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MECHANISM OF ACTION OF A MULTI-HERBAL EXTRACT BLEND (KARALLIEF EASY CLIMB) IN SUPPORTING JOINT HEALTH

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ABSTRACT: Osteoarthritis (OA) commonly affects many joints in the human body, including the knee joints. The knee joint is made up of two parts - the patella-femoral (PF) and tibiofemoral (TF) compartment. Animal models for OA studies are well-established and serve as an important tool for understanding the impact of OA in humans. This study evaluates the anti-OA potential of a multi-herbal extract blend product – KEC (KARALLIEF EASY CLIMB) against monosodium iodoacetate induced OA in wistar rats *in-vivo*. Animals have equally divided into four groups, of which one group was the control, and other three groups were experimental groups. Biomarker estimation and histopathological evaluation were carried out. All values were expressed as mean ± SEM. The significant difference between the treatment and control group was estimated using one-way ANOVA with Dennett's test. All results of the statistical analysis were summarized in separate tables. In any case, the values were considered statistically significant at $P<0.05$. This study found that treatment with KEC reduced the Monosodium Iodoacetate (MIA) induced osteoarthritis condition. Anti-osteoarthritis activity of this product was confirmed through the measurement of various biomarker levels. Histopathological observations also confirmed that the treatment with KEC has inhibited/reversed the MIA-induced joint cartilage degeneration and subchondral bone alterations that lead to osteoarthritis.

INTRODUCTION: More than 100 types of arthritis have been identified [1]. Osteoarthritis (OA), also known as degenerative joint disease, is the most common form of arthritis [2]. Osteoarthritis (OA) commonly affects the knee joints [3]. The knee joint is made up of two parts: the patella-femoral (PF) and tibiofemoral (TF) compartment [3]. There are three main categories of animal models for OA: [1].

Those naturally develop OA overtime 2) Models that develop OA after intra-articular injection of pro-inflammatory or chondrotoxic agents 3) Models that develop OA after physical trauma or surgery [3]. Pro-inflammatory and pro-catabolic mediators are found localized in synovial fluid and

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hydrolytic enzymes, such as matrix metal loproteinases (MMPs), are associated with cartilage degeneration. Extracellular matrix breakdown can trigger the accumulation of innate immune cells that lead to inflammation and tissue destruction. Current pharmacotherapy provides options for alleviating pain and symptoms of OA and RA [4]. However, there are various side effects associated with these treatments that may limit their use.

NSAIDs may be associated with gastrointestinal, cardiovascular, and nephrotoxic effects and have been excluded for long-term treatment of arthritis. Acetaminophen can induce hepatotoxicity. Tramadol can alter the gastrointestinal and central nervous systems. Intra-articular corticosteroids may have questionable efficacy for OA treatment and may further damage joints and tissues [5]. Medical care in osteoarthritis is provided by a multi-disciplinary team and may be challenging because of the co-morbidities that coincide with osteoarthritis (OA), a chronic pain disorder involving all components of synovial joint, represents one of the most frequent causes of physical disability; according to the World Health Organization, OA is on the top ten disabling chronic disorders in developed states [6]. MIA (monosodium iodoacetate) is a chemical agent that, when injected intra-articularly, disrupts the cellular aerobic glycolysis pathway and causes cell death by halting the activity of a key enzyme in chondrocytes [1]. This MIA-induced OA leads to a reduction in the number of chondrocytes and alters the articular cartilage architecture in ways similar to that of human OA [1, 7]. Intra-articular injection of MIA also leads to histopathological changes in synovial membranes and joint capsules.1Given the similarities of MIA-induced OA to human OA; this study used an intra-articular injection of MIA in rats to investigate histopathological changes in the knee joint.

MATERIALS AND METHODS

Experimental Animals and Animal Care: All procedures involving animals were conducted humanely and were performed by or under the direction of trained or experienced personnel. Prior to completing any animal work, all protocols were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of Radiant Research Services Pvt. Ltd. Animal experiments were conducted in accordance with the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA Registration Number-1803/ PO/ RcBi/ S/2015/ CPCSEA). Twenty-four male Wistar rats (8-10 weeks old) were used for this study. Six rats were used as the normal control group, and 18 rats were used in the experimental groups. Animals were housed at a temperature of 22 ± 3 ºC, relative humidity of 30-70%, and 12 h light and 12 h dark cycle. Six animals were housed together in standard polypropylene cages with stainless steel lids containing pelleted food and water bottle slots. Sterile paddy husk was used as bedding material and changed daily.

Randomization: Each animal was marked by picric acid and numbered individually. Each cage was numbered separately for easy identification of the group. All animals were randomized based on body weights.

Induction of Osteoarthritis: Osteoarthritis was induced by injecting Monosodium iodoacetate (MIA) into the right knee joint. The MIA injection was dissolved in 50 µl of normal saline. Before the administration of MIA, all the animals were shaved and disinfected with 70% ethanol, followed by povidone-iodine. The MIA injection was administered as 3 mg weight under Isoflurane inhalation anesthesia. The animals were incised at the center of the right knee joint to expose the patellar ligament. The animal was kept on its back, and the leg was flexed 90º as the MIA was injected to the right knee joint (50 µl) [6]. rats were used for each dose of MIA. The normal control group received normal saline. After injection, all the animals were returned to their cages and kept with food and water under 12 h dark-light cycles. On the 28th-day post-MIA injection, the knee joint was examined with histology. The cartilage was stained by using a special stain, and MIA induction was evaluated.

Dose and treatment information for each experimental group is detailed in **Table 1.** Group 4 was administered the multi-herbal extract blend KEC - a blend of uniquely standardized proprietary extracts of *Cardio spermumhalicacabum, Boswellia serrata, Vitexne gundo, Bambusa arundinacea, Curcuma longa,* and *Citrus sinensis*.

TABLE 1: GROUP, DESIGNATION AND DOSE LEVELS

Groups	Group Description	Treatment	Dose Level	Dose Volume (ml/kg)	No. of animals
Group 1	Normal Control	(Vehicle)	(0.5% Carboxy Methylcellulose) 10 ml/kg/ B.wt.	10 ml	6
Group 2	Positive control	Monosodium iodoacetate (MIA)	3mg/Animal (0.5% Carboxy Methylcellulose)	10 ml	6
Group 3	Standard (Diclofenac)	MIA + Diclofenac	10 mg/kg	10 ml	6
Group 4	KEC	MIA + Test (KEC)	103.33mg/kg (dissolved in 10ml CMC)	10 ml	6

Clinical Signs: Cage-side evaluation was conducted for visible clinical signs of OA once daily throughout the study period. Detailed clinical examinations were conducted prior to treatment (once during acclimatization and once after randomization) and at least once a week thereafter *i.e.,* on the day of weekly body weights, excluding the days of necropsy. Detailed clinical examinations included changes in the skin, fur, eyes, mucous membranes, behavioral patterns, and respiratory and circulatory patterns. Additionally, tremors, convulsions, salivation, diarrhea, lethargy, and coma were all evaluated.

Biochemical Parameters: Clinical chemistry: Serum was separated by centrifuging at 10000 rpm for 10 min and analyzed using fully Automated Clinical Chemistry Analyzer MISPA ace, Agape Bio-medicals Ltd, for the parameters mentioned below.

- Hyaluronic acid
- Glycosaminoglycan
- Serum Creatine kinase
- Alkaline phosphatase levels
- Collagen and uronic acid levels in synovial fluid

Biomarker Estimation: At the end of the 29th day, synovial fluid was collected from the knee joints. While taking synovial fluid, 50 µl of Phosphate-buffered saline (PBS) was injected into the knee joint and gently massaged on the joint.

Fluid from the joint was taken 45 sec later and transferred into the tubes containing EDTA. Approximately 75 µl of synovial fluid aspirates with PBS were centrifuged at 24 °C at 3000 rpm for 15 min to clear samples of cells and then stored at -40 °C until analysis of biomarkers with ELISAs.

Histopathological Evaluation: Following blood collection, knees were harvested by separating the hip joints of both hind limbs and taking out the knee joints. Knee joints were stored in in 10% buffered neutral formalin for 72 h and then decalcified for 72 h. The right knee joints were cut sagittal and frontally and then analyzed with histology. Knee joints were de-acidified in 5% sodium sulfate solution for 72 h washed with water, dehydrated in 100% ethanol, and then embedded in paraffin wax. Three µm sectioned slides were stained separately with hematoxylin and eosin staining. Histopathology was evaluated and reported.

Statistical Analysis: All data, including body weight, clinical chemistry, hematology, and electrolytes, were statistically analyzed using Graph-Pad Prism Software, version 5.01. All values were expressed as mean ± SEM. The significant difference between the treatment and control group was evaluated using one-way ANOVA followed by Dunnett's Multiple Comparisons test. All results of the statistical analysis were summarized in separate tables. The values were considered statistically significant at $p<0.05$.

Results: Animals in all groups were observed to be normal throughout the experimental period. No morbidity or mortality was observed in vehicle control and treated groups throughout the experimental period **Table 2.** During the study period, normal control, standard, and KEC treated animals didn't show any significant changes in body weight when compared to that of the positive control during the first week. However, by Day 14, the positive control group weights decreased lower than the other groups, and by day 21 and day 28, body weights of positive control group animals were significantly lower than those in the control

and treatment groups **Table 3**. Even though animal body weights in the positive control group were significantly lower than the other groups by day 21 of the study, there was no significant difference in the food consumption (g/rat/day) between treatment groups **Table 4.**

TABLE 2: SUMMARY OF MORTALITY AND MORBIDITY DATA IN RATS

	Mortality & Morbidity Data													
Group	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**
Group 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D15	**D16**	**D17**	**D18**	**D19**	**D20**	**D21**	**D22**	**D22**	**D23**	**D24**	**D25**	**D26**	**D27**	**D28**
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 3: SUMMARY OF WEEKLY BODY WEIGHTS DURING THE TREATMENT PERIOD

Day	**Group**											
	G1 (Control)			**G2 (Positive Control)**			**G3 (Standard)**			**G4 (KEC)**		
	Mean	**SEM**	**N**	**Mean**	**SEM**	**N**	**Mean**	**SEM**	**N**	**Mean**	**SEM**	**N**
1	191.83	1.97	6	192.33	1.99	6	191.33	2.22	6	193.17	3.13	6
8	202.50	1.69	6	198.17	1.85	6	201.00	2.03	6	201.17	3.10	6
14	213.00	1.75	6	204.50	2.14	6	209.33	1.98	6	209.00	3.08	6
21	224.00	1.65	6	210.83	2.18	6	220.50	2.35	6	217.83	3.18	6
28	233.17	1.85	6	217.50	2.23	6	229.00	2.31	6	226.17	3.29	6

TABLE 4: SUMMARY OF WEEKLY FEED INTAKE DURING THE TREATMENT PERIOD

Day	**Groups**											
	G1 (Control)			**G2 (Positive Control)**			**G3 (Standard)**			**G4 (KEC)**		
	Mean	**SEM**	**N**	**Mean**	**SEM**	**N**	**Mean**	**SEM**	**N**	**Mean**	**SEM**	**N**
8	98.43	0.90	6	91.57	0.75	6	94.29	1.08	6	92.86	0.80	6
14	102.00	1.00	6	94.43	0.95	6	96.71	0.42	6	95.86	0.83	6
21	104.57	0.72	6	98.14	0.74	6	100.43	0.57	6	98.43	0.65	6
28	108.29	0.75	6	103	0.72	6	105.14	0.59	6	103.86	0.63	6

Biochemistry Parameters: The biochemistry parameters demonstrated a significant decrease in serum alkaline phosphatase (ALP), creatinine kinase (CK-Nac), glycosaminoglycan, and hyaluronic acid levels for the test substances treatment groups when compared to the positive control **Table 5** and **6**. Collagen levels were significantly increased in the test groups compared to the positive control group. Additionally, collagen levels were increased, and D-glucuronic acid levels were decreased in synovial fluid from the KEC group compared to the positive control group **Table 7.**

TABLE 5: SUMMARY OF ALKALINE PHOSPHATE & CK-NAC LEVELS IN SERUM

Group	**Treatment**	**Dose Level**	**ALP(U/L)**	**CK-Nac(U/L)**
Group 1	Normal Control	0.0 mg/kg (Vehicle)	159.67±5.32***	37.50±1.43***
Group 2	Positive control	3 mg/Animal (Normal Saline)	241.67±4.92	77.83±1.87
Group 3	Standard	10 mg/kg	190.83±2.48***	48.33±1.31***
Group 4	KEC	103.33 mg/kg Bodyweight	201.17±2.85***	55.50±1.77***

Values were expressed as mean ± SEM (n = 6), Statistical significance are compared between Positive control (Group 2) versus other treatment groups (G1, G3 & G4) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

TABLE 6: SUMMARY OF GAGS & HA LEVELS IN RAT SERUM

Group	**Treatment**	**Dose Level**	**GAGs(ng/mL)**	**HA (ng/mL)**
Group 1	Normal Control	0.0mg/kg (Vehicle)	46.67±1.57***	306.25±2.81***
Group 2	Positive control	3mg/ kg b.wt (Normal Saline)	96.18±0.31	417.26±9.16
Group 3	Standard	10mg/ kg b.wt	69.14±1.74***	376.22±7.36***
Group 4	KEC	103.33mg/ kg b.wt	78.27±2.10***	361.88±4.16***

Values were expressed as mean ± SEM (n = 6), Statistical significance are compared between Positive control (Group 2) versus other treatment groups (G1, G3 & G4) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001)

TABLE 7: SUMMARY OF COLLAGEN AND D-GLUCURONIC ACID LEVELS IN SYNOVIAL FLUID

Group	Treatment	Dose Level	Collagen (ng/mL)	D-Glucuronic acid (ng/mL)
Group 1	**Normal Control**	0.0 mg/kg (Vehicle)	6.72±0.17***	3.47±0.08***
Group 2	**Positive control**	3 mg/ kg b.wt (Normal Saline)	3.53±0.14	10.95±0.30
Group 3	**Standard**	10 mg/ kg b.wt	5.08±0.25***	6.73±0.19***
Group 4	**Test (KEC)**	103.33 mg/ kg b.wt	4.92±0.10***	7.40±0.25***

Values were expressed as mean ± SEM (n = 6), Statistical significance are compared between Positive control (Group 2) versus other treatment groups (G1, G3, G4) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

Histopathology Observations: Tissues were harvested from four individual animals for histological analysis (Figure 1). The normal control group exhibited normal bone and cartilage architecture with bone marrow elements and a smooth surface. **Fig. A1 - A4** under **Group I**.

In contrast, the positive control group exhibited partial damage of the synovial membrane, infiltration of inflammatory cells into the articular tissue and synovial space, cartilage erosion, and synovial hyperplasia. Pannus formation (an abnormal layer of tissue) was also observed. **Fig. A1 - A4** under **Group II**. The standard group had a lesser degree of cartilage damage and lesser cellular deformities than the positive control. Joint cartilage from the femur and tibia was normal with well-distributed chondrocytes and a smooth surface. **Fig. A1 - A4** under **Group III**. The KEC treated group has improved the pathological condition observed in the positive control group.

Treatment with KEC protected the normal texture synovial membrane similar to that of the normal control group, and the KEC group exhibited relatively little damage to the cartilage surface. KEC group showed normal bone and cartilage with bone marrow elements, almost found to be normal with a well-developed smooth surface. **Fig. A1 - A4** under **Group IV**.

Group 1: Normal Control:

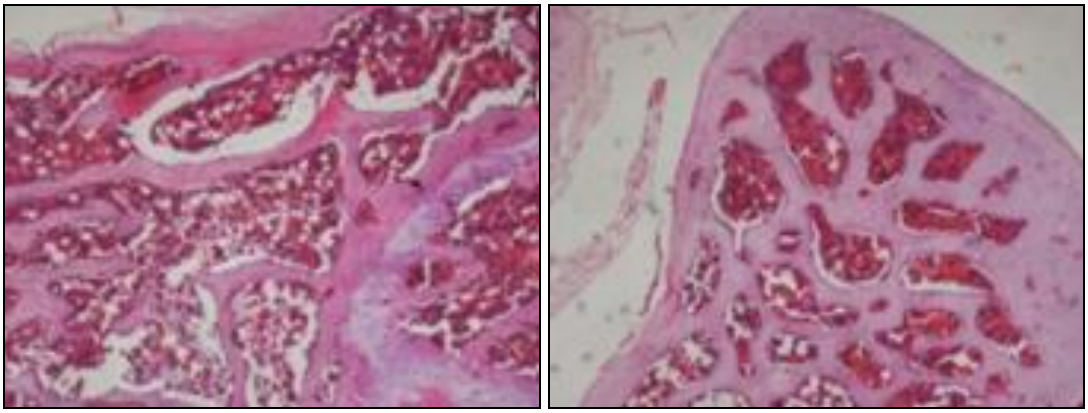

FIG. A: 1 - BONE WITH JOINT **FIG. A: 2 - BONE WITH JOINT**

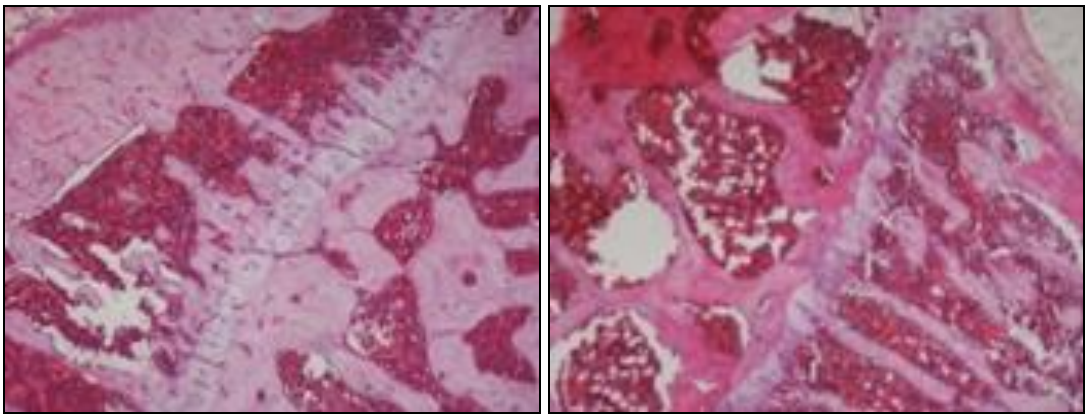

FIG. A: 3 - BONE WITH JOINT **FIG. A: 4 - BONE WITH JOINT**

FIG. 1: EFFECT OF TEST SUBSTANCE ON BONE WITH JOINT

Group 2: Positive Control:

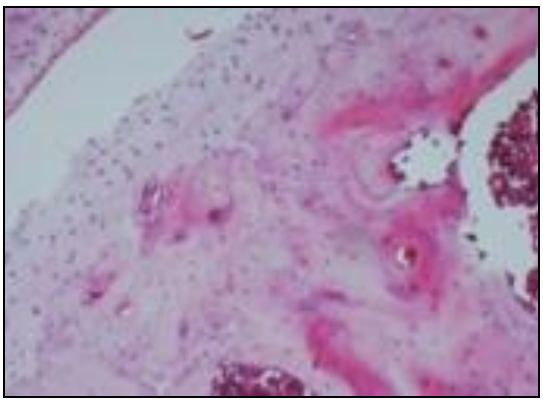

FIG. A: 1 - BONE WITH JOINT

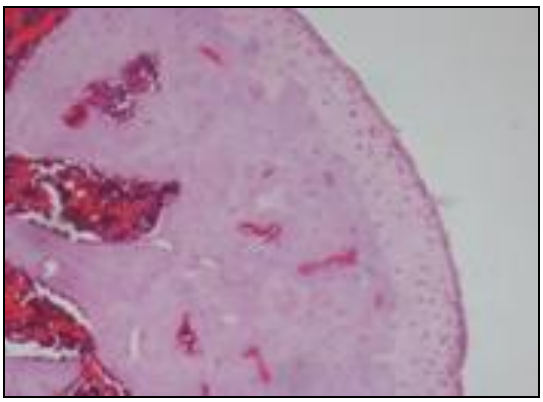

FIG. A: 2 - BONE WITH JOINT

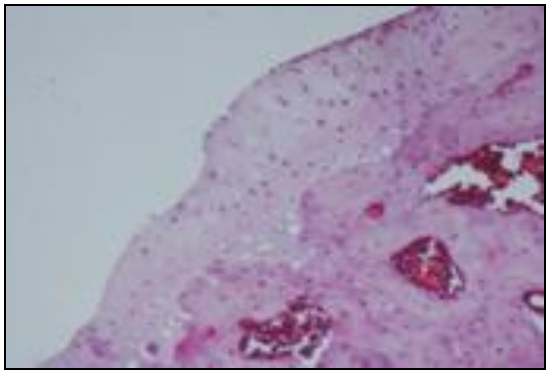

FIG. A: 3 - BONE WITH JOINT

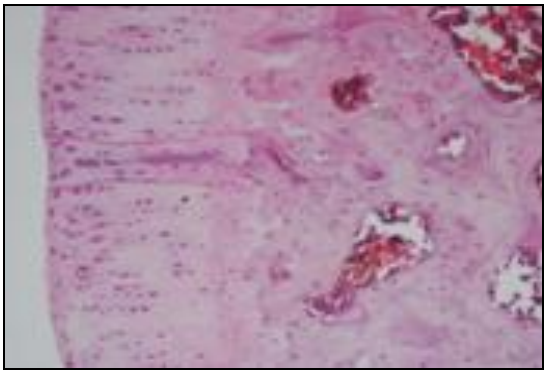

FIG. A: 4 - BONE WITH JOINT

FIG. 1: EFFECT OF TEST SUBSTANCE ON BONE WITH JOINT

Group 3: Standard:

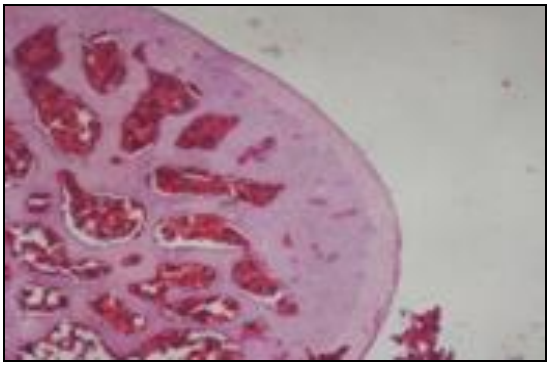

FIG. A: 1 - BONE WITH JOINT

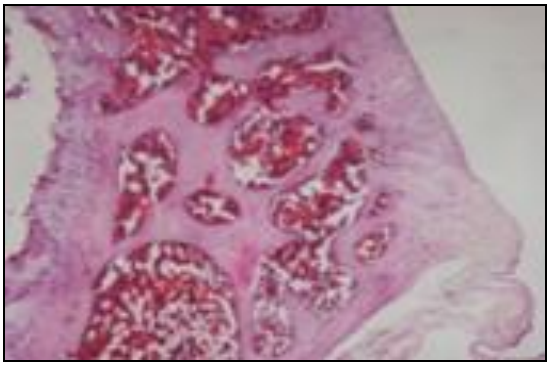

FIG. A: 2 - BONE WITH JOINT

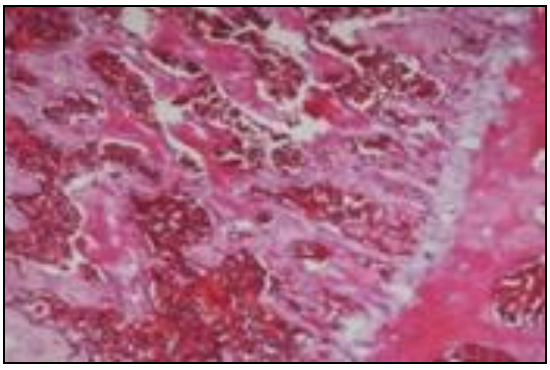

FIG. A: 3 - BONE WITH JOINT

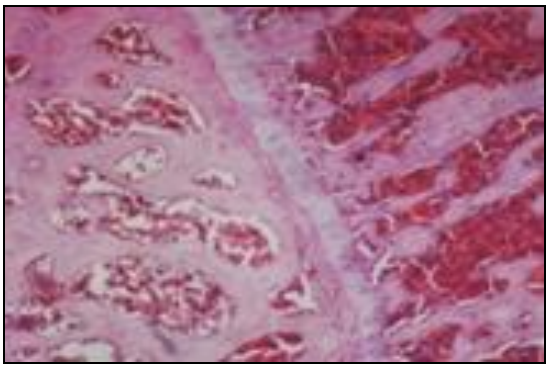

FIG. A: 4 - BONE WITH JOINT

FIG. 1: EFFECT OF TEST SUBSTANCE ON BONE WITH JOINT

Group 4: Test (Kec):

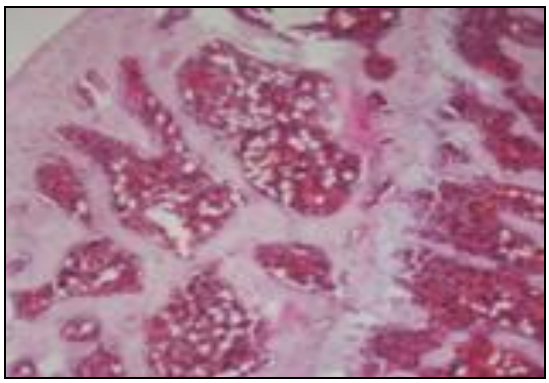

FIG. A: 1 - BONE WITH JOINT

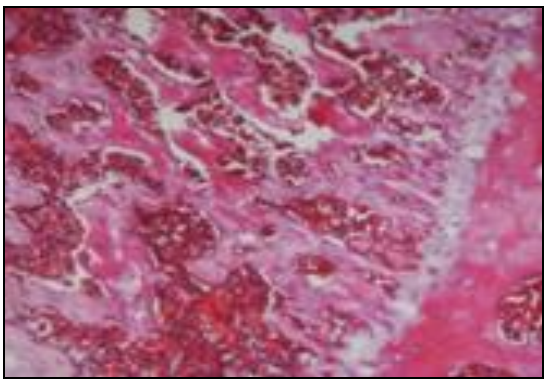

FIG. A: 2 - BONE WITH JOINT

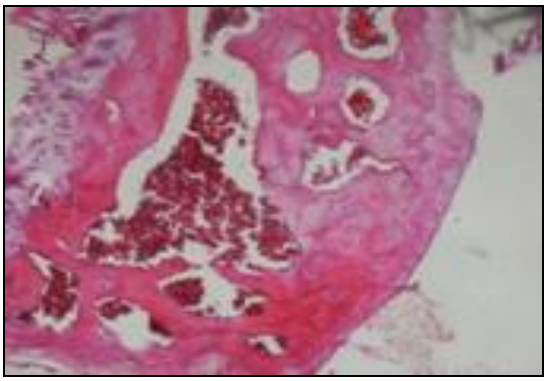

FIG. A: 3 - BONE WITH JOINT

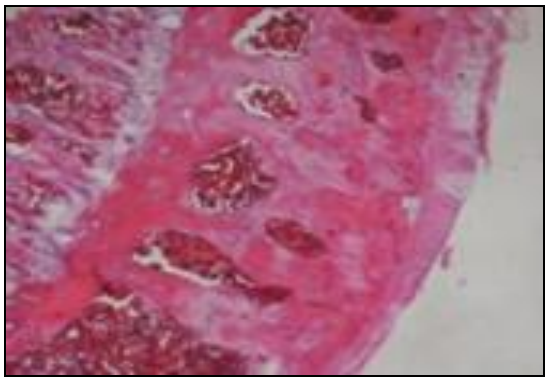

FIG. A: 4 - BONE WITH JOINT

FIG. 1: EFFECT OF TEST SUBSTANCE ON BONE WITH JOINT

DISCUSSION: OA is a complex yet common joint disease that causes a loss of articular cartilage, bone spurs, sub-chondral bone remodeling, ligament laxity, thickening of the capsule, and the synovial membrane, and weakening of the peri-articular muscles. OA patients tend to experience stiffness, pain, and functional limitations. In the present study, monosodium iodoacetate (MIA) induced OA was used to evaluate the efficacy of KEC formula (Karal -lief Easy Climb). This experimental model is a commonly used experimental model of OA. MIA induces acute inflammation, cartilage degradation, and joint pain.

In our study, Wister rats of 8-10 weeks were used similar to a study done by Takahashi I *et al.* (2018) 3 and Udo M *et al.* (2016) 8 on Wister rats that were 9 weeks old and 8 weeks old, respectively. ALP (Alkaline phosphatase) is mainly present in human tissues, including bone, liver, kidney, and intestine. When any of these tissues get impaired, ALP can leak into the blood. Abnormal levels of ALP occur in the case of bone/joint impairment, such as degenerated joints in OA. In our study, MIA treatment has elevated the ALP levels (indicating the OA condition), and treatment with KEC has significantly lowered the ALP levels. So KEC may help to reduce bone and joint erosion. Animals treated with MIA had elevated N-acetyl-cystein-(NAC)-activated creatine kinase (CK-Nac) levels in the blood, which indicates muscle damage and inflammation (including the joint muscles). Treatment with KEC helped significantly lower the CK levels indicating its role in reducing muscle inflammation. OA is characterized by degenerated joint cartilage tissue, subchondral bone remodeling (abnormal increase in the thickness of the bone present below the cartilage), and joint inflammation.9Glycosaminoglycan (GAG) is an important constituent of the joint connective tissue. Impaired cartilage metabolism leads to depolymerization, which releases Glyco-saminoglycan (GAG); GAG levels in the blood can be used as an indicator of cartilage degradation at the joint [10]. Hyaluronic acid (HA) is one of the most basic GAGs and a serum biomarker for knee OA. Synoviocytes produce HA and is a key component of articular cartilage; an increased systemic level could be an early indicator of joint

cartilage structural damage [11]. HA is present throughout the body. It plays a crucial role in many functions, including lubricating the joints, promoting the growth of cartilage and bone and reducing inflammation and pain caused by injury or tissue degradation. The KEC treated group showed a significant reduction in HA levels in the bloodstream. This could indicate that KEC may have helped significantly reduce joint degradation and may also help in supporting the rebuilding of the joint tissue. Hence more HA is available at the joints (especially in the synovial fluid). Synovial fluid helps to keep the joints lubricated by decreasing the friction between the articular cartilages [12]. HA provides the synovial fluid with the adequate viscosity it needs to effectively carry out its joint lubrication role 12 effectively. Thus, the KEC group saw an increase in synovial fluid viscosity, which improves joint lubrication.

This could be one explanation for the mechanism of action of KEC in helping build strong and more mobile joints - by increasing the synovial fluid viscosity and, consequently, joint lubrication. This mechanism of action goes beyond just reducing the symptoms of OA (such as joint pain), but shows that the product may be addressing the root cause of OA, which is degenerated and rigid joints. Treatment with KEC significantly increased the collagen levels.

Collagen is found in many different parts of the body, such as the bones, skin, tendons, and muscles. Collagen provides strength and support to the extracellular matrix in the joints. MIA treatment has lowered collagen levels, and treatment with KEC has significantly elevated the collagen levels towards normal. This evidence could further support the argument that KEC may help to regenerate the joint tissues since the increased collagen helps provide more strength and support to the joint tissue.

Treatment with KEC has significantly decreased the D-glucuronic acid levels in the synovial fluid. Higher Glucuronic acid levels may significantly increase pain sensitivity [13]. Elevated levels of D-glucuronic acid by MIA induction were reduced by treatment with KEC. So KEC may help reduce pain sensitivity, a common problem for OA patients. Lastly, a histopathological evaluation of the animal joint tissue revealed that KEC improved the condition of the joint tissues significantly over those observed in the positive control group. KEC treated group showed a uniform synovial membrane similar to that of the normal control group. The KEC group exhibited relatively little damage to the cartilage surface. KEC group showed normal bone and cartilage with bone marrow elements, almost found to be normal with a well-developed smooth surface.

CONCLUSION: From the present study, it can be concluded that KEC has reduced the MIA-induced osteoarthritis condition. This product's anti-osteoarthritis activity was confirmed by the measurement of various biomarker levels, which confirmed the potential of this product. Furthermore, histopathological observations also confirmed that the treatment with KEC had reversed the joint cartilage degeneration and subchondral bone alterations that lead to OA. It also shows that KEC goes beyond just addressing the symptoms of OA (like pain reduction and reducing inflammation). It also goes a step further and may also address the root cause of OA (degenerated joints) by helping rebuild the joint connective tissue

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