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RESEARCH ARTICLE

NATURAL FLAVONOIDS OBTAINED FROM THE FLOWERS OF BUTEA MONOSPERMA INHIBITS CYCLOOXYGENASE-2 AND 5-LIPOOXYGENASE INFLAMMATION IN VARIOUS MODELS

Satyajit*[1], D.Pradhan[2]

1. Pinnacle Bio-Medical Research Institute, Bhopal, M.P. India

2. Department of Pharmacy, Utkal University, Bhubaneshwar, Orissa, India

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***Correspondence for Author:**

Mr. SATYAJIT

Department of Pharmacology,

Pinnacle Bio-Medical Research Institute, Bhopal, M.P. India.

Email: satyajitsahoo@rediffmail.com

Abstract:

In this study, the flavonoid obtained from the flowers of Butea monosperma shows anti inflammatory activity by inhibiting COX-2 and 5-LOX. Also, flavonoid obtained from the flowers of Butea monosperma exhibits in-vitro on key enzymes of arachidonic acid cascade involved in the mediation of inflammation The flavonoid obtained from the flowers of Butea monosperma inhibited the COX-2 and 5-LOX enzymes with an IC_{50} of 56.07 μgmL^{-1} and 62.30 μgmL^{-1} respectively. Based on the in-vitro studies data, the in-vivo anti inflammatory activity of flavonoid obtained was evaluated by using carrageenan induced paw oedema and cotton-pellet induced granuloma. The flavonoid obtained from the flowers of Butea monosperma significantly reduced the inflammation in the carrageenan induced rat paw oedema and cotton-pellet induced granuloma in rats. The flavonoid obtained from the flowers of Butea monosperma did not inhibit the gastric acid secretion. Thus, it shows that its anti-ulcerogenic effect which can be attributed to its action on the mucosa defence factors. The safety and efficacy profiles indicated that the flavonoid obtained from the flowers of Butea monosperma is safe for inflammatory disorders with gastric cytoprotective properties.

Keywords: Butea monosperma, Flavonoid obtained from flowers of Butea monosperma, Cyclooxygenases, Lipoxygenases, Anti inflammatory activity; Gastric acid

Introduction:

Flavonoids, one of the abundant classes of plant constituents are known to be nature's tender drug showing various pharmacological activities such as anticancer, antibacterial, antiviral, anti-inflammatory, immunomodulatory activities (Middleton et al., 2000)[1]. Numerous studies have demonstrated that the anti-inflammatory activity of certain flavonoids might be contributed by inhibiting enzyme activity involved in arachidonic acid cascade related enzymes such as phospholipaseA2 (PLA2), cyclooxygenase (COX) and lipoxygenases LOXs)[2,3]. Thus reduced the inflammation in the carrageenan induced rat paw oedema and in cotton pellet induced granuloma. Thus found to be effective in both acute as well as chronic inflammatory conditions, which reflected its efficacy in inhibiting the increase in the number of fibroblasts and synthesis of collagen and mucopolysaccharides during granuloma tissue formation. In the pylorus ligation method it was observed that the flavonoid obtained did not inhibit gastric acid secretion at the test dose levels. So the flavonoid obtained might favours one of the defense factors of the rat gastric mucosa by increasing gastric glycoproteins[4]. This suggests that the anti-ulcerogenic effect of the flavonoid fraction against different necrotizing agents may be due to a cytoprotective activity. Histamine (H2) receptor antagonists and proton pump (H+, K+) ATPase inhibitors suppress gastric acid secretion and secondarily include hypergastrinemia. Sustained hypergastrinemia has atrophic effect on the fundic mucosa, resulting in enterochromaffin like ECL cell hypertrophy and hyperplasia (Hakanson et al, 1992)[5].So it is of interest that the flavonoid obtained exerts an effective anti ulcerogenic action without modifying gastric acid secretion. Thus, from the above studies it is quite sure that the flavonoid obtained from the flowers of Butea monosperma possess significant anti-inflammatory activity by modulating cyclooxygenase, lipoxygenase enzymes and augmenting antioxidant defense system in the inflammation bearing arachidonic acid cascade related enzymes such as phospholipase A2 (PLA2), cyclooxygenase (COX) and lipoxygenase (LOXs).Inflammation is a protective mechanism that is triggered in response to be noxious stimuli,trauma or infection to guard the body and to hasten up, the recovery process. However, inflammation that is unchecked leads to chronic inflammatory disorders. Arachidonic Acid (AA) metabolism plays a crucial role in inflammatory process and associated diseases. Some of the anti- inflammatory drugs inhibit the lipoxygenase pathway,

and some inhibit cyclooxygenase pathway and these two pathways can be used for potential interventions against inflammation. Unfortunately, most of the anti-inflammatory drugs, especially

steroids and cyclooxygenase inhibitors are often associated with adverse side effects including GI irritation, ulcers, hypertension and cardiac abnormalities (William,1989; Wolfe, 1999)[6,7]. There has been some concern over the use of COX-2 inhibitors for therapeutic intervention, especially since some of the products based on COX-2 were either withdrawn or made to carry warning by the US FDA (Naesdal et al., 2006;Salmon, 2006)[8,9].

5-Lipoxygenase (5-LOX) inhibitors of herbal origin, on the other hand, are reported to offer significant relief and avoid adverse effects.5-LOX inhibitors are thus becoming first choice of treatment for chronic inflammatory disease such as arthritis (Krishanu et al., 2008; Oliver, 2007)[10,11]. Butea monosperma (Lam.) Taub (Syn. Butea frondosa; Family Fabaceae) popularly known as 'dhak' or 'palas', commonly known as 'Flame of forest', palash, mutthuga, bijasneha, khakara, chichara, Bastard teak, Bengal kino.[12] .This is a moderate sized deciduous tree which is widely distributed throughout India, Burma and Ceylon extending in the north west himalayas as far as jhelum except in very acrid parts [13]. Butea monosperma is extensibly used in Ayurveda, Unani and Homeopathic medicine and has become a cynosure of modern medicine. Flowers are astringent to bowel, in cure "Kapha", leprosy, strangury, gout, skin diseases, thirst, sensation; flower juice is useful in eye diseases. Flower is bitter, aphrodisiac, expectorant, tonic, emmenagogue, diuretic, and good in biliousness, inflammation and gonorrhoea. They are used to disperse swelling and to promote menstrual flow. They are given to pregnant women in case of diarrhoea. It is also useful to prevent pus from urinogenital tracts of males[14].

Anti-inflammatory activity have been reported on the methanolic extract of Butea monosperma Lam. flower (V.M. Shahavi et al.,2008)[15]. The enzyme responsible for PGs synthesis exists as two isoforms, COX-1 (constitutive isoform) and COX-2 (inducible form) (Maier et al.,1990; O'Banion et al., 1992)[16,17]. Arachidonic acid can also be converted to leukotrienes (LTs) by the action of 5-LOX. So, the development of dual inhibitors that can simultaneously inhibit COX-2 as well as 5-LOX. Thus degranulation reaction might enhance their individual anti-inflammatory effects and reduce the undesirable side effects that are associated with NSAIDs. The present study evaluated the flavonoid obtained from the flower of Butea monosperma shows anti inflammatory activity by inhibiting COX-2 and 5-LOX.

MATERIALS AND METHODS

Plant material

Flowers of Butea monosperma Tam. was collected from the Chandaka forest, Bhubaneswar. The flowers of Butea monosperma was authenticated by Prof. P. K. Sahu, Taxonomist, Botany Department, Utkal University, Vani Vihar, Bhubaneswar.

Extraction

The flower was allowed to dry in shade for 3 days. Flowers of Butea monosperma were crushed into powder and extracted with methanol for 48 hrs with the help of Soxhlet apparatus. The flower extract of individual plant was collected in conical flasks, filtered and the solvents were evaporated to dryness under reduced pressure[15]. The flower extract was analyzed by qualitative tests and was found to contain flavonoids[19].

Isolation of flavonoids[20]

Flower extract of Butea monosperma was subjected to column chromatography for isolation of flavonoids on silica gel and eluted with gradient solvent system (Petroleum ether, n-butanol, Ethyl acetate). Fractions were collected and monitored by TLC analysis. Based on the Rf value, fractions were obtained. Fraction with ethyl acetate gave good resolution.

Total flavonoid analysis[21]

Total flavonoid content of the extract will be determined according to reported method. 0.5 ml of sample solutions (1 mg/ml) will be mixed with 2 ml of distilled water and subsequently with 0.15 ml 5% of $NaNO_2$ solution. After 6 min incubation, 0.15 ml of 10% $AlCl_3$ solution will be added and allowed to stand for 6 min, followed by adding 2 ml of 4% NaOH solution to the mixture. The mixture will be made up to 5 ml with methanol and mixed well. The absorbance will be measured at 510 nm after incubation for 15 min. The total flavonoid

Content will be expressed in milligrams of rutin equivalents (RE) per gram of extract.

Cyclooxygenase Assay

Enzymatic activity of COX-2 was measured according to the method of Copeland et al., (1994)[22] with slight modifications using a chromogenic assay based on the oxidation of N,N,N,N,-tetra methyl-p- phenylene diamine (TMPD) during the reduction of PGG_2 to

PGH_2. The assay mixture contained Tris-HCl buffer (100mM, pH 8.0), haematin (15 µM)EDTA (3µM) enzyme (100 µg COX-2) and the test drugs. The mixture was pre-incubated at 25°C for 15 min. And then the reaction was initiated by the addition of arachidonic acid and TMPD in total volume of 1 mL.The enzyme activity was measured by estimating the initial velocity of TMPD oxidation for the first 25 sec of the reaction by following the increase in absorbance at 603 nm. A low rate of non- enzymatic oxidation observed in the absence of COX-2 was subtracted from the experimental value while calculating the percent inhibition.

Lipoxygenase Assay

5-LOX enzyme inhibitory activity of flavonoid obtained from flowers of Butea monosperma was measured using the method of Reddanna et al.,(1990) modified by Ulusu et al., (2002)[23,24]. The assay mixture contained 80 mM linoleic acid and 10 µl of enzyme 5-LOX in 50 mM phosphate buffer (pH 6.3).The reaction was initiated by the addition of the enzyme buffer mix to linoleic acid and the enzyme activity was monitored as the increase in absorbance at 234 nm. The reaction was monitored for 120 sec and the inhibitory potential of the test substances was measured by incubating various concentrations of test substances for two minutes before addition of linoleic acid. All assays were performed in triplicate.

Percentage inhibition was calculated by comparing a slope of test substances with that of enzyme activity.

Animals

Adult male Wistar albino rats weighing 150-200 g were used for the present investigation. They were housed in clean polypropylene cages and were fed with standard pellet diet and water ad libitum with light-dark cycle. Ethical Committee clearance was obtained from IAE (Institutional Animal Ethical Committee) of CPCSEA (Ref.No.1283/c/09/CPCSEA).

Acute toxicity studies

The acute toxicity of flavonoid obtained from Butea monosperma flower was determined as per the OECD guideline no. 423 (Acute toxic class method). Based on the results obtained from this study, the dose for anti- inflammatory activity was fixed to be 200 mg kg^{-1} b.w. and 400 mg kg^{-1} b.w. for dose dependent study. (OECD, 2002)[25].

Carrageenan induced rat hind paw oedema:

The method of Winter et al., (1962)[26] was used with slight modification. The apparatus used for the measurement of rat paw volume was that of Buttle et al., modified by Sharma et al[27]. The animals were divided into seven groups of six animals each. Group 1 served as control (normal saline) and Group 2 served as a standard (Diclofenac sodium) for Carrageenan induced. Group 3 served as a standard (Diclofenac sodium) for Cotton pellet-induced granuloma. Group 12 and groups 13 were orally administered with 600 mg kg^{-1} b.w. and 800 mg kg^{-1} b.w. respectively. Group 14 and 15 were orally administered with 600 mg kg^{-1} b.w. and 800 mg kg^{-1}b.w. of flavonoid respectively with inflammation in animal by Cotton-pellet induced granuloma method. The animals pretreated with test substances or diclofenac sodium one hour before were injected with 0.05 ml of 1% carrageenan (in normal saline) solution into the sub-plantar region of right hind paw. The volume of the injected paw was measured with a plethysmograph immediately. The paw volume was again measured after 3 hours. Reduction in the paw volume compared to the vehicle-treated control animals was considered as anti- inflammatory response and the percentage inhibition of oedema was calculated using the formula (1).

$$\textbf{Inhibition (\%)} = (1 - V_t / V_c) \times 100 \quad (1)$$

where V_t is Mean volume of the test drug, and V_c is Mean volume of the control.

Biochemical estimations:

Biochemical changes in carrageenan induced paw oedema were estimated. The rats were anaesthetized under light ether anaesthesia and Liver was removed and subjected for homogenization and aliquots of the homogenate were suitably processed for the assessment of reduced glutathione (GSH), Catalyse and lipid peroxidation. GSH was estimated by the method of George L. Ellman (1959)[28], Catalase activity was assayed according to the method of Cohen et al., (1970)[29] and lipid peroxidation by the method of Ohkawa et al., (1979)[30]. The % inhibition of lipid peroxidation by the test or standard drug was calculated by using following formula (2).

$$[(A-B)/B] \times 100 \quad \text{.....(2)}$$

where A is Control group and B is Test or standard group.

Cotton pellet-induced granuloma:

The test was performed on the rats using the cotton pellet induced granuloma method. The rats were anesthetized under light ether, and an incision was made on the lumbar region by blunted forceps, a subcutaneous tunnel was made, and a sterilized cotton pellet (100 ± 1 mg) was inserted in the groin area. All the animals received either test substances or diclofenac sodium or vehicle (normal saline) orally depending upon their respective grouping for seven consecutive days from the day of cotton pellet insertion (Winter et al., 1962)[26]. On the 8th day,animals were anesthetized again and cotton pellets were removed and dried to constant mass.

Effect of Flavonoid fraction on Gastric acid secretion:

Albino rats weighing 150-200 g were placed in individual cages with bottoms to prevent caprophagy. The animals were kept under standard conditions at 22 ± 1°C with water ad libitum and deprived of food for 24 h before the experiments. The technique of ligated pylorus was used (Shay et al., 1945)[31]. After anesthetizing with ether an incision was made in the abdomen, and the ligature was performed below the pylorus. Care was taken not to damage the blood supply. The animals were divided into 3 groups of 6 animals each. After closing the incisions group 1 (Control) was orally administered with 1 ml of saline (vehicle),Group 2 and 3 were orally administered with 600 and 800 mg kg-1 b.w. of flavonoid obtained from flowers of Butea monosperma respectively. All animals were placed in their cages and deprived of water and food for the rest of the experiment. Four hours after the pyloric ligation, the animals were sacrificed by decapitation. A ligature was placed at the oesophago- cardiac junction and the stomach was removed. The gastric content was collected and centrifuged. Supernatant volumes were measured and the pH of the supernatants was measured using a pH meter. The acid concentration was estimated by titration to pH 7.0 with 0.1N NaOH.

Statistical Analysis:

For in vitro assays linear regression analysis was used to calculate the IC_{50} values. In case of in vivo studies the experimental results were expressed as mean ± SD. Results were analyzed by the one- way ANOVA followed by Tukey-kramer post hoc multiple comparison test using graph pad. P-value of <0.05 was considered as statistically significant.

Cyclooxygenase Assay:[22]

The flavonoid obtained from flowers of Butea monosperma inhibited the COX-2 enzyme with an IC_{50} of 56.07 µg ml^{-1} where as the standard drug celecoxib inhibited the COX-2 enzyme with an IC_{50} of 52nM. The results are shown in Table1.

Lipoxygenase Assay:[23,24]

The flavonoid obtained from flowers of Butea monosperma inhibited the 5-LOX enzyme with an IC_{50} of 62.30 µg mL^{-1}. The flavonoid obtained exhibited moderate 5-LOX, inhibitory activity, when compared with known standard Nordihydroguaretic acid (NDGA). The results are shown in Table 1.

Table 1: IC_{50} Values of flavonoid obtained from Butea Monosperma flower on COX-2 and 5-LOX enzymes *in vitro*

Drug/Extract	COX-2	5-LOX
Celecoxib	52 nM	-
NDGA	-	1.5µM
flavonoid obtained from Butea Monosperma flower	56.07 µgml^{-1}	62.30 µgml^{-1}

Carrageenan induced rat hind paw oedema:[26,27]

The effect of flavonoid obtained from the flowers of Butea monosperma in carrageenan induced paw oedema in rats is shown in Table 2. The result obtained indicates that the flavonoid obtained found to have significant ($P < 0.05$) anti-inflammatory activity in rats. The flavonoid obtained at the test doses 600 and 800 mg kg^{-1} b.w. reduced the oedema induced by carrageenan by 72.60 % and 85.88 % respectively at 3 h, whereas the diclofenac sodium at a dose 100 mg kg^{-1} b.w. showed 90.28% of inhibition as compared to the control group.

Table 2: Effect of flavonoid obtained from Butea Monosperma flower on carragenan induced paw oedema in rats

Groups	Dose (mg kg^{-1})	Mean odema volume 0-3hr	% Inhibition
Control	Normal saline	0.956±0.0046	-
Standard	100 mg	0.093±0.0028	90.28
BM 600	600 mg	0.262±0.0061 **	72.60
BM 800	800 mg	0.135±0.0036 **	85.88

Standard: Diclofenac sodium (100mg kg^{-1} b.w.), BM 600 : Flavonoid obtained at dose 600 mg kg^{-1} b.w. BM 800: Flavonoid obtained at dose 800 mg kg^{-1} b.w. Each value is the Mean ± S.D. for 6 rats. **P < 0.05 compared with control

Biochemical estimations:[29,30,31]

The results of biochemical changes in carrageenan induced rat paw oedema are shown in Table 3.Treatment with flavonoid obtained from the flowers of Butea monosperma decreased the levels of lipid peroxidation and increased the levels of GSH and catalase. The results were found to be significant (P < 0.05) as compared to control groups.

Table 3: Effect of flavonoid obtained from Butea Monosperma flower on various biochemical changes in carrageenan induced rat paw oedema

Groups	Dose (mg kg^{-1})	GSH (ng mg^{-1} protein)	Lipid Peroxidation	Catalase (µg mg^{-1} protein)
Control	Normal saline	3.23±0.0513	99.38±0.098	24.58±0.429
Standard	100 mg	4.70±0.0810 **	64.34±0.093 **	40.12±0.364 **
BM 600	600 mg	3.94±0.029 **	93.83±0.012 **	26.34±0.421 **
BM 800	800 mg	4.68±0.0312 **	86.34±0.054 **	28.56±0.234 **

Standard: Diclofenac sodium (100mg kg^{-1} b.w.), BM 600 : Flavonoid obtained at dose 600 mg kg^{-1} b.w. BM 800: Flavonoid obtained at dose 800 mg kg^{-1} b.w. Each value is the Mean ± S.D. for 6 rats. **P < 0.05 compared with control

Cotton pellet-induced granuloma:[26]

The flavonoid obtained from the flowers of Butea monosperma was screened for cotton pellet induced granuloma in rats, and the results are shown in Table 4. The flavonoid fraction exhibited

32.4 % and 45.2 %.inhibition of granuloma formation at the doses 600 and 800. mg kg^{-1} b.w respectively, whereas diclofenac sodium showed 49.8 % when compared to control group.

Table 4: Effect of flavonoid obtained from Butea Monosperma flower on cotton-pellet induced granuloma in rats

Groups	Dose (mg kg^{-1})	Granuloma dry weight (mg)	% Inhibition
Control	Normal saline	72.3432±0.4346	-
Standard	100 mg	36.0269±0.2329 **	49.8
BM 600	600 mg	23.4391±0.3225 **	32.4
BM 800	800 mg	32.6991±0.3529 **	45.2

Standard: Diclofenac sodium (100mg kg^{-1} b.w.), BM 600 : Flavonoid obtained at dose 600 mg kg^{-1} b.w. BM 800: Flavonoid obtained at dose 800 mg kg^{-1} b.w. Each value is the Mean ± S.D. for 6 rats. **P < 0.05 compared with control

Effect of Flavonoid obtained on Gastric acid secretion:[31]

The effect of flavonoid obtained from the flowers of Butea monosperma on the gastric acid secretion in the pylorus ligation method is shown in the Table 5. The results obtained showed that the flavonoid obtained did not inhibit the gastric secretion in rats. The volume of gastric content was significantly increase.

Table 5: Effect of flavonoid obtained from Butea Monosperma flower on the gastric acid secretion in rats

Groups	Dose (mg kg^{-1})	Volume (ml)	pH	Titrable acid conc. (µEq ml^{-1})	Total acid output (µEq ml^{-1})
Control	Normal saline	4.22±0.03	1.98±0.45	56.45±4.16	230.18±34.5
Standard	100 mg	4.51±0.05	1.62±0.45	52.24±3.21	284.56±33.05
BM 600	600 mg	4.68±0.05 **	2.16±0.45	50.24±3.1	240.56±33.05
BM 800	800 mg	5.67±0.06 **	2.15±0.53	48.38±3.25	258.45±32.33

Standard: Diclofenac sodium (100mg kg^{-1} b.w.), BM 600 : Flavonoid obtained at dose 600 mg kg^{-1} b.w. BM 800: Flavonoid obtained at dose 800 mg kg^{-1} b.w.Each value is the Mean ± S.D. for 6 rats. **P < 0.05 compared with control

RESULTS AND DISCUSSIONS

The results of the present investigations revealed that the flavonoid obtained from flowers of Butea monosperma possess significant anti-inflammatory activity against acute inflammatory models like; carrageenan induced paw oedema and chronic models like; cotton-pellet induced granuloma in rats in a dose dependent manner. In spite of tremendous development in the field of synthetic drugs during recent era, they are found to have some or other side effects whereas plants still hold their own unique place, by the way of having no side effects. Therefore, a systematic approach should be made to find out the efficacy of plants against inflammation so as to exploit them as herbal anti inflammatory agents. Chronic use of these drugs is associated with severe side effects, mainly gastrointestinal injury and renal irritations, apparently due to suppression of COX-1- derived PGE2(Rainsford, 2007)[32]. COX-2-selective inhibitors were designed to minimize gastrointestinal complications of traditional NSAIDs, but recent clinical studies indicated small but significantly increased risks for cardiovascular events (McGettigan and Henry, 2006)[33].It is well known that carrageenan induced paw edema is characterized by biphasic event with involvement of different inflammatory mediators. In the first phase (during the first 2 h after carrageenan injection), chemical mediators such as histamine and serotonin play role, while in second phase (3–4 h after carrageenan injection). Kinin and prostaglandins are involved (Hernandez *et al.*, 2002)[34].Our results revealed that administration of flavonoid obtained from the flowers of Butea monosperma inhibited the oedema starting from the first hour and during all phases of inflammation, which is probably inhibition of different aspects and chemical mediators of inflammation. The cotton-pellet granuloma is widely used to evaluate the transudative and proliferative components of the chronic inflammation. The moist weight of the pellets correlates with transuda, the dry weight of the pellet correlates with the amount of granulumatous tissues (Castro *et al*. 1968)[35]. Chronic inflammation occurs by means of the development of proliferate cells. These cells can be either spread or in granuloma form. Non-steroidal anti-inflammatory drugs decrease the size of granuloma which results from cellular reaction by inhibiting granulocyte infiltration, preventing generation of collagen fibbers and suppressing mucopolysaccharides (Della *et al.*,1968; Alcaraz and Jimenez, 1988)[3]. The flavonoid obtained from the flowers of Butea monosperma showed significant anti-inflammatory activity in cotton pellet induced granuloma and thus found to be effective in chronic inflammatory conditions, which reflected its efficacy in inhibiting the increase in the

number of fibroblasts and synthesis of collagen and mucopolysaccharides during granuloma tissue formation. In the pylorus ligation method it was observed that the flavonoid obtained did not inhibit gastric acid secretion at the test dose levels, so the flavonoid obtained might favours one of the defense factors of the rat gastric mucosa by increasing gastric glycoproteins. This suggests that the anti ulcerogenic effect of the flavonoid obtained against different necrotizing agents may be due to a cytoprotective activity. Histamine (H2) receptor antagonists and proton pump (H+, K+) ATPase inhibitors suppress gastric acid secretion and secondarily include hypergastrinemia. Sustained hypergastrinemia has atrophic effect on the fundic mucosa, resulting in enterochromaffin like ECL cell hypertrophy and hyperplasia (Hakanson *et al.*, 1992)[5]. Therefore it is of interest that the flavonoid obtained exerts an effective anti ulcerogenic action without modifying gastric acid secretion. Thus, from the above studies it is quite sure that the flavonoid obtained from flowers of Butea monosperma possess significant anti-inflammatory activity by modulating cyclooxygenase, lipoxygenase enzymes and augmenting antioxidant defense system in the inflammation bearing rat.

CONCLUSION

The present study showed that the flavonoid obtained from the flowers of Butea monosperma may be a useful biochemical and pharmacological tool for determining the role of COX-2/5-LOX dual inhibitors.It may represent a suitable drug for the therapy of chronic inflammatory diseases with gastric cytoprotective properties. Thus, in other words, it may represent a suitable drug for the therapy of chronic inflammatory diseases with low risks of adverse effects. However, further studies are needed to isolate and characterize the specific chemical constituents present in the flavonoid obtained from the flowers of Butea monosperma showing anti-inflammatory activity by inhibiting COX-2 and 5-LOX.

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