

# Potential nutraceutical benefits of basmati rice bran oil as analgesic, anti-inflammatory and anti-arthritis

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**Abstract:** Numerous nutraceutical applications have been explored during the last decades. The present study is based on extraction of oil from super kernel basmati rice which has shown effective analgesic, anti-inflammatory, and anti-arthritic activities. The feeding experiments on male Wister rats and female Sprague-dawley (SD) rats have elaborated the therapeutic value of variety of bioactive components including  $\gamma$ -oryzanol present in the oil.

**Keywords:** Rice bran, inflammation, anti-arthritis, analgesic activity, gamma oryzanol.

## INTRODUCTION

The nutraceutical importance of rice bran and its oil may be registered by citing consecutive reviews published during the last five years (Law, Waye, & So, 2017; Sirithunyalug *et al.*, 2018; Nayik *et al.*, 2015; Sanghi and Tiwle, 2015; Sharma *et al.*, 2015) and another one is year earlier 2014 where Ozdestan and Coworker reviewed the medicinal importance of phytosterols in rice bran. A review article was also reported in 2011, giving a bird's eye view of the health benefits of rice bran (Nagendra Parasad, 2011). The significant functional/ health benefits of rice bran indicating substantial potentials in modulating pituitary secretion from inhibiting the gastric acid secretion, antioxidant role against hyperlipidemia have been reviewed, and the disease prevention/ cure properties studied in cases of rats, rabbits, monkeys, and humans have been highlighted (Cicero & Derosa, 2004). The most bioactive components of rice bran oil are reported as the  $\gamma$ -oryzanol, consisting combinations of ferulic acid esters of sterols that have been exclusively reviewed for its high nutritive value (Patel & Naik, 2004). Numerous research papers have appeared in the literature during the past few years, highlighting the importance of rice bran to be used as part of the daily diet for human foods. Its oil not only recommended as cooking oil but also enhancing the nutritive value of various foods. Seema and coworkers (Ashraf *et al.*, 2012; Tabassum *et al.*, 2005) have explored rice bran for fat replacement in bakery products and other nutraceutical product developments.

Rice bran oil (RBO) has been found to possess healing properties against active in improving dyslipidemia. Because of its high antioxidant activity, it can reduce

oxidative stress due to the presence of various reactive oxygen species (ROS). Rice bran oil has played a very beneficial role in controlling a variety of cardiovascular diseases. RBO responded well in lowering total cholesterol, LDL, VLDL among the children at the age of six years and even within four weeks. It also and controlled nephrotic syndrome (Tabassum *et al.*, 2005). Recently Ranjbar-Zahedani and coworkers (2015) have reported the hypolipidemic effect of RBO as it lowered the total cholesterol, triglycerides, LDL cholesterol, and platelet aggregation, and simultaneously, it raised the HDL-cholesterol. Apart from the potent antioxidant activity in RBO, anti-inflammatory activity in Thai colored rice extract has been observed that effectively controlled the functionality of specific cytokines like IL-6, TNF and NF-KB that promote inflammation (Kitisin *et al.*, 2015). Recently it has been found that phytochemicals such as some of the phenolic acids including the ferulic acid, gallic acid and chlorogenic acid present in Hashemi rice bran oil promoted the health benefits being the potent antioxidants (Ghasemzadeh *et al.*, 2015).

It is observed that the various extract of rice bran has been proved itself to be nontoxic or GRAS (GRAS (Generally regarded as safe) because of a daily dose of 1g oil as the diet supplement when fed and was found to be safe for human consumption (Heikal *et al.*, 2015). The residue from extracts represents dietary fibers that have shown multi-beneficial effects in promoting colon health. Basmati rice, a superior variety of rice in Asian countries, has shown a higher concentration of bioactive components (Bopitiya and Madhith, 2014) indicating that consuming brown basmati rice is far more healthy than polished rice.

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Antioxidant activity of both rice bran oil (RBO) and rice bran extracts (RBE) were studied (Muthal *et al.*, 2015). Anti-inflammatory effect of RBO has shown superiority as compared to non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly prescribed for a variety of acute and chronic inflammatory symptoms. NSAIDs results in a variety of adverse effects such as gastric lesions formation due to their inhibitory action on two cyclooxygenases, COX-1 and COX-2. The two enzymes are responsible for the synthesis of prostaglandins from arachidonic acid. Prostaglandins are known for their active participation in promoting colon health. RBO perform similar functions as NSAIDs without any side effects (Manoharsalis and Ramabhimaiah, 2013; Tabassum *et al.*, 2005). Earlier the anti-inflammatory effect was attributed to the ferulic acid moiety present in phytosteryl ferulates generally found in RBO. The RBO can control colitis induced by dextran sulfates sodium (DSS) in mice because of various antioxidants present in the bran (Islam *et al.*, 2008). Apart from antioxidant activity, the stabilized rice bran diet showed strong serotonergic effects (Jabeen *et al.*, 2008) and controlled the stress, while increased brain serotonin (5-hydroxytryptamine 5-HT). Brain health may be maintained if rice bran is included in the diet regularly or brown rice may be taken as part of the food. Recently Rahman and coworker (2015) studied the anti-arthritis activity (Rahman *et al.*, 2015) by using the method of protein denaturation, the bovine serum protein, and egg albumin denaturation showed better inhibition of denaturation than the standard drug Diclofenac using BRBO (Basmati rice bran oil).

The present study is based on exploring the anti-arthritis activity, pain-killing effect including the anti-inflammatory effect of the BRBO as to the best of our knowledge the oil has not been previously investigated for its nutraceutical effects against arthritis, pain, and inflammation.

## MATERIALS AND METHODS

All reagents used during the study were of analytical grade. The carboxymethylcellulose (CMC), tragacanth, carrageenan, diethyl ether and indomethacin were purchased from Sigma Aldrich Co. (St. Louis, MO, USA) while *Mycobacterium tuberculosis* (MT H37Ra) obtained from Detroit, MI, USA as test sample.

### Animals

Male Wister rats (120-180g) and Sprague-Dawley (SD) female rats (200-250g) provided by the animal house of the International Center for Chemical and Biological Sciences (ICCBS). The ethical guidelines for the handling of laboratory animals were followed via clearance from the animal house of the institute. A group of twelve animals was kept individually in a cage in the same

environmental condition of temperature ( $22\pm 2^{\circ}\text{C}$ ) and humidity ( $50\pm 10\%$ ) with light and dark cycle (12 h) to standardize the environmental conditions. The standard rodent diet and water ad libitum were given for three days before experimentation. For Analgesic activity, the healthy NMRI mice (20-30g), of either sex were obtained from the animal house of ICCBS, University of Karachi. The Group of six animals was kept individually in a cage. All procedures were carried out following animal care and use committee of ICCBS.

### Basmati rice bran oil extraction

Rice bran was collected after fresh dehulling of Basmati rice at Matco Rice Pvt. Ltd. Located in FB area, Karachi. Rice bran was taken in a 10cm diameter petri dish of 5mm height and heated for 1 minute in the microwave oven for deactivation of the lipase enzyme present in fresh bran. The heated sample is further referred to as stabilized rice bran (SRB). Approximately 500g of stabilized rice bran was taken in the 5-liter flask, and 800ml of hexane was added. It was left over night on a shaking incubator at  $40^{\circ}\text{C}$ . The supernatant was collected after filtering it through Whatman filter paper. The solvent from the extract was removed on the rotary evaporator at  $50^{\circ}\text{C}$ . Finally, the concentrate was filtered and dried at  $70^{\circ}\text{C}$  in an oven and stored at  $-20^{\circ}\text{C}$  for further use. It is referred to as stabilized basmati rice bran oil (SBRBO).

### Sample preparation

Samples were tested orally for analgesic effect at the effective dose of 50, 100 and 200mg/Kg weight was observed lethal. Morphine sulphate (10mg/Kg) ip and 0.5% gum tragacanth were used as standard drug and vehicle respectively.

### Analgesic activity

The analgesic activity of SBRBO was carried out by using Eddy's hot plate methodology (Eddy & Leimbach, 1953). Animals were individually kept on the hot plate (Ugo Basile, model-DS 37, 25 X 25cm, Italy) temperature of which was hold at  $50\pm 1^{\circ}\text{C}$ . After 30 min of oral administration of aforementioned, the animals were placed on hot plate and the latency time between the placement and response as licking of the paws or flicking of hind limbs or jumping was recorded at 0, 30, 60, 90 and 120 min with a cut off period of 30 sec to avoid damage of paw 30 min. after giving the dose. The latency time was recorded in sec. as the time at which animals showed response to the pain stimulus by jumping or paw licking. The cut off time for the reaction was 45 sec to avoid tissue damages (Mekonnen, Urga, & Engidawork, 2010). Control group received 0.5% gum tragacanth suspension (po), test groups received test samples (50mg, 100mg, and 200mg of SBRBO) suspended with 0.5% gum tragacanth (po) while standard group received morphine sulphate 10mg/Kg (ip). Analgesic activity was

monitored at 30, 60, 90, 120, and 180 min and the results were summarized in the form of latency time. The average latency time exhibited by the control animals (base line latency) and treated group SBRBO (drug latency) were compared and expressed as percent pain protection using following formula:

$$\text{Percent pain protection} = \frac{\text{Drug latency} - \text{Base line latency}}{\text{Base line latency}} \times 100$$

### **Anti-inflammatory assay**

#### **Sample Preparation and pre drug animal treatment**

The SBRBO with moisture level less than 0.1% was taken as the standard sample. Fasted male Wister rats in a group of 12 received 0.5ml of SBRBO in 0.5% carboxy-methyl-cellulose (CMC) to each treated group whereas control group received only 1.0ml of 0.5% of CMC. The rats were lightly anaesthetized after 1 hr of drug administration. Paw edema is induced by 1% carrageenan injection. The procedure was repeated at an interval of 1 hr for total 5 hrs of experimental duration.

#### **Carrageenan-induced paw edema in rats**

The hind paw edema was induced in rats by injecting 1% carrageenan as acute inflammatory animal model (Winter et al, 1962). The Plethysmometer (Ugo Basil, Italy) was used to determine the paw volume at different interval (1-5 hour). Only saline solution at dose 1ml was given to the normal group, sample group was given vehicle 0.5% CMC along with the 100mg of SBRBO, without carrageenan was given to the control group at a dose of 1 ml, while reference anti-inflammatory drug indomethacin (100mg/Kg) for comparison were also used.

The following formula was used to evaluate the percentage of inhibition was calculated as:

$$\text{Percentage inhibition} = \frac{(C_t - C_0) \text{ Control} - (C_t - C_0) \text{ treated}}{(C_t - C_0) \text{ Control}} \times 100$$

$C_0$  is volume of paw measured at time zero while  $C_t$  is the time of interval taken volume of paw measured after treatment. The edema was measured by considering the inhibitory activity after every 1 hr.

### **Anti-arthritic activity**

#### **Adjuvant Preparation**

Fresh adjuvant prepared by mixing of finely powdered adjuvant with the mineral oil (10mg/ml) to hold the uniform suspension except the sample group.

#### **Induction of arthritis and monitoring of health status**

A dose of 0.1ml of 10mg/ml of MT H37Ra was injected intradermally at the base of the tail to induce arthritic condition. After the induction of arthritis, the animals were monitored carefully for a time period of 14-22 days. Treatment was initiated at the same time of arthritic induction.

### **Animal treatment before experiment**

The animals were randomly distributed into their specific group. Sulfasalazine Indomethacin was used as the reference drug.

### **STATISTICAL ANALYSIS**

Activities were expressed as mean  $\pm$  SEM and statistically tested by applying one way analysis of variance (ANOVA). The differences between the means were tested using post hoc LSD and values of  $p < 0.05$  were statistically measured as significant. SPSS for windows version 17 was used for the statistical analysis.

### **RESULT**

The results for the Analgesic activity are reported in table 1 and fig. 1 while anti-inflammatory and anti-arthritis activities are reported in fig. 2 and fig. 3 respectively.

### **DISCUSSION**

#### **Analgesic activity**

Analgesic activity of SRBO reported in table 1 that shows 50mg SBRBO exhibited non-significant from 0-60 min at 90 min showed 83% analgesia, followed by 100% analgesia at 120 min. 100mg showed a slight increase in latency time at 60 min which kept increasing and from 90-120 min showed significant activity (fig. and table no.1) followed by a decrease in latency time and at 200mg SBRBO, showed a gradual increase in antinociceptive effect from 30-60 min followed by significant i.e. 100% at 90 min which maintained even after 180 min.

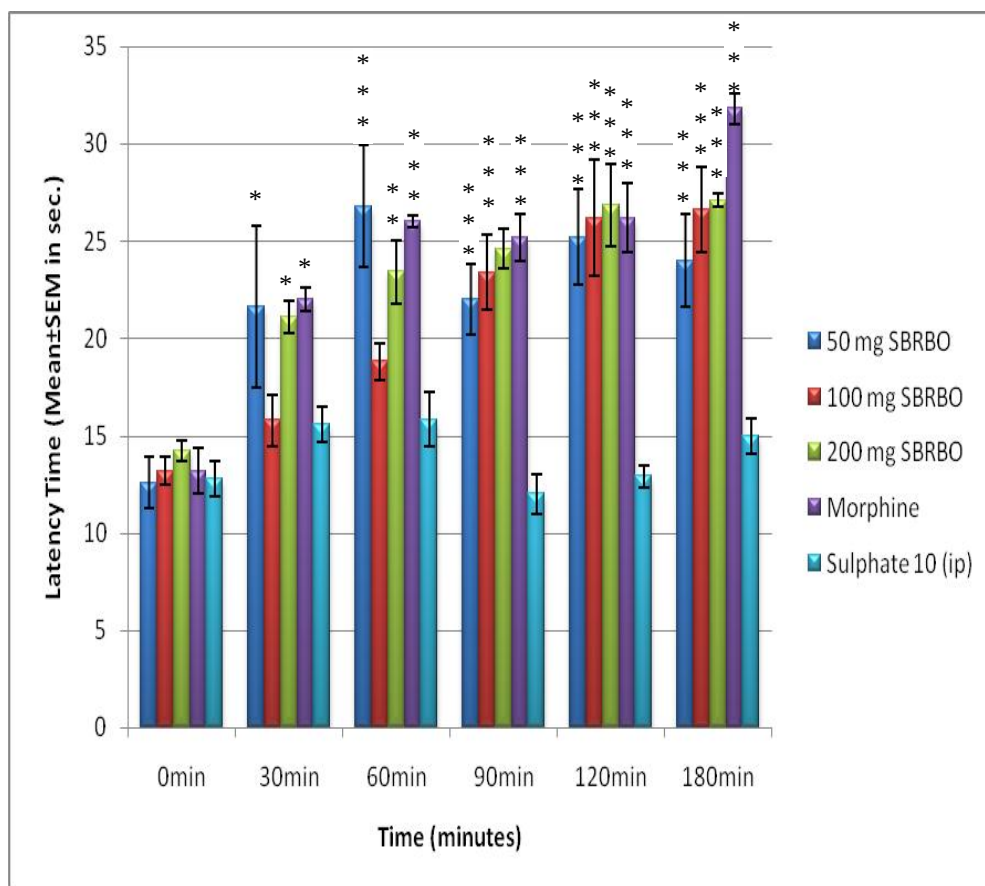
#### **Anti-inflammatory activity**

Carrageenan-induced paw edema is a reliable and straightforward animal model to screen the anti-inflammatory activity. It consists of two phases initial (0-2.5 hour) and late phase (3-5 hour). The inflammatory mediators as histamine, serotonin, and bradykinin get released during the first phase, whereas the arachidonate metabolites (prostaglandins and leukotrienes) participate in the reactions during the later stage. A significant increase in the paw edema ( $p < 0.001$ ) in the carrageenan control group was observed as compared to the normal control rats. Although, we have found an increase in the paw inflammation of Indomethacin treated animals but the intensity of edema (paw inflammation) was not as severe as in the carrageenan control animals, and there was a significant difference ( $p < 0.02$ ) as compared to their other respective control groups, i.e., carrageenan control group. Stabilized basmati rice bran oil (SBRBO 100mg) treatment strongly inhibited ( $p < 0.001$ ) the increase in paw edema as compared to a carrageenan control group and the pattern was the same as in case of the normal control animals. The SBRBO was found to be very successful in

**Table 1:** Analgesic effects of SBRBO and morphine on centrally mediated pain using hot plate test in mice.

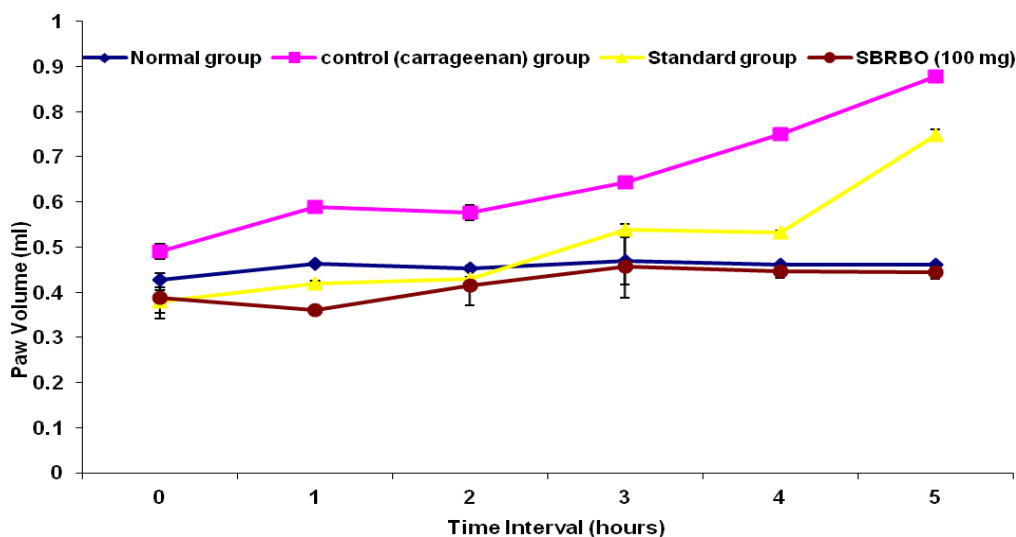
| Treatments/<br>Dose mg/kg          | Latency time (sec) |               |                 |                 |                 |                 |
|------------------------------------|--------------------|---------------|-----------------|-----------------|-----------------|-----------------|
|                                    | 0min               | 30min         | 60min           | 90min           | 120min          | 180min          |
| 50 mg SBRBO                        | 12.60 ± 1.32       | 21.66 ± 4.15* | 26.80 ± 3.12*** | 22.00 ± 1.81*** | 25.20 ± 2.45*** | 24.0 ± 2.36***  |
| 100 mg SBRBO                       | 13.2 ± 0.73        | 15.80 ± 1.31  | 18.80 ± 0.96    | 23.40 ± 1.93*** | 26.20 ± 2.97*** | 26.6 ± 2.20***  |
| 200 mg SBRBO                       | 14.21 ± 0.51       | 21.11 ± .82*  | 23.43 ± 1.61**  | 24.61 ± 1.04*** | 26.85 ± 2.13*** | 27.11 ± 2.34*** |
| Morphine<br>Sulphate 10 (ip)       | 13.20 ± 1.15       | 22.00 ± 0.63* | 26.00 ± 0.31*** | 25.20 ± 1.2***  | 26.20 ± 1.77*** | 31.80 ± 0.8***  |
| Control Gum<br>tragacanthin (0.5%) | 12.81 ± 0.89       | 15.58 ± 0.9   | 15.85 ± 1.43    | 12.0 ± 1.02     | 12.91 ± 0.59    | 15.00 ± 0.92    |

Asterisks indicate \* (p<0.05), \*\* (p<0.001) and \*\*\* (p<0.005); Latency time (sec) of control and treated groups, which are mean ± SEM of 6 animals in three independent experiment; Values represented in parenthesis are percent protection from centrally mediated pain.

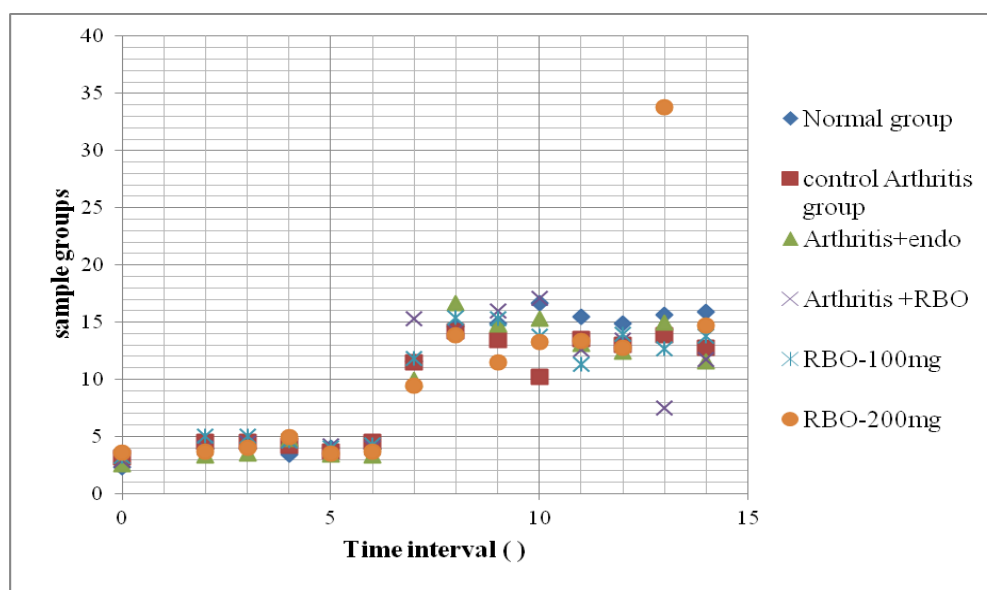
**Fig. 1:** Analgesic activity of Rice bran oil

reducing the inflammation against carrageenan-induced paw inflammation, as shown in fig. 2. This animal model provides a suitable parameter for its assessment as anti-inflammatory agents, particularly in the case of NSAIDs acting as COX inhibitors (Patel *et al.*, 2012). In the present study, the test agent (BRBO) reduce the paw edema particularly during the 3rd and 4th h, i.e., during the last phase of carrageenan-induced inflammation possibly by inhibiting the synthesis of arachidonate metabolites.

Various acute inflammatory animal models such as carrageenan-induced paw edema (Winter *et al.*, 1962), carrageenan-induced pleurisy in rats (Mikami and Miyasaka, 1983), acetic acid-induced vascular permeability (Whittle, 1964) and ear edema in mice (Young *et al.*, 1984) have been evaluated for the screening of anti-inflammatory activity. The carrageenan-induced paw edema offers particular advantages among them, as it is simple, quick and widely used for the screening anti-inflammatory activity of COX and LOX.



**Fig. 2:** Anti-inflammatory activity of basmati rice bran oil



**Fig. 3:** Anti-arthritic activity of basmati rice bran oil

Same as the studies have proposed the possible mode of action in case of acute inflammation (Vane and Botting, 1995).

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present study, the test agent (BRBO) reduce the paw edema particularly during the 3rd and 4<sup>th</sup> h, i.e., during the last phase of carrageenan-induced inflammation possibly by inhibiting the synthesis of arachidonate metabolites. The present observations support that the Stabilized basmati rice bran oil (SBRBO) reduces the inflammation by interfering the arachidonate metabolites. The study recommends the SBRBO for use in the treatment of such inflammations.

#### **Anti-arthritic activity**

One of the parameter parameters to identify arthritis is the appearance of the swelling at the joints that promotes bone stiffness, joint immobility and pain. The osteoarthritis or rheumatoid arthritis (RA), is the outcome

of adverse functional consequences of pro-inflammatory cytokines (interleukins) and inflammatory enzymes like COX and LOX that produce prostaglandins and leukotrienes, respectively. It has been reported that 33 to 75% of RA patients believe in diet therapy. Indeed, food plays a distinct healing function in reducing the severity of the disease and 20 to 50% of the beneficial activity will be taken up dietary management as a challenge (Stamp et al., 2005; Cerhan et al., 2003).

Inhibitory actions of SBRBO investigated against arthritic joints revealed that 200mg dose is mildly effective than a half dose of 100mg of the SBRBO when both were compared with the standard drug (fig. 3). SBRBO reduced the carrageenan-induced inflammation possibly by inhibiting the bioactivity of arachidonic acid metabolites. These inflammatory mediators participate in the metabolism of arthritis, and their reduction may be responsible for their anti-arthritis effect. The inhibitory properties of rice extracts have been reported earlier for the two critical therapeutic targets COX-1, COX-2, and 5-LOX enzymes and showed the inhibitions of these enzymes (Cicero and Derosa, 2005; Patel and Naik, 2004). Further study related to inactivation of COX enzymes by SBRBO will support our investigation.

## CONCLUSION

In conclusion, it may be said that rice bran, a by-product of the rice milling industry, is an excellent dietary supplement to control inflammation, arthritis, and pain in humans. The oil SBRBO has tremendous potential for nutraceutical product development because of its anti-inflammatory and anti-arthritic pain resistant activities. The rice bran is a rich source of bioactive components such as gamma oryzanol, flavonoids, dietary fibers, minerals, etc. The commercialization of rice bran will be highly productive in promoting the economic growth of Pakistan because production of rice stands third position of all over the world.

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