ANTI-INFLAMMATORY, ANALGESIC AND ULCEROGENIC POTENCY OF CURCUMIN IN COMPARISON WITH CELECOXIB AND PREDNISOLONE

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The present study investigates the anti-inflammatory, analgesic effect, and gastric disturbance of curcumin compared with celecoxib and prednisolone. Sixty male rats divided into (Group 1 and G2: control, G3, G4, and G5: orally received celecoxib, prednisolone, and curcumin respectively then received carrageenan in paw after 14 days. Edema, oxidative markers, analgesic, ulcerogenic activity, and skin expression of (nuclear factor kappa-β (NF-kappaβ), tumor necrosis factor-alpha (TNF-α), Interleukin-1β (IL1β), IL 6 and IL 10) and gastric mRNA expression of (Heme oxygenase-1 (HO1), interleukin 8 (IL8), nuclear factor erythroid 2-related factor 2 (Nrf2), NFκβ and Superoxide dismutase (SOD)) were measured. This result revealed that curcumin significantly improved edema, ulcerogenic, analgesic activity, and oxidative markers like celecoxib and prednisolone effect when compared with carrageenan. Curcumin significantly downregulated mRNA expression of the inflammatory markers of skin and gastric mucosae like celecoxib and prednisolone effect when compared with carrageenan. Curcumin, celecoxib, and prednisolone significantly upregulated skin (IL10) compared with carrageenan. Curcumin significantly upregulated Ho1, SOD, and Nrf2 compared with carrageenan, celecoxib, and prednisolone. Based on the above it could conclude that curcumin displayed anti-inflammatory and analgesic with minimum gastric disturbance, unlike celecoxib and prednisolone.

Keywords: Carrageenan, Celecoxib, Curcumin, Inflammation, oxidative stress and Prednisolone

INTRODUCTION

Inflammation is one of the most important mechanisms in animal cells' protection against injuries and microbial infections⁷. Several chronic diseases, such as arthritis, diabetes, obesity, cancer, neurodegenerative diseases, autoimmune disorders, dementia, scleroderma, allergy, asthma, bronchitis, inflammatory bowel disease, and cardiovascular diseases, may be caused by inflammation, which has increased dramatically in the last three decades⁸. Inflammation is characterized by a series of well-organized, complex responses that include both cellular and vascular events as well as unique humeral secretions. Changes in the physical position of white blood cells (monocytes, basophils, eosinophils, and
neutrophils), plasma, and fluids at the inflamed site are involved in these pathways. Immune defense cells release a group of secreted mediators and other signaling molecules (e.g., histamine, prostaglandins, leukotrienes, oxygen- and nitrogen-derived free radicals, and serotonin) as a part of the process that can lead to inflammation. The inflammatory process is linked to a number of cytokines. Interleukin-1β, IL-6, IL-13, and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines. Inflammation can be caused by a variety of factors, and the NF-κB/cyclooxygenase-2 (COX-2)/inducible nitric oxide synthase (iNOS) pathway is one of them. Notably, nuclear factor kappa B (NF-kappaB) regulates numerous molecules, including cytokines (e.g., IL-1β, TNF-α), iNOS, and chemokines, to govern various stages of inflammation and immunological modulation.

Anti-inflammatory medications are classified as either steroidal or nonsteroidal which are used to treat both acute and chronic inflammatory conditions such as osteoarthritis and rheumatoid arthritis. However, both selective COX2 non-steroidal anti-inflammatory drug (NSAID) and steroidal anti-inflammatory drug (SAID) displayed several adverse effects regarding the integrity of gastric mucosa, GIT bleeding, and renal impairment. As a result, finding newer pharmacological alternatives for the treatment of inflammation with minimum side effects is mandatory.

Curcumin is a natural medicine made from a polyphenol present in the spice turmeric. Curcumin has a wide range of physiological effects, including anti-inflammatory, antioxidant, and cancer-fighting properties in comparison with SAID and NSAID.

**MATERIALS AND METHODS**

**Experimental design and ethical statement**

Sixty male adult Wister rats aged 8 weeks and weighing 200-220 gm, were used in the experimental investigation of this study. The institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, Zagazig University approved our study ZU-IACUC/2/F/61/2020. All animals were adapted for a small period of one week before the current study.

**Materials**

Celebrex100 mg (celecoxib) was purchased from Pfizer pharmaceutical company, Solupred 20 mg (prednisolone) was purchased from Sanofi-Aventis company, and Curcumin was purchased from Sisco Research Laboratories Pvt. Ltd –Mumbai-India.

**Animals groups and dosing**

The study was performed on Sixty male Sprague-Dawley rats divided into five equal groups (12 rats each) G 1: control group without drugs, G 2: control without drugs and received carrageenan injection after 14 days, G 3: received celecoxib (10 mg /kg) orally for 14 days then injected with carrageenan, G 4: received prednisolone (5 mg /kg) orally for 14 days then injected with carrageenan and G 5: received curcumin (100 mg /kg) orally for 14 days then injected with carrageenan. The hot plate test was performed on a number of rats that weren’t treated with carrageenan for detecting the analgesic activity of these drugs so this test was performed on 4 groups only without carrageenan group (GP 1, GP 3, GP 4, and GP 5). After 2 hrs of subcutaneous carrageenan injection in the left hind paw, the rats were sacrificed, the skin of the hind left paw and gastric mucosa were collected. Gastric mucosa was scored for the presence of ulcers. The paw skin was divided in to 2 parts. Gastric mucosa and the first part of skin immersed on triazol for gene expression study and the second part of the skin used for assaying oxidant/antioxidant activity.

**Anti-inflammatory activity (Induction and assessment of carrageenan-induced paw edema)**

Carrageenan caused a biphasic inflammatory response (early and delayed phases). Serotonin, bradykinin, and histamine are primarily involved in the early period (0 to 1 hr after injection). The local blood flow and capillary permeability increased throughout this phase, culminating in the onset of edema. The delayed phase (after 1 hr) is linked to leukocyte migration and prostaglandins, both of which are essential for its survival. Carrageenan-induced inflammation has been used as a model for finding new anti-inflammatory drugs.
Following 30 min of oral administration of the last doses of the treated drugs, groups 2, 3, 4 and 5 were received subcutaneous carrageenan injection, 0.1 ml carrageenan sodium (1.5 % solution in saline) and carrageenan-induced paw edema was persuaded according to the method described by\(^\text{18}\).

**Analgesic Activity (Hot plate test)**

By studying the reaction to pain caused by heat, the hot plate test is used in basic pain research and in evaluating the efficacy of analgesics according to the method described by\(^\text{19}\). Mice were placed on a 52°C hot plate after 30 minutes of treatment with a transparent glass cylinder to keep them on the heated surface of the plate. A thermally controlled water-circulated pump controls the hot plate temperature. The time of latency is defined as the time between when the animal is placed on the hot plate surface and when it licks its paw or jumps off to prevent thermal pain. This approach was repeated after 30, 60, 90, and 120 min to determine the duration of each drug's analgesic effect.

**Ulcer formation (Ulcerogetic effect in the stomach)**

At the end of our study, rats were sacrificed. The stomach was taken for detecting the presence of an ulcer and scoring the numbers of the ulcers in each rat according to\(^\text{20}\).

**Biochemical determination**

Oxidant /antioxidant activity: Catalase was assayed using the kit (Cat. No - MBS726781) according to the method described by\(^\text{21}\), Glutathione peroxidase was measured using the kit (Cat. No - MBS744364) according to the method described by\(^\text{22}\), Superoxide dismutase was assayed using the kit (Cat. No - SD 25 21) according to the colorimetric method described by\(^\text{23}\), and lipid peroxidation marker (Malondialdehyde) (MDA) assayed using the kit (Cat. No - MBS268427) according to the method adopted by\(^\text{24}\).

**Table. 1:** Primers used in PCR

| Primer name | Forward primer   | Reverse primer   | product length | Accession No. |
|-------------|------------------|------------------|----------------|--------------|
| IL-10       | GCTCAGCACTGCTAT  | TTGTCAACCCGGATG  | 76             | NM_012854.2  |
|             | GTTGC             | GAATG            |                |              |
| IL-8        | ACAGGCAGCTGTAG    | ATCACGAGGTGTT    | 70             | NM_019310.1  |
|             | TTGTC             | CCCAG            |                |              |
| Gapdh       | GCATCTTCTGTGCAG   | GGTAACCCGGTGTC   | 91             | NM_017008.4  |
|             | TGCC              | GATAC            |                |              |
| Nrf-2       | GGTGGCCCATATCCCA  | GGCTGGGAATAATCCA| 116            | NM_031789.2  |
|             | AAAC              | GGGCA            |                |              |
| IL-1β       | GAGTCTGCACAGTTC   | TCCTGGGGAAGGCA   | 158            | NM_031512.2  |
|             | CCCAA             | TAGGA            |                |              |
| NF-κβ       | CCACGTCAACAGAT    | CTTCGGGGAAGCAT   | 177            | NM_001276711.1|
|             | GGCCC             | TAGGA            |                |              |
| TNF-α       | GGCTTTCGGAAAAGGTA | GGGGAACTTGGGA    | 164            | NM_012675.3  |
|             | CTGGA             | AGCTC            |                |              |
| SOD-1       | TTGGCCGTAATGG     | GGGCAATCCCAAATCA| 120            | NM_017050.1  |
|             | TGTCG             | CACCA            |                |              |
| IL-6        | AGAGACTTCCAGCCA   | AGTCTTCTCCGGA    | 85             | NM_012589.2  |
|             | GTTGC             | CTTGT            |                |              |
| HO-1        | CCCAGAGCTGTGAA    | AGGCCAAGAAAAG    | 79             | NM_012580.2  |
|             | CTCTG             | AGAGCC           |                |              |
Molecular determinations

The real-time Polymerase Chain Reaction procedure was carried out as described before\textsuperscript{25,26}. Total RNA was isolated from 50 mg of Paw skin and stomach tissue using Trizol (Invitrogen; Thermo Fisher Scientific, Inc.), and quality and concentration were determined using the NanoDrop® system Spectrophotometer ND-1000 (NanoDrop Technologies, Wilmington, Delaware USA). cDNA was synthesized using a HiSenScript\textsuperscript{TM} RH (−) cDNA Synthesis Kit (iNtRON Biotechnology Co., South Korea). A Rotor-Gene Q 2 plex (Qiagen, Germany) Real-Time PCR System was used to perform real-time RT-PCR with a total reaction volume of 20 µL (10 µL top real syber Green master mix (Enzynomics, Korea),1 µL of cDNA template (1 µL of both forward and reverse primer) and nuclease-free water up to 20 µL with a cycling condition of initial denaturation at 95°C for 12 minutes was followed by 40 cycles of denaturation at 95°C for 20 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. The PCR product was amplified with oligonucleotide-specific primers listed in Table 1. (Beijing, China). A melting curve analysis was performed following PCR amplification. The expression level of the target genes was normalized using the mRNA expression of a known housekeeping gene: Gapdh. Results are expressed as fold-changes compared to the control group following the 2–ΔΔCT method\textsuperscript{27}.

Statistical analysis

To assess the influence of the five treatment groups on the different biochemical parameters, one-way analysis of variance (ANOVA) and two-way repeated measures followed by Tukey’s Honestly Significant Difference (Tukey’s HSD) test as post hoc test were used.

All Analyses and charts were done using Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp., Armonk, NY) and Graph Pad Prism 8.0.2 (GraphPad Software, Inc).

Results were reported as mean ± SEM (Standard Error of Mean). The value of $P<0.05$ was used to indicate statistical significance.

RESULTS AND DISCUSSION

Analgesic, anti-inflammatory and ulcerogenic effect of celecoxib, prednisolone and curcumin

After 60 min of carrageenan administration, the result of the current work showed a significant $P<0.05$ increase in the mean value of the thickness of paw edema when compared with the control group with a rank order of carrageenan then celecoxib then curcumin and prednisolone groups.

![Fig. 1](image_url)

Fig. 1: Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on the mean value of the thickness of paw edema in different times in carrageenan-induced paw edema in rats (A) and on the average of analgesic test in different times (B). (*) Indicate a significant mean value ±SEM ($P<0.05$)
While after 120 min the result showed a significant $P < 0.05$ decrease in thickness of paw edema in celecoxib, prednisolone and curcumin groups when compared with carrageenan group fig (1) (A). The findings of the present work regarding the anti-inflammatory effects of curcumin showed that the curcumin-treated group extended a significant reduction in paw edema after 2 hr or more from carrageenan injection as in celecoxib and prednisolone. That goes hand in hand with$^{28}$ who suggested that curcumin had anti-inflammatory and anti edematous action via inhibiting cyclooxygenase and lowering prostaglandins$^{29}$.

After 60 min of administration of the last doses of drugs, the result of the current work showed a significant $P < 0.05$ increase in the mean value of analgesic effect when compared with the control group with a rank order of celecoxib then prednisolone and curcumin groups. There was a non-significant difference in the mean value of analgesic effect after 30 min in celecoxib, prednisolone, and curcumin groups when compared with the control group fig (2) (B). The analgesic effect of curcumin could be refereed to several activities, first of all, curcumin increases the level of 5-Hydroxy tryptophan (a precursor of serotonin) and postsynaptic cell's sensitivity to this matter and high serotonin levels are increased. Curcumin enhances the effects of neurotransmitters by inhibiting monoamine neurotransmitter oxidase A, B (enzymes that break down dopamine and serotonin in the synaptic space) and increasing their sustainability$^{30}$ . Second of all, curcumin also raises noradrenaline levels in the frontal lobe and hippocampus, which helps to relieve pain. It can be used to relieve discomfort in uncomfortable body positions. Curcumin has been shown in many studies to influence opioid receptors, and its impact on pain and pain reduction is mediated by the opioid system$^{31}$.

Third of all, inflammatory chemicals such as cyclooxygenase-2 are inhibited by curcumin. Cyclooxygenase-2 produces prostaglandins (inflammatory and fever-inducing mediators), and curcumin inhibits this pathway and reduces inflammation$^{32}$ . PKC (protein kinase C) is a molecule that boosts the expression of cyclooxygenase-2. Curcumin inhibits PKC, which prevents the expression of cyclooxygenase 2 and decreases inflammation.

The result of the contemporary investigation showed a significant $P < 0.05$ increase in the mean value of ulcer count in celecoxib and prednisolone groups when compared with the control group. While the result showed a significant $P < 0.05$ decrease in the mean value of ulcer count in the curcumin group when compared with celecoxib and prednisolone groups table (2). The results of the present work showed that both celecoxib and prednisolone caused gastric ulcers in treated rats. However, curcumin appeared to have no ulcerogenic effect$^{33}$ . The ulcerogenic effect of SAID and NSAID could be discussed by blocking the development of prostaglandins by COX-2 in the presence of inflammation can interfere with tissue healing mechanisms and thus be harmful. On the other hand, the antiulcer function of curcumin might be owed to the antioxidant activity and free radical scavenging properties of curcumin that came from either the phenolic OH group or the CH₂ group of the b-diketone moiety$^{34}$.

**Table 2 :** Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on formation of ulcers in stomach(Ulcer count):-

| Group | Ulcer count |
|-------|-------------|
| 1 (Control) | 0 |
| 2 (carrageenan) | 0 |
| 3 (celecoxib) | 2 |
| 4 (prednisolone) | 4 |
| 5 (curcumin) | 0 |

**Effect of celecoxib, prednisolone and curcumin on mRNA expression of skin inflammatory and anti-inflammatory markers**

The result of the current work showed a significant $P < 0.05$ increase in the mean fold change of skin ($\text{NFK}\beta$), tumor necrosis factor-alpha ($\text{TNF}\alpha$), interleukin 1β, interleukin 6) and a significant decrease in IL 10 of carrageenan group when compared with control one.
Fig. 2: Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on the mean fold change of skin nuclear factor kappa (NFKβ), tumor necrosis factor-alpha (TNFα), interleukin 1β, interleukin 6 and interleukin 10 mRNA relative expression /Graph (% control) in carrageenan-induced paw edema in rats From (A-E). A-(NFKβ), B-(TNFα), C-(IL1β), D-(IL6), E-(IL10). (*) Indicate a significant mean value ±SEM (P < 0.05) Values are mean of 8 rats per group ±S.E.M

However, celecoxib, prednisolone and curcumin administration induced a significant improvement in these parameters, which might be owed to several causes, first of all, the anti-inflammatory activity of curcumin since it increased IL-10 expression and production while also improving its activity in a variety of tissues. Curcumin’s effect on IL-10 release can modify the disease pathophysiology of disorders like pain and neurological diseases, intestinal inflammation, and allergies, as well as infections and cancer, in vitro and preclinical models. At least a portion of curcumin’s beneficial impacts on human health
could be attributed to its capacity to increase IL-10-mediated effects. Second of all, the molecular mechanisms of its effects are diverse, involving various signaling pathways (such as NF-κβ and STAT3 signaling)\textsuperscript{36}. Sandur et al.\textsuperscript{37} reported that curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the active substances in C. longa that suppressed TNF-induced NF-κβ activation. Their effects were found to be due to the methoxy groups on the phenyl ring.

\textbf{Fig. 3}: Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on the mean fold change of gastric nuclear factor kappa (NFKB), Heme oxygenase-1 (HO-1), interleukin 8, nuclear factor erythroid 2-related factor 2 (Nrf2) and Superoxide dismutase (SOD) mRNA relative expression /Graph (% control) in carrageenan-induced paw edema in rats From (A-E). A- (NFKB), B- (HO-1), C- (IL8), D- (Nrf2), E- (SOD). (*) Indicate a significant mean value ±SEM (P < 0.05) Values are mean of 8 rats per group ±S.E.M.
Effect of celecoxib, prednisolone and curcumin on mRNA expression of gastric inflammatory and anti-inflammatory markers

The result of the current work showed a significant $P<0.05$ increase in the mean fold change of gastric (NFKβ), interleukin 8, and a significant decrease in HO-1, nuclear factor erythroid 2-related factor 2 (Nrf2) and SOD of carrageenan group when compared with control one. However celecoxib, prednisolone administration induced a significant improvement in these parameters. Interestingly, the curcumin group showed a significant decrease in inflammatory markers and a significant increase in anti-inflammatory markers (HO-1, Nrf2 and SOD) compared with celecoxib and prednisolone groups. The results illustrated that curcumin has a gastroprotective effect, unlike celecoxib and prednisolone, since Curcumin interacts with Cys151 in Keap1 to substantially increase nuclear expression levels and facilitate the biological effects of Nrf2, making it a promising therapeutic candidate for a wide variety of oxidative stress-related diseases, including type 2 diabetes (T2D), neurodegenerative diseases (NDs), cardiovascular diseases (CVDs), cancers, viral infections, and more recently SARS-CoV-2. Currently, the multifactorial nature of diseases and a lack of adequate medical care, especially in viral diseases, necessitate the development of new drug discovery strategies. Curcumin has the ability to open up new avenues as a potential Nrf2 activator. When Nrf2 is activated by curcumin, it can inactivate the NF-kβ and AP-1 signaling pathways, preventing them from being activated by different stimuli. This result was shown that curcumin has anti-inflammatory properties, these findings are in accordance with who reported that curcumin can inhibit inflammation due to several reasons i) Inhibit pro-inflammatory transcription factors (NF-κβ and AP-1); ii) Down-regulate enzymes such as 5-lipoxygenase and COX-2 iii) Reduce the pro-inflammatory cytokines TNFα, IL-1b, IL-2, IL-6, IL-8, MIP-1a, MCP-1, CRP, and PGE2; and iv) Inhibit the mitogen-activated protein kinases (MAPK) and pathways involved in nitric oxide synthase (NOS) enzymes synthesis.

![Fig. 4: Effect of oral administration of celecoxib (10 mg/kg), prednisolone (5 mg/kg) and curcumin (100 mg/kg) on the mean value of antioxidant enzymes level (Catalase, GPx and SOD) and lipid peroxidation marker (MDA) in carrageenan-induced paw edema in rats from (A – D). A-(CAT), B-(GPx), C-(SOD), D-(MDA). (*) Indicate a significant mean value ±SEM ($P < 0.05$)](image-url)
Effect of celecoxib, prednisolone and curcumin on skin oxidant/antioxidant activity

The result of the present study showed a significant $P<0.01$ decrease in the mean value of (CAT, GPX, SOD) and a significant increase in MDA of the carrageenan group when compared with the control group. However, celecoxib and prednisolone administration induced a significant improvement in these parameters. Interestingly, the curcumin group showed a significant increase in antioxidant markers and a significant decrease in lipid peroxidation marker compared with celecoxib and prednisolone groups. It could be attributed to curcumin's electron-donating groups, particularly the phenolic hydroxyl group, which are the key contributors to its antioxidant action, according to a study on its chemical structure. Curcumin works by scavenging free radicals to alleviate oxidative stress.

Conclusion
Based on the previous mentions it could be speculated that curcumin represents a new valid analgesic and anti-inflammatory candidate without gastric mucosa perturbation unlike SAID and selective NSAID. Histological assessment for the changes in rat paw skin and gastric tissues will be considered in future work.

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قوة الكركمين المضادة للالتهابات والعمل كمسكن والتأثير التقرحي بالمقارنة مع سيليوكسبيب والأزيديزولون

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تبحث الدراسة الحالية في التأثير المضاد للالتهاب والمسكن واضطراب المعدة للكركمين مقارنة

مع السيليوكسبيب والأزيديزولون. أجريت الدراسة على 60 جرذا من ذكور الجرزان البالغة والتي

تم تقسيمها إلى خمس مجموعات متساوية. المجموعة 1: المجموعة الضابطة ، المجموعة 2: المجموعة

الضابطة دون دواء والتي تلقى الكركمين بعد 14 يوم من بدء التجربة ، المجموعة 3: والتي

تناولت السيليوكسبيب (10 ملغ / كغ) عن طريق الفم لمدة 14 يوما ثم حقنها بالكركمين ،

المجموعة 4: تناولت الأزيديزولون (5 ملغ / كغ) عن طريق الفم ثم حقنها بالكركمين بعد 14

يوما ، والمجموعة 5: تناولت الكركمين (100 ملغ / كغ) عن طريق الفم ثم حقنها بالكركمين بعد 14

يوما. تم قياس تورم المخلب، واعلامات الإجهاد التأكسدي، والمكسات، ونشاط ضامة، التعبير عن

mRNA و SOD، وثبات النشاط الأساسي مثل السيليوكسبيب والبروبوسون عند مقارنته مع الكركمين ،

الدراسات الالتهابية للجزء والغشاء المخاطي في المعدة المساوية للكركمين. أظهرت هذه النتيجة أن الكركمين يحسن بشكل ملحوظ أدوية النمو، والبروميسلين، وuates السكريات الأكاذيب مثل السيليوكسبيب والبروبوسون عند مقارنته مع الكركمين، يجعل الكركمينات والسيليوكسبيب والبروبوسولون على زيادة (IL10، IL6، IL1β، TNFa، NFκβ) للجلد والبط المجرى، والمعدة (IL6، IL1β، TNFa، NFκβ، SOD، Nrf2) و mRNAs، و و SOD و Nrf2 و NFκβ. يمكن أن يستنتج أن الكركمين يظهر مصدرا للالتهابات ومسكنا مع الحد الأدنى من اضطراب المعدة على عكس السيليوكسبيب والأزيديزولون.