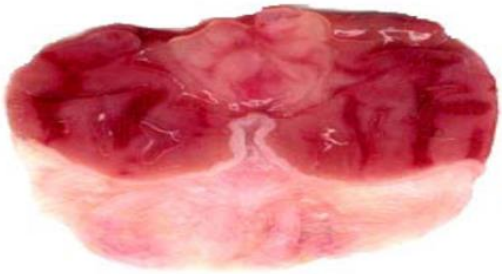
Normal control **Negative control**



Sucralfate **Omeprazole**



QE **PIO**



QE+PIO

Fig. 1: Efect (Photographic representation) of pioglitazone (Pio) and quercetin (Q) and their combination (Pio+Q) on gross gastric lesions in diabetic gastric ulcer in rats. Blue arrow: ulcerated areas. (Scale= 1 mm)

Table 4: Macroscopic features of gastric ulcers in different groups (Indomethacin and Ethanol Models)

Group	Erosion/ulceration	Hemorrhagic patches	Infammatory cells infltrate	Blood vessels congestion	Oedema
Normal Control	-	-	-	-	-
Negative Control	+++	+++	++	+++	+++
Omeprazole	-	-	++	++	++
Pioglitazone (Pio)	++	++	+	++	++
Quercetin (QE)	+	-	+	+	++
Pio+QE	-	-	+	-	+

Nil (-) = no lesion was evidenced,+= mild lesion records evidenced in less than 15% of examined tissue sections,++= moderate lesion records evidenced in 16–35% of examined tissue sections,+++= severe lesion records evidenced in more than 35% of examined tissue sections. Pio – Pioglitazone, QE-Quercetin

Table 5: Efect of quercetin (QE) and pioglitazone (Pio) and their combination (QE+Pio) on lesion score records obtained from the histological examination in Ethanol-induced gastric ulcer in rats

Group	Erosion/ulceration	Hemorrhagic patches	Infammatory cells infltrate	Blood vessels congestion	Oedema
Normal Control	-	-	-	-	-
Negative Control	+++	+++	++	+++	+++
Sucralfate	-	-	++	+	++
Pioglitazone (Pio)	+	+	+	+	++
Quercetin (QE)	++	-	++	++	++
Pio+QE	-	-	+	+	+

Nil (-) = no lesion was evidenced,+= mild lesion records evidenced in less than 15% of examined tissue sections,++= moderate lesion records evidenced in 16–35% of examined tissue sections,+++= severe lesion records evidenced in more than 35% of examined tissue sections. Pio – Pioglitazone, QE-Quercetin

DISCUSSION

Metabolic disorder is designated by congregate of unhealthy changes such as obesity, impaired glucose tolerance (IGT) and resistance to insulin activity. Modification of diet containing high amount of fructose was developed in our laboratory [18] because the incidences of developing diabetic complications is more vulnerable when fructose is consumed instead of glucose [36, 37]. The complicatedness and the vulnerability of complexity raises as the uncontrolled hyperglycemic state escalate [38]. Gastric ulceration in NIDDM is predisposed due to its defenselessness to ulcerogenic stimuli has been reported several times. Visceral autonomic neuropathy [39], caused due to increase in free radicals is generated by uncontrolled diabetes mellitus. The therapeutic agents possessing both anti-hyperglycemic and anti–ulcer activities are the choice of agents to treat diabetes induced ulcer. These agents could prove more cost-effective and less incidence of adverse effects.

Quercetin, among many flavonoids, causes enhanced hypoglycemic condition through promotion of beta cell proliferation and insulin secretion. We observed a marked decline in postprandial glucose strength and enhanced insulin sensitivity index from 30 min onwards during OGTT in diabetic rats and was identical with previous results that were proved in earlier studies [40, 41]. Choi *et al.* also demonstrated that the quercetin at a dose of 100 mg/kg, ameliorated resistance towards insulin. It also lowered the sustained raise of glucose post 30 min during OGTT [42]. Gohlke *et al.* observed that the plasma concentration of glucose declined, which might be due to elevated insulin release and insulin sensitivity when quercetin was administered to diabetic rats [43]. Quercetin was proven to heal gastric ulcer caused by indomethacin in diabetic rats [44].

The increase in insulin sensitivity produced by quercetin was much pronounced when compared with the low dose of pioglitazone. L. Past studies have proven that quercetin exhibited the mechanism as that of rosiglitazone in enhancing the utility of glucose through glucose transports [45, 46]. Querctin could be effective in diminishing fasting as well as postprandial blood glucose concentration in diabetic animal model [47]. High doses of quercetin and pioglitazone, when administered for a prolong time might lead to hypoglycaemic incidences. Previous studies have also show that pioglitazone has the tendency to cause severe fluid retention. Hence, adopted a combined reduced dose of both quercetin and pioglitazone to reduce the hypoglycemic when treated for a longer period. This combination had shown significant increase in insulin sensitivity and reduced the postprandial glucose level significantly, which is very much essential in preventing the increase in susceptibility of gastric mucosa to ulcerogenic stimuli. Our earlier study demonstrated the combined effect of an antidiabetic drug (acarbose) with *Syzygium cumini* seed extract in countering the susceptibility of diabetic gastric mucosa towards ulcerogenic stimuli. This combination was much superior to quercetin [20]. *Syzygium cumini* and acarbose have been proven to possess the α-glucosidase inhibition that is very much essential in curbing the postprandial glucose level. Similarly, Joshi M. C. *et al.* proved the α-glucosidase indering action of quercetin [48].

Pretreatment with pioglitazone has reduced the percentage of ulerative area when compared to untreated ethanol ulcerated rats [49]. Brzozowski *et al.* have demonstrated the gastric ulcer healing effect of pioglitazone via the stimulation PPAR-ɣ receptors and enhance the angiogenesis around ulcer margin [50]. Previous study has mentioned the anti-inflammatory effect of pioglitazone was through the suppression of proinflammatory cytokines and cyclooxygenase-2 [51]. AMPK signaling pathway corrects resistance towards insulin that is independent to the insulin-regulated mechanism for the generation of GLUT4. Quercetin as well as insulin-sensitizing agents, are proved for the management type 2 diabetes via AMPK pathway activation [52, 53].

In the present study, the pioglitazone (low dose) had shown less significant effect in decreasing postprandial glucose level and could be the reason for the less ulcer protective effect but the low dose combination of both the agents (quercetin and pioglitazone) had a noteworthy effect in decreasing the postprandial glucose level, thus ameliorating diabetes induced susceptibility to ulcerogenic stimuli.

Type 2 diabetes rats have exhibited an enhanced propensity towards gastric ulceration due to elevated offensive factors and simultaneous decline in antioxidant status there by increasing the ulcer index values [54, 55]**.** The elevated offensive and submissive defensive factors were ameliorated due to the effect of quercetin on antioxidant scavenging activity, delay in peroxidation of lipids as well as reduced copper induced LDL oxidation. Identical results were documented elsewhere also [56-58]. Segovia G. R *et al.* have proven that quercetin was effective in preventing ulcer in diabetic rats by restoring the levels of SOD and catalase [59]. Similarly, present study has also exhibited an increase in antioxidant enzyme status in hyperglycemic rats on quercetin therapy alone and as well as when combined with pioglitazone.

The combined effect of low dose of quercetin and pioglitazone have proven more effective in decreasing the vulnerability gastric lining towards ulcerogenic agents due to their balancing nature effect between offensive as well as defensive factors on gastric mucosa on elevated acid – pepsin secretion prompted by uncontrolled diabetic condition.

In view of the above evaluation, we agree that the simultaneous therapy of quercetin with pioglitazone at doses lower than that of conventional usage would be beneficial in preventing the susceptibility of diabetic gastric mucosa towards ulcerogenic agent by amelioarting oxidative stress as well as by effective postprandial glucose suppression leading to gastro protective effect.

CONCLUSİON

Approach of reduced dosage of both agents provides ulcer amelioarting effect in diabetic gastric mucosa susceptible to ulcerogenic agents as well preventing hypoglycemia. In constinuation of this study, further study is neccessary to prevent the adverse effect (hypoglycemia) of the conventional antidiabetic agents when therapy is for a prolong period. Before proposing for clinical trial, our study outcome has opened new possibilities for the delay in the progression or prevention the susceptibility of diabetic gastric mucosa towards ulcerogenic stimuli and long term study is essential before proposing for clinical trials inorder to validate efficacy in diabetic patients with gastric ulcers.

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Nil

AUTHORS CONTRIBUTIONS

Prem Kumar Nanjundan: supervising, conceptualizing, literature review, writing original draft, and critical evaluation,;Ghassan Adel Alkhalifah: data curation, literaturereview, writing original draft; SreeharshaNagaraja: criticalevaluation, editing, and proof reading; Afzal Haq Asif: critical evaluation, editing, and proof reading.

CONFLICT OF INTERESTS

Declared none

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