PREVENTION OF NEPHROTOXICITY BY CURCUMIN IN CHEMICALLY INDUCED OSTEOARTHRITIS

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Abstract:
Osteoarthritis is a degenerative disorder resulting in degeneration of cartilage and osteophytes formation. Non steroidal anti inflammatory drugs are commonly used drugs to alleviate the pain in most of the chronic inflammatory conditions like osteoarthritis. These drugs alleviate the pain by inhibiting the synthesis of prostaglandins. Although these drugs reduce the pain, they have several limitations as they cause nephrotoxicity. In recent years several works have been carried out to improve the therapeutic strategy in osteoarthritis. The present study was carried out to investigate the role of curcumin in osteoarthritis when it is used as an adjuvant to Diclofenac sodium. Osteoarthritis was induced by administering nalidixic acid. Animals were divided into 5 groups and were treated accordingly. Group I was considered as control, group II animals were disease control i.e they were induced with osteoarthritis and were given no treatment. Group III animals were induced with Osteoarthritis and were treated with diclofenac sodium. Group IV animals were induced with osteoarthritis and were treated with the combination of diclofenac sodium and curcumin. Group V animals were pre-treated with curcumin and then induced with osteoarthritis. Parameters like serum creatinine levels, serum uric acid levels, serum potassium levels, serum ALP levels, blood urea nitrogen (BUN), urine potassium, urine creatinine, urine output, kidney weight were estimated. Histopathological studies were also carried out. Animals treated with curcumin along with the standard drug or animals with pretreated curcumin have shown fewer incidences of nephrotoxicity. Histopathology also supports low incidence of nephrotoxicity in those animals. It demonstrates that curcumin when used along with the conventional NSAIDs as an adjuvant therapy has a role in treating osteoarthritis effectively.

Key words: Osteoarthritis, nephrotoxicity, nonsteroidal anti inflammatory drugs, curcumin and prostaglandins.

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INTRODUCTION:
Osteoarthritis is a pro-inflammatory degenerative disorder effecting millions of individuals in whole over the world [1]. It is the most common type of arthritis. Soreness and stiffness in joints, heberden nodes [2] and pain are the common symptoms experienced in Osteoarthritis. Alleviating pain is the treatment goal in the treatment of osteoarthritis. NSAIDs like Diclofenac sodium, Naproxen, Indomethacin, Ibuprofen are conventionally used to reduce the pain. Although these drugs help in reducing the pain but they cause many adverse effects of which gastric ulceration is important. Curcumin is an active constituent available in the rhizome of Curcuma longa (Turmeric) which belongs to the family Zingiberaceae. Curcumin is thought to possess anti-inflammatory, antioxidant, anti-fungal, anti viral properties. It also suppresses the tumor formation and blood vessel formation.

Quinolone antibiotics are the drugs which act by inhibiting DNA gyrase and topoisomerase enzyme in bacteria. In addition to this activity it degenerates articular cartilage due to their affinity towards the cartilage and bone. Blisters like lesions are formed on the cartilage followed by its degeneration after 24 hours of its administration. This is evidenced by the appearance of nodules [3].

The present study is aimed to investigate the effect of curcumin when used with standard drug in the treatment of Osteoarthritis and also its role in the prevention of gastric ulceration when animals are pretreated with it. Parameters like ulcer area, ulcer index, free acidity, total acidity, volume of gastric juice were studied. Histopathological studies were also carried out.

MATERIALS AND METHODS:
Animals: 24 female Wistar rats weighing around 180-250 g were used for this study. The animals were accommodated in standard conditions of ventilation and temperature (25±2° C), humidity (60-70%) and light/dark condition (12/12). They were housed in pathogen-free conditions. The animal procedures were conducted according to CPCSEA guidelines. Chemicals: Curcumin, Nalidixic acid, Dimethyl Sulfoxide were purchased from Hychem Laboratories, Hyderabad.

Nalidixic acid was administered at a single dose of 400mg/Kg subcutaneously.

Diclofenac sodium was administered orally at a dose of 13mg/Kg for 21days. Curcumin was given orally at a dose of 200mg/Kg for 21 days.

Experimental design: The animals were allowed for stabilization or acclimatization for one week. Then they were grouped under 5 groups each containing 6 animals.
Group I: Control group – The animals were administered with DMSO for 21days.
Group II: Disease control – Animals were administered with nalidixic acid and observed for 48 hrs.
Group III: Standard group- Animals was administered with nalidixic acid and after 48 hrs they were treated with NSAIDs for 48 hrs.
Group IV: Test group- Test Animals were administered with nalidixic acid and after 48 hrs they were treated with NSAIDs and curcumin for 21 days.
Group V: Pretreated group- Animals were pretreated with curcumin for 21 days before the administration of Nalidixic acid.
RESULTS:

Fig 1: Effect of various treatments on serum creatinine in (OA) induced rats. All the data are expressed in mean ± SD, n=6. The level of serum creatinine was found to be lower and normal in group I control (0.333±1.51) and in group II (0.567±0.082). It has increased significantly in group III (0.983±0.223) animals which were treated with diclofenac sodium (p<0.0001) when compared to the control group. The values were decreased and were approximately normal in the group IV (0.683±0.183) – animals which were treated with diclofenac sodium and curcumin and group V (0.350±0.164) - animals which were pretreated with curcumin.

Fig 2: Effect of various treatments on serum uric acid levels in Osteoarthritis (OA) induced rats. All the data are expressed in mean ± SD, n=6. Group I control (3.70±1.746) and group II (4.033±1.632) osteoarthritis induced animals without treatment has shown normal values. It has increased significantly in group III (9.550±2.559) osteoarthritis induced animals treated with diclofenac sodium when compared to control (p<0.001). Group IV (7.350±2.542) osteoarthritis induced animals treated with diclofenac sodium and curcumin and group V (5.10±0.590) animals which were pre-treated with curcumin has shown decrease levels of serum creatinine when compared to group III.
Fig 3: Effect of various treatments on serum potassium levels in Osteoarthritis (OA) induced rats. All the data is expressed in mean ±SD, n=6. Group I control (6.467±1.382) and group II (5.733±0.703) osteoarthritis induced animals without treatment has shown normal values. It has increased significantly in group III (9.700±2.373) osteoarthritis induced animals treated with diclofenac sodium when compared to control (p<0.001). Group IV (6.483±0.958) osteoarthritis induced animals treated with diclofenac sodium and curcumin and group V (6.483±0.958) animals which were pre-treated with curcumin has shown decrease levels of serum potassium when compared to group III.

Fig 4: Effect of various treatments on ALP in Osteoarthritis induced rats. All the data is expressed in mean ±SD, n=6. Group I was considered as control (69±9.038). Administration of nalidixic acid has not shown any significant effect on the ALP levels (86±15.363). Osteoarthritis induced animals which were treated with diclofenac sodium i.e group III animals (186±10.936) has shown increased levels of ALP significantly (p<0.0001). Group IV (61±10.024) animals which were treated with the combination of diclofenac sodium and curcumin and group V (81.717±16.415) has shown the normal values of ALP.
Fig 5: Effect of various treatments on blood urea nitrogen levels in OA induced rats. All the data is expressed in mean ±SD, n=6. Group I (32±2.280) control and group II (38±5.292) animals induced with osteoarthritis without treatment has shown the normal levels of ALP. Group III (62±7.155) animals which were treated with diclofenac sodium has significant increased levels of ALP (p<0.0001) and group IV (36.333±3.882) animals which were treated with the combination of diclofenac sodium and curcumin has significant decreased levels of ALP when compared to group III (p<0.5) and groupV (35.333±3.077) animals which were pre treated with curcumin also has shown decreased levels non significantly when compared to group III.

Fig 6: Effect of various treatments on urine potassium levels in osteoarthritis induced rats. All the data is expressed in mean ±SD, n=6. The urine potassium levels were found to be normal in group I (6.333±0.602) control animals and group II (6.283±0.436) OA induced animals without treatment. Group III (2.567±1.009) animals treated with diclofenac sodium has shown significant decreased levels of urine potassium when compared to control (p<0.001). Group IV (6.217±0.585) and group V (6.033±0.781) animals which were treated with combination of diclofenac sodium and curcumin and pretreated with curcumin respectively have shown non significant increased urine potassium levels when compared to group III.
Fig 7: Effect of various treatments on urine creatinine in osteoarthritis induced rats. All the data is expressed in mean ±SD, n=6. Urine creatinine levels were found to be normal in group II (0.463±0.173). Group I (0.468±0.235) was considered as control. Group III (0.173±0.075) osteoarthritis induced animals treated with diclofenac sodium has shown decreased levels of urine creatinine significantly (p<0.001) when compared to control. Group IV (0.413±0.222) animals treated with the combination of diclofenac sodium and curcumin has shown significant increase in urine creatinine values (p<0.5) when compared to group III. Group V (0.345±0.083) animals pre-treated with curcumin have also shown increased levels non significantly when compared to group III.

Fig 8: Effect of various treatments on urine output in OA induced rats. All the data is expressed in mean ±SD, n=6. The urine output was found to be normal in group I control (28.5±2.258) and OA induced animals with no treatment i.e group II (30.500±2.739). Group III (11.833±2.317) animals treated with diclofenac sodium has shown significant decrease in urine output (p<0.001) when compared to control. Group IV (24.167±3.067) has significant increased urine output values (p<0.5) when compared to group III. Group V (24±3.347) animals which were pre-treated with curcumin have also shown increased urine output non significantly when compared to group III.
Fig 9: Effect of various treatments on kidney weight in OA induced rats. All the data is expressed in mean ±SD, n=6. Group I (0.765±0.05) was considered as control. Nalidixic acid when administered to induce osteoarthritis did not show any significant effect on kidney weight in group II (0.766±0.0432). Treatment with diclofenac sodium has increased the kidney weight in group III animals (1.273±0.442) significantly when compared to control (p<0.01). Group IV (0.82±0.065) animals treated with the combination of diclofenac sodium and curcumin has shown decreased kidney weight significantly when compared to group III (p<0.01). Group V (0.785±0.0327) animals pre-treated with curcumin also have shown decreased or normal kidney weight significantly when compared to group III (p<0.01).

**Histopathological studies:**

Fig 10: Histopathology of kidney
From the histopathological observation, it is evident that the kidneys in Group I and Group II were found to be normal with normal architecture. Glomerular morphology was preserved with intact distal convoluted tubule. Nalidixic acid has not shown marked histopathological changes and hence did not cause damage to the kidney as such. Group III animals which were treated with NSAIDs has shown marked histopathological changes in the tissue. There is an intense vacuolation with a typical moth eaten appearance. Mild necrotic areas were also observed. Blood vessel congestion was also observed. Group IV has shown mild vacuolation, without any necrotic foci with preserved glomerular architecture and distinct distal convoluted tubule. Group V kidney tissues which were pre-treated with curcumin have shown less damage without vacuolation or necrotic areas with well preserved architecture with an intact distal convoluted tubule. Hence, the study suggests the nephro protective action of curcumin.

**DISCUSSION:**

The major drawback of usage of NSAIDs is nephrotoxicity which may be immune mediated or hemodynamically mediated. They inhibit the synthesis of prostaglandins which have renal hemostasis effect. They cause vasodilation of renal afferent arteriole which is required to maintain GFR which in turn is responsible for the maintenance of Blood pressure.

To combat this adverse effect of NSAIDs nephroprotective agent Curcumin was used as an adjuvant drug and the effect on kidneys in rats was studied. The Kidney injury caused due to the administration of NSAIDs is usually immune mediated where leukotrienes synthesis is increased due to the preferential conversion of arachidonic acid to leukotrienes. These leukotrienes activates T-lymphocytes then mediates the immune response.

Leukotrienes such as LTC₄, LTD₄, and LTE₄ increase micro vascular permeability and are potent chemotactic agents. They also increase the expression of Tumor Necrosis Factor-α (TNF-α) which causes gastric and renal damage. The hydrostatic pressure which is reduced due to inhibition of prostaglandins is also involved in initiation of renal injuries. The injury is characterized by tubular atrophy, inflammatory inflammation of leucocytes, fibroblast activation, proliferation, increase in matrix proteins and progressive intestinal fibrosis with a loss of renal parenchyma. Curcumin acts as antagonist for cysLT1, receptor where leukotrienes act thereby decreases / inhibits the effect of leukotrienes.

TNFs are the important mediators of inflammation and inflammation related disorders. TNF binds to 2 important receptors TNFRSF1A and TNFRSF1B and activates caspase-mediated apoptosis, NF-κB, JNK, p38MAPK and ERK signaling. TNF stimulates collagenase and PGE₂ production in synovial cells representing that it plays a major role in tissue destruction and remodeling associated with inflammatory disorders [4].

There has been an extensive research and the studies suggest that curcumin down regulates the expression of the TNF-α [5-7]. Curcumin suppresses TNF at transcription level. Different transcription factors involved in the transcription of TNF are: - qTranscription factor ETS [8], Activating transcription factor -2, SP1, Nuclear factor of activated T-cell transcription factor (NFAT) [9], NF-κB [10], Early growth response protein-1 [11] and CAMP response element binding protein (CREB) [12]. Several of these transcription factors have found to be modulated by Curcumin. The most important action of curcumin is down regulation of activation of NF-κB which suppresses the expression of TNF-α thereby helping in preventing the renal injury [13].

**Statistical Analysis:**

The data was expressed as Mean±S.D values. Results were analyzed statistically by One-way ANOVA followed by Dunnett’s Test using standard statistical software package of Graph pad prism. The difference was considered significant if p<0.05.

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