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ORIGINAL ARTICLE

Taurine: A promising agent of therapeutic potential in experimentally-induced arthritis

Hala F. Zaki *, Hesham A. Salem, Mohammed F. El-Yamany

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt

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KEYWORDS

Taurine;
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Interleukin-1beta

Abstract *Introduction:* Taurine is an amino acid whose protective effects were shown in certain inflammatory conditions.

Aim of the work: The present work aimed to explore the possible anti-arthritic effects of taurine in comparison with diclofenac.

Materials and methods: Rats were allocated into five groups ($n = 10$). The normal and control groups received normal saline. The remaining three groups were treated with diclofenac (2 mg/kg), taurine (5 mg/kg), or taurine (50 mg/kg), respectively. Drugs were i.p. injected for 26 successive days starting from the onset of adjuvant induction. Arthritis was induced by s.c. injection of 0.4 ml of Freund's complete adjuvant (FCA) into the subplantar region of the right hind paws of rats in all groups except the normal one. Paw volume was measured before and at different time intervals after adjuvant inoculation. After the last measurement, blood samples were collected and were used for estimation of serum levels of lipid peroxides, nitrite, total antioxidants, tumor necrosis factor-alpha, and interleukin-1beta as well as lactate dehydrogenase activity. Histopathological examination of knee tissues of all rats was also performed.

Results: Injection of FCA induced marked arthritis manifested by paw edema during the 26-day experiment period. Treatment with diclofenac or taurine (50 mg/kg) markedly inhibited adjuvant arthritis as well as its associated biochemical and histological changes. Taurine (5 mg/kg) did not affect FCA-induced paw edema but it attenuated some of the induced biochemical changes.

* Corresponding author. Tel.: +20 101040447; fax: +20 224073411.
E-mail address: halafzaki@gmail.com (H.F. Zaki).

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Conclusions: Taurine effects could be explained by inhibition of pro-inflammatory cytokines production as well as its antioxidant effects.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disorder which often leads to disability and can considerably affect the patient's quality of life [1]. The pathogenesis of RA is predominantly associated with the formation of reactive oxygen species (ROS), pro-inflammatory cytokines, and other inflammatory mediators as prostaglandins at the site of inflammation [1,2].

Conventional therapies in RA as steroids and non-steroidal anti-inflammatory drugs (NSAIDs) help in controlling symptoms of arthritis, nevertheless their effects on disease progression as well as their adverse effects make them unsatisfactory [3].

Taurine is a semi-essential non-protein amino acid that is present abundantly in several mammalian tissues as well as pro-inflammatory cells as polymorphonuclear leukocytes [4]. Taurine's protective effects have been demonstrated in some inflammatory conditions [5–7]. One of the proposed protective mechanisms of taurine is its reaction with hypochlorous acid, produced via myeloperoxidase pathway, to produce taurine chloramines, a powerful anti-inflammatory agent [8].

The present work was designed to investigate the possible anti-arthritic effect of taurine, in an experimental model of arthritis, and to compare such effects with diclofenac, a known anti-inflammatory agent. In an attempt to understand the possible underlying mechanism(s) of taurine effects, assessment of certain biochemical parameters related to arthritis, as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), nitric oxide metabolites, total antioxidant capacity, lactate dehydrogenase (LDH) activity, and formation of thiobarbituric acid reactive substances (TBARS), were also done in serum. In addition, histopathological examination of joint tissue was performed.

2. Materials and methods

2.1. Animals

Male Wistar rats of 120–150 g body weight were used in the current investigation. They were obtained from the National Cancer Institute (Cairo, Egypt) and were kept in the animal house of the faculty of Pharmacy, Cairo University at a temperature of 25 ± 1 °C, humidity of 60 ± 5% and natural lighting conditions. Rats were fed on a standard pellet chow (El-Nasr Chemical Company, Cairo, Egypt) and allowed free access to water. The study was carried out according to the international guidelines of the Care and Use of Laboratory Animals and approved by the Ethics Committee for Animal Experimentation at the Faculty of Pharmacy, Cairo University.

2.2. Chemicals

Taurine and Freund's complete adjuvant (FCA) were purchased from Sigma Chemical Company, USA. Diclofenac sodium was purchased from Novartis Pharma, Egypt. Taurine and diclofenac were dissolved in normal saline prior to administration. Kits for determination of TNF-α and IL-1β were purchased from Quantikine, R&D Systems, USA. Kit for determination of LDH was obtained from Stanbio, USA. Kits for determination of total antioxidants, nitrite, and lipid peroxides were purchased from Biodiagnostic, Egypt. All other used chemicals were of analytical grade.

2.3. Experimental design

Rats were randomly allocated into five groups each consisting of 10 animals. Three groups were treated with diclofenac sodium (2 mg/kg), taurine (5 mg/kg), or taurine (50 mg/kg), respectively. Drugs were dissolved in normal saline and were i.p. injected to rats. The other two groups were i.p. injected with normal saline; one served as normal group and the other served as control group. Polyarthritis was induced by s.c. injection of 0.4 ml of FCA [9] into the subplantar region of the right hind paws of rats of all groups except the normal one. Drugs were administered once daily for 26 consecutive days starting from the onset of adjuvant inoculation. To assess the time course of adjuvant-induced edema, paw volume was measured before and after 4, 7, 11, 14, 19, 21, and 26 days of adjuvant inoculation by volume displacement method using a water plethysmometer (Ugo Basile, Italy). The last measurement of paw volume was performed 1 h after administration of the last dose of the test agents. Then, blood samples were collected via the retro-orbital venous plexus of each rat and were used for serum separation and estimation of LDH activity as well as TBARS, nitrite, total antioxidants, TNF-α and IL-1β concentrations.

2.4. Biochemical measurements

Serum LDH activity was estimated kinetically and expressed as U/ml. Serum TBARS and nitrite were determined colorimetrically using commercially available kits; their concentrations were expressed as nmol/ml. Serum TNF-α and IL-1β concentrations were determined by sandwich enzyme linked immunosorbent assay (ELISA) technique and their concentrations were expressed as pg/ml. Total antioxidants were determined colorimetrically using commercial kits and expressed as μmol/ml. The assay reflects the integrative potential of all enzymatic and non-enzymatic antioxidants present in serum.

2.5. Histopathological examination

The limbs of all animals were dissected and placed in a 0.4 M EDTA, 0.3 N NaOH, solution, which was changed every 3 days, for 4–5 weeks to achieve decalcification (end-point determined by physical assessment). Each specimen was embedded in paraffin wax and sectioned in the sagittal plane starting from the medial margin. Serial sections in knee joints with a thickness of 6 μm were taken. The sections were stained with hematoxylin and eosin for histopathological

investigation. Images were captured and processed using Adobe Photoshop version 8.0.

Statistics. Values were presented as means ± S.E. One-way analysis of variance (ANOVA) followed by Least Significant Difference (LSD) post hoc test was used to determine the difference between the groups in terms of all studied parameters using SPSS software (version 11.0). Results were considered statistically significant when $p < 0.05$.

3. Results

FCA injected into the hind paw of rats induced marked edema during the 26 days experiment period. In the control group, the percentage of edema volume to initial paw volume (% edema) maximally recorded 77% after the 19th day from adjuvant inoculation (Fig. 1). Diclofenac (2 mg/kg/day) significantly inhibited FCA-induced paw edema at all the studied time intervals when compared to the control group. Treatment with taurine (5 mg/kg/day) showed no significant effect on paw edema as compared to the control group. On the other hand, taurine (50 mg/kg/day) afforded significant reduction in % edema at days 4, 7, 11, 19, 21, and 26 (Fig. 1).

Serum LDH activity of the normal group recorded 0.16 ± 0.01 U/ml. FCA markedly elevated such activity to 0.41 ± 0.04 U/ml in the control group. Treatment with diclofenac, the low and high doses of taurine significantly reduced FCA-induced activation of serum LDH recording 68.7%, 48.5%, and 27.2% of the control value, respectively (Fig. 2A). In addition, the obtained results revealed that taurine by either dose lowered serum LDH activity significantly as compared to diclofenac treatment in dose-dependent manner.

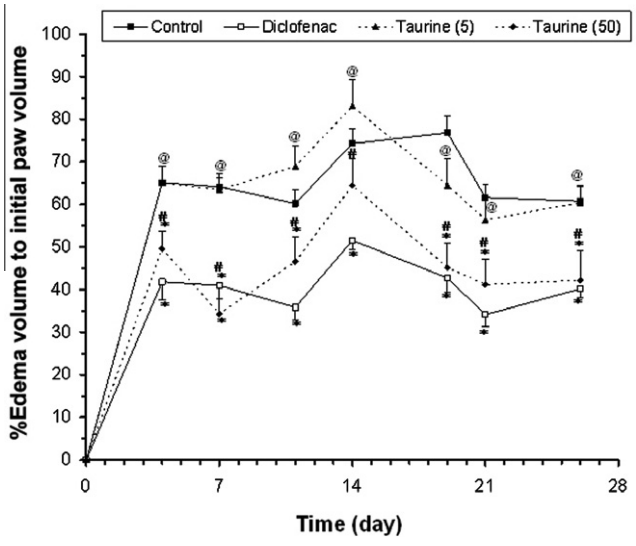

Figure 1 Time course effects of diclofenac (2 mg/kg) and taurine (5, 50 mg/kg) on Freund's complete adjuvant-induced hind paw edema. Drugs were administered i.p. once daily for 26 consecutive days starting from the onset of adjuvant inoculation. Control group received saline daily. Paw volume was measured before and after 4, 7, 11, 14, 19, 21, and 26 days of adjuvant inoculation by volume displacement method. The last measurement of paw volume was performed 1 h after the last dose administration. Each point represents the mean of nine experiments ± S.E. $^{*}p < 0.05$ vs. control, $^{@}p < 0.05$ vs. diclofenac, $^{\#}p < 0.05$ vs. taurine (5).

Normal serum TBARS level was 9.12 ± 0.93 nmol/ml. FCA increased lipid peroxidation as manifested by 1.5-fold increase in serum TBARS level recording 13.83 ± 1.15 nmol/ml in the control group. Daily treatment with diclofenac, taurine (5 mg/kg), and taurine (50 mg/kg) produced significant reductions in FCA-induced lipid peroxidation recording 71.7%, 42.5%, and 46.8% of the control value, respectively (Fig. 2B). Also, when compared to diclofenac, serum TBARS levels of taurine-treated groups were significantly lower than that of diclofenac-treated group.

Normal level of serum nitrites was 8.84 ± 1.04 nmol/ml. FCA significantly elevated nitrites level to 12.95 ± 1.19 nmol/ml in the control group. Treatment with diclofenac and taurine (50 mg/kg) significantly reduced such level to 61.3% and 47.4% of the control value, respectively (Fig. 2C). On the contrary, the low dose of taurine did not produce any significant change in this parameter.

Serum total antioxidant capacity was not significantly changed by adjuvant arthritis or by treatment with any of the test agents (Fig. 2D).

Serum TNF-α level of the normal group recorded 15.61 ± 2.01 pg/ml. FCA significantly increased this level to 25.34 ± 3.33 pg/ml in the control group. Treatment with diclofenac, the low and high doses of taurine significantly decreased TNF-α to 56%, 63%, and 52% of the control value, respectively (Fig. 2E).

Serum level of IL-1β was 65.26 ± 6.86 pg/ml in the normal group. FCA markedly increased IL-1β level to 97.58 ± 7.80 pg/ml in the control group. Diclofenac produced a significant reduction in this level recording 73% of control value. On the contrary, treatment with taurine by either dose failed to reduce IL-1β level (Fig. 2F).

On examining the histological sections, a healthy articular surface was observed in the normal control animals with a smooth, uninterrupted surface and an even distribution of chondrocytes often arranged in columns (Fig. 3A–C); whereas, in arthritic control animals joint surfaces were abraded and contained fibrotic tissue (Fig. 3D–F). The present results revealed that using diclofenac (Fig. 4A–C) and taurine in the large dose level (Fig. 4G–I) reduced the damaging effect of adjuvant arthritis especially on the articular surfaces. Lesser protective effects were shown by the small dose of taurine (Fig. 4D–F).

4. Discussion

In the current study, FCA resulted in marked paw edema during the 26-day experiment period. Prophylactic daily treatment with diclofenac markedly inhibited the adjuvant-induced arthritis at all studied time intervals.

Adjuvant-induced arthritis is commonly used in evaluating the anti-arthritic potential of new drugs [10]. The inflammatory response in RA is complicated and involves immunologic reactions, complement activation, release of various mediators and chemotactic factors as well as leukocytic infiltration of joints [11,12].

Diclofenac is one of the widely used NSAIDs in treatment of RA and other inflammatory conditions [13]. Suppression of paw edema by diclofenac can be largely attributed to inhibition of PGs-mediated vasodilation and exudation [14] as well as its antioxidant and free radical scavenging properties

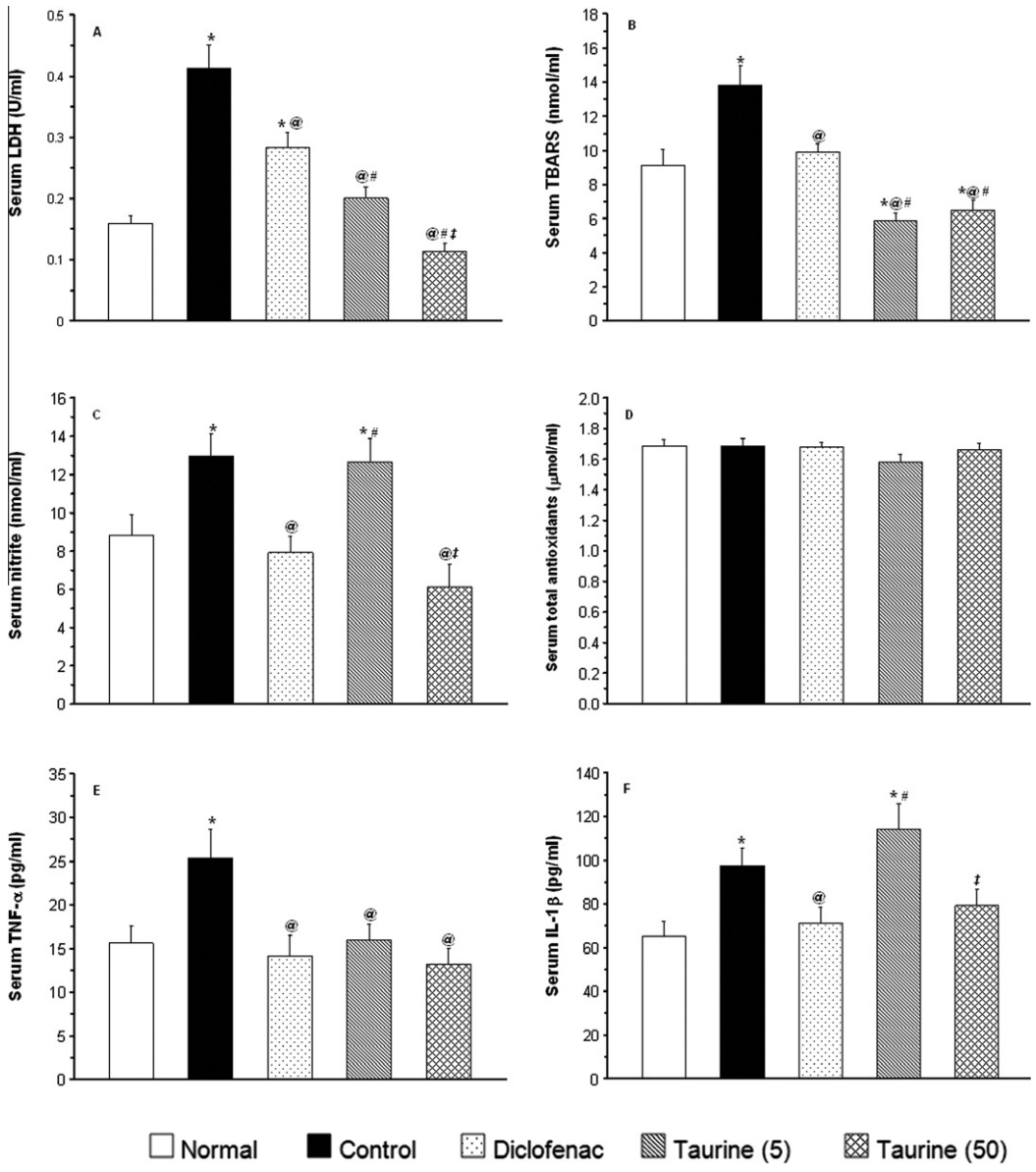

Figure 2 Effects of diclofenac (2 mg/kg) and taurine (5, 50 mg/kg) on serum levels of: (A) LDH activity, (B) TBARS, (C) nitrite, (D) total antioxidants, (E) TNF-α, and (F) IL-1β of rats subjected to Freund's complete adjuvant-induced polyarthritis. Polyarthritis was induced in all groups except the normal one. Drugs (saline for normal and control groups) were administered i.p. once daily for 26 consecutive days starting from the onset of adjuvant inoculation. Blood samples were collected 2 h after the last dose administration. Each bar represents the mean of 5–10 experiments ± S.E.M. shown by vertical line. $^{*}p < 0.05$ vs. normal, $^{@}p < 0.05$ vs. control, $^{\#}p < 0.05$ vs. diclofenac, $^{\ddagger}p < 0.05$ vs. taurine (5).

[15,16]. Moreover, diclofenac was shown to attenuate certain factors known to aggravate joint destruction in rheumatic diseases as myeloperoxidase produced by activated neutrophils [17] and release of lysosomal enzymes [18].

In the present study, administration of taurine in the large dose level (50 mg/kg) significantly reduced paw edema induced in rats by FCA. The effects of taurine were even comparable to that of diclofenac, one of the standard anti-rheumatic drugs.

The present results support those of other investigators, about the anti-inflammatory effect of taurine in models of acute inflammation in rats [19,20].

It was found that taurine chloramine, formed *in vivo* by activated neutrophils, inhibits secretion of some pro-inflammatory cytokines which are crucial in pathogenesis of RA as interleukin-6 (IL-6) and interleukin-8 (IL-8) [21]. Moreover, taurine chloramine was found to inhibit IL-1β-induced production of cyclo-oxygease-2 (COX-2) and generation of prostaglandins (PGE_2) by RA synoviocytes [22].

In the present study, induction of adjuvant arthritis was coupled by marked increases in serum TBARS level and LDH activity. Moreover, prophylactic treatment with diclofenac or taurine in both dose levels reduced lipid peroxidation as evidenced by decreased formation of TBARS and reduced LDH activity, as compared to the control arthritic group. The effects of taurine were even significantly better than those of diclofenac.

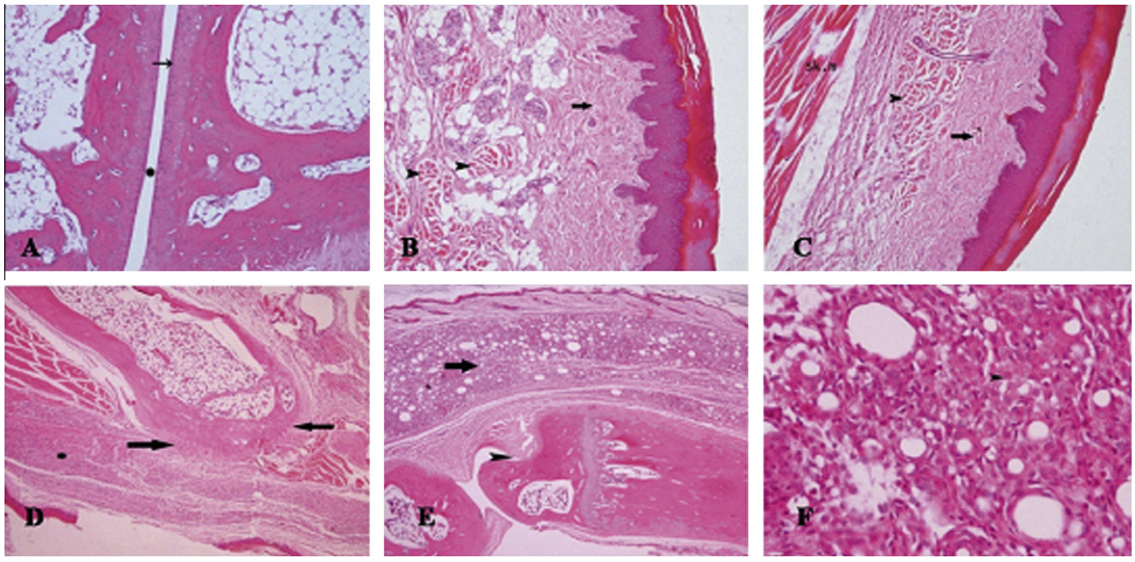

Figure 3 Histopathological changes in knee joint of arthritic rats. (A) Shows a normal structure of a joint where the articular surfaces are covered with a smooth layer of hyaline cartilage (arrow). The synovial space is of normal width (star). (B and C) Show the soft tissue of the limb composed mainly of collagen fibers (arrow) in which bundles of skeletal muscle fibers and fat cells are embedded (arrow head). (D) Shows section in control arthritic group revealing degradation of the articular surface where it becomes adherent and continuous with the connective tissue around (arrow). The connective tissue itself is highly infiltrated with cellular infiltrates (star). (E) Shows also cartilaginous degradation (arrow head) and signs of inflammation in the soft tissue in the form of highly cellular infiltrates and vacuolar degeneration (arrow). (F) Higher magnification of the site of inflammation that shows that the cellular infiltrates are mainly composed of neutrophils (arrow head) denoting acute inflammation. (H&E × 40, 1000).

Inflammation and oxidative stress are two closely related events that contribute to the pathophysiology of arthritis [23,24]. Several studies have documented an imbalance in the body's reduction/oxidation homeostasis in arthritic subjects and experimental animals [23,25,26]. A frequently used marker of lipid peroxidation is malondialdehyde (MDA) assessed as an adduct with thiobarbituric acid. Studies have shown increased plasma level of MDA in patients and animals with RA [27,28]. Lipid peroxidation produces marked alteration in molecular organization of membrane lipid resulting in increased membrane permeability and leakage of cytoplasmic markers as LDH into circulation [29] which could account for the rise in LDH activity observed in the control arthritic group.

The observed protective effects of diclofenac on serum TBARS level and LDH activity could be attributed to its documented antioxidant and free radical scavenging properties [15,16]. Concerning taurine, it was shown to reduce lipid peroxidation and restore depleted glutathione and antioxidant stores in a model of endotoxin-induced lung inflammation [6]. In a study performed by Das et al. [30], taurine supplementation was shown to reduce acetaminophen-induced increase in serum LDH, NO, TNF-α and lipid peroxide products. The antioxidant effects of taurine were demonstrated in several other studies both *in vivo* [31] and *in vitro* [32]. The antioxidant effect of taurine is unique as it can attenuate lipid peroxidation and antioxidant defenses depletion in models of oxidative stress despite lacking a readily oxidizable functionality [4,33].

The observed lack of change in serum total antioxidants level by the experimentally-induced arthritis or treatments in the present study is strange considering that oxidative stress was evident from the elevated TBARS level and LDH activity. Total antioxidants assay reflects the total capacity of different antioxidants present in serum including enzymes as superoxide dismutase, glutathione peroxidase and catalase as well as non-enzymes as reduced glutathione, vitamin C, uric acid and others. During oxidative stress, individual antioxidants may either be depleted or increased as a compensatory mechanism. Hence, perhaps RA led to an increase of one or more of these members and depletion of others leading to a net result of unchanged total antioxidants level. Further experiments may be needed to clarify this point.

Pretreatment of rats with diclofenac, in the present study, reduced arthritis-induced elevation in serum levels of nitrite, TNF-α and IL-1β. Diclofenac treatment was shown to reduce elevated serum levels of NO and TNF-α in arthritic rats [34].

In RA, the synovium is intensively infiltrated by macrophages which are the major source of TNF-α, IL-1β and inducible nitric oxide synthase (iNOS) mediated NO generation during immune response [35]. Both TNF-α and IL-1β play a key role in the induction and perpetuation of immunological inflammation by activating T cells and macrophages and by up-regulating other pro-inflammatory cytokines and endothelial adhesion molecules [36,37]. Consequently, the levels of both cytokines are expected to decrease with diclofenac treatment owing to reduction of inflammation and lipid peroxidation which are major inducers of cytokines production by macrophages [38].

Prophylactic treatment of arthritic rats with taurine reduced elevated serum levels of nitrite and TNF-α whereas no effect was observed on the level of IL-1β. The present findings are supported by previous reports that taurine chloramine inhibits production of NO, TNF-α, and other pro-inflammatory mediators by activated cells from various tissues [21,39].

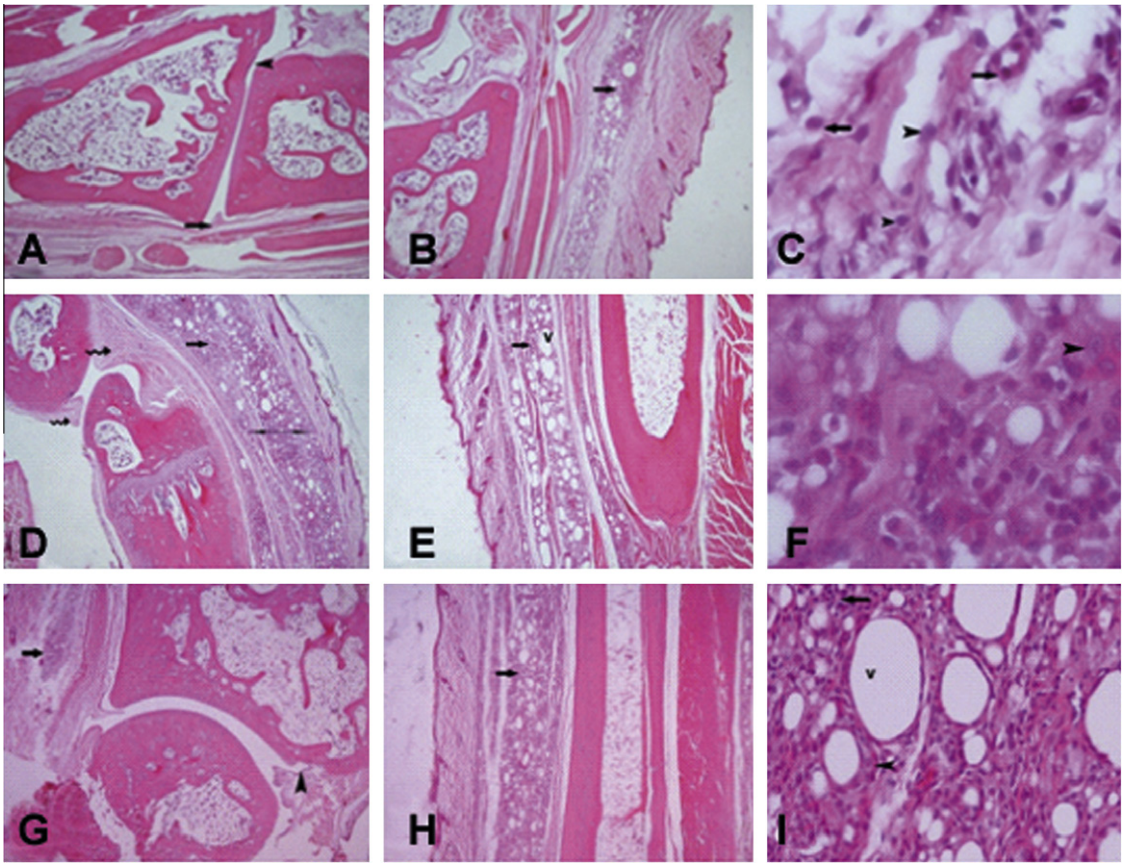

Figure 4 Histopathological changes in knee joint of arthritic rats treated with diclofenac or different dose levels of taurine. (A) Section in a synovial joint from an animal treated with diclofenac, where repair of articular surfaces is markedly observed except for small areas at one side (arrow head) and remaining fibrous tissue invading the joint (arrow). (B) Shows the soft tissue around the joint where edema, vacuolar degeneration and cellular infiltrates are markedly reduced (arrow) by diclofenac. (C) Higher magnification of the site of inflammation showing that the cellular infiltrate is being made up of neutrophils (arrow head) and lymphocytes (arrow). (D) Shows a section in a synovial joint and the soft tissue around it from a rat treated with taurine in a dose of 5 mg/kg, where irregularities in articular surfaces and invasion of connective tissue is still present (wavy arrow). Also the cellular infiltrate (arrow) and the edema (double-ended arrow) in soft tissues are still observed. (E) Vacuolar degeneration (v) is still seen. (F) Shows the components of the cellular infiltrate that is made up from segmented neutrophils of variable sizes with some lymphocytes. (G and H) Show sections in a synovial joint and the soft tissue around it from a rat treated with taurine in a dose of 50 mg/kg, where there is normalization of the articular surfaces except for a very small area at one side (arrow head) with reduction in signs of inflammation of the soft tissue (arrow). (I) Section from the same group showing the cellular infiltrate which is composed of neutrophils (arrow head) and some localized lymphocytes (arrow) in addition, large areas of vacuolar degeneration (v) exist. (H&E × 40, 1000).

Moreover, Marcinkiewicz et al. [40] demonstrated similar protective effects by taurolidine, a derivative of taurine, in various experimental models of synovitis.

Production of pro-inflammatory cytokines is regulated at the genetic level through the activity of certain transcription factors as nuclear factor-kappa (NF-κB) which regulates expression of iNOS, TNF-α and other pro-inflammatory mediators [41]**.** Taurine chloramine was shown to inhibit the expression of iNOS and TNF-α by inhibiting NF-κB signal transduction pathway [42].

Histological examination of knee tissues of control arthritic rats revealed inflammation and degradation of the articular surface accompanied by marked cellular infiltration of connective tissues coupled with vacuolar degeneration of cartilages. Diclofenac and taurine in the large dose level led to marked repair of articular surfaces and reduction of soft tissue edema, vacuolar degeneration and cellular infiltration. Lesser protective effects were observed by the small dose of taurine. These findings correlate with the measured biochemical parameters and the results of paw edema.

In conclusion, taurine attenuated most of the biochemical and pathophysiological aspects of RA. Such effects could be explained by the observed effects of taurine on oxidative stress biomarkers, production of NO and pro-inflammatory cytokines as TNF-α. The effects of taurine were comparable to that of diclofenac which is an important finding to consider owing to the documented adverse effects of NSAIDS and other RA conventional therapies.

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References

[1] Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356–61.

[2] Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. In: Kelly WN, Ruddy S, Harris ED, Sledge CB, editors. Textbook of rheumatology. Philadelphia: Saunders; 1996. p. 851–97.

[3] Scheiman JM. The impact of non-steroidal anti-inflammatory drug-induced gastropathy. Am J Manag Care 2001;7:10–4.

[4] Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of taurine, hypotaurine and their metabolic precursors. Biochem J 1988;256:251–5.

[5] Son MW, Ko JI, Doh HM, Kim WB, Park TS, Shim MJ, et al. Protective effect of taurine on TNBS-induced inflammatory bowel disease in rats. Arch Pharm Res 1998;21(5):531–6.

[6] Bhavsar TM, Patel SN, Lau-Cam CA. Protective action of taurine, given as a pretreatment or as a posttreatment, against endotoxin-induced acute lung inflammation in hamsters. J Biomed Sci 2010;17(Suppl 1):S19–31.

[7] Nakajima Y, Osuka K, Seki Y, Gupta RC, Hara M, Takayasu M, et al. Taurine reduces inflammatory responses after spinal cord injury. J Neurotrauma 2010;27(2):403–10.

[8] Verdrengh M, Tarkowski A. Inhibition of septic arthritis by local administration of taurine chloramines, a product of activated neutrophils. J Rheumatol 2005;32(8):1513–7.

[9] Barbier A, Navarro J, Breliere JC, Roncucci R. Biochemical and clinical changes in rats with developing adjuvant arthritis. Agents Actions 1984;15:103–5.

[10] Weichmann BM. Rat adjuvant arthritis. A model of chronic inflammation. In: Weichmann BM, editor. Pharmacological methods in the control of inflammation. New York: Alan R. Liss Inc.; 1989. p. 363–80.

[11] Swingle KF. Evaluation of anti-inflammatory activity. In: Scherrer RA, Whitehouse MW, editors. Anti-inflammatory agents: Chemistry and pharmacology. New York: Academic Press; 1974. p. 34–122.

[12] Rotelli AE, Guardia T, Juarez AO, de la Rocha NE, Pelzer LE. Comparative study of flavonoids in experimental models of inflammation. Pharmacol Res 2003;48:601–6.

[13] Hickey EJ, Raie RR, Reid VE, Gross SM, Ray SD. Diclofenac induced in vivo nephrotoxicity may involve oxidative stress-mediated massive genomic DNA fragmentation and apoptotic cell death. Free Radic Biol Med 2001;31:139–52.

[14] Ku EC, Wasvary JM, Cash WD. Diclofenac sodium (GP45840, Voltaren), a potent inhibitor of prostaglandin synthetase. Biochem Pharmacol 1975;24:641–3.

[15] Bell AL, Adamson H, Kirk F, McCaigue MD, Rotman H. Diclofenac inhibits monocytes superoxide production ex vivo in rheumatoid arthritis. Rheumatol Int 1991;11:27–30.

[16] Curcelli EC, Muller SS, Novelli Filho JL. Beneficial effects of diclofenac therapy on serum lipids, oxidized low-density lipoprotein and antioxidant defenses in rats. Life Sci 2008;82:892–8.

[17] Zuurbier KW, Bakkenist AR, Fokkens RH, Nibbering NM, Wever R, Muijers AO. Interaction of myeloperoxidase with diclofenac. Inhibition of chlorinating activity of myeloperoxidase by diclofenac and oxidation of diclofenac to dihydroxyazobenzene by myeloperoxidase. Biochem Pharmacol 1990;40:1801–8.

[18] Menassé R, Hedwall PR, Kraetz J, Pericin C, Riechester L, Sallmann A, et al. Pharmacological properties of diclofenac sodium and its metabolites. Scand J Rheumatol 1978;22:5–16.

[19] Bhattacharya SK, Sarkar MK. Effect of some centrally administered putative amino acid neurotransmitters on carrageenan-induced paw oedema in rats. J Pharm Pharmacol 1986;38(2):144–6.

[20] Stapleton PP, Mahon TM, Nowlan P, Bloomfield FJ. Effects of in-vivo administration of taurine and HEPES on the inflammatory response in rats. J Pharm Pharmacol 1994;46(9):745–50.

[21] Kontny E, Grabowska A, Kowalczewski J, Kurowska M, Janicka I, Marcinkiewicz J, et al. Taurine chloramine inhibition of cell proliferation and cytokine production by rheumatoid arthritis fibroblast-like synoviocytes. Arthritis Rheum 1999;42:2552–60.

[22] Kontny E, Rudnicka W, Kowalczewski J, Marcinkiewicz J, Maslinski W. Selective inhibition of cyclooxygenase 2-generated prostaglandin E_2 synthesis in rheumatoid arthritis synoviocytes by taurine chloramines. Arthritis Rheum 2003;48:1551–5.

[23] Hitchon CA, El-Gabalawy HS. Oxidation in rheumatoid arthritis. Arthritis Res Ther 2004;6:265–78.

[24] Kunsch C, Sikorski JA, Sundell CL. Oxidative stress and the use of antioxidants for the treatment of rheumatoid arthritis. Curr Med Chem Immunol Endocr Metab Agents 2005;5:249–58.

[25] Bauerova K, Bezek A. Role of reactive oxygen and nitrogen species in etiopathogenesis of rheumatoid arthritis. Gen Physiol Biophys 1999;18:15–20.

[26] Bohanec GP, Logar D, Tomsic M, Rozman B, Dolzan V. Genetic polymorphisms modifying oxidative stress are associated with disease activity in rheumatoid arthritis patients. Dis Markers 2009;26:41–8.

[27] Baskol G, Demir H, Baskol M, Kilic E, Ates F, Kocer D, et al. Assessment of paraoxonase 1 activity and malondialdehyde levels in patients with rheumatoid arthritis. Clin Biochem 2005;38:951–5.

[28] He YH, Zhou J, Wang YS, Xiao C, Tong Y, Tang JC, et al. Anti-inflammatory and anti-oxidative effects of cherries on Freund's adjuvant-induced arthritis in rats. Scand J Rheumatol 2006;35:356–8.

[29] Mason RP, Walter MF, Mason PE. Effect of oxidative stress on membrane structure: small-angle X-ray diffraction analysis. Free Radic Biol Med 1997;23:419–25.

[30] Das J, Ghosh J, Manna P, Sil PC. Acetaminophen induced acute liver failure via oxidative stress and JNK activation: protective role of taurine by the suppression of cytochrome P450 2E1. Free Radic Res 2010;44(3):340–55.

[31] Li CY, Deng YL, Sun BH. Taurine protected kidney from oxidative injury through mitochondrial-linked pathway in a rat model of nephrolithiasis. Urol Res 2009;37:211–20.

[32] Pan C, Giraldo GS, Prentice H, Wu JY. Taurine protection of PC 12 cells against endoplasmic reticulum stress induced by oxidative stress. J Biomed Sci 2010;17(Suppl 1):S1–S17.

[33] Hanna J, Chahine R, Aftimos G, Nader M, Mounayar A, Esseily F, et al. Protective effect of taurine against free radicals damage in the rat myocardium. Exp Toxicol Pathol 2004;56:189–94.

[34] El-Ghazaly MA, El-Naby DH, Khayyal MT. The influence of irradiation on the potential chondroprotective effect of aqueous extract of propolis in rats. Int J Radiat Biol 2011;87(3):254–62.

[35] Ma Y, Pope RM. The role of macrophages in rheumatoid arthritis. Curr Pharm Des 2005;11:569–80.

[36] Beutler B, Cerami A. The biology of cachectin/TNF-α primary mediator of the host response. Ann Rev Immunol 1989;7:625–55.

[37] Molloy RG, Mannick JA, Rodrick ML. Cytokines, sepsis and immunomodulation. Br J Surg 1993;80:289–97.

[38] Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907–16.

[39] Kim C, Park E, Quinn MR, Schuller-Levis G. The production of superoxide anion and nitric oxide by cultured murine leukocytes and the accumulation of TNF-α in the conditioned media is inhibited by taurine chloramine. Immunopharmacology 1996;34:89–95.

[40] Marcinkiewicz J, Gluszko P, Kontny R, Kwaśny-Krochin B, Bobek M, Wierzchowski W, et al. Clin Exp Rheumatol 2007;25(2):211–8.

[41] Baldwin Jr AS. The NF-κB and IκB proteins: new discoveries and insights. Annu Rev Immunol 1996;14:649–83.

[42] Barua M, Liu Y, Quinn MR. Taurine chloramine inhibits inducible nitric oxide synthase and TNF-α gene expression in activated alveolar macrophages: Decreased NF-κB activation and IκB kinase activity. J Immunol 2001;167:2275–81.