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Research Article

POTENTIAL ACTIVITY OF *MADHUCA LONGIFOLIA* AGAINST MSU-INDUCED ARTHRITIS IN FEMALE WISTER ALBINO RATS

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ABSTRACT

Gout is a well-known form of arthritis which is caused due to deposition of monosodium urate crystals on joints throughout the body. *Madhuca longifolia* is evergreen tree that is known to have anti-arthritic activity. The aim of this study is to evaluate the Anti-arthritic activity on female Wistar albino rats by using aqueous extract of *Madhuca longifolia* leaf and its different patterns of interaction between receptors responsible for gout. Animal experiment was carried out with 30 female rats. MSU was induced on Group II, Group III and Group IV. In which Group III received aqueous leaf extract of *Madhuca longifolia*. After the study duration the rats were tested for the level of renal enzyme markers, renal antioxidant and renal histopathology. *In silico* docking analysis was carried out with the active components of *Madhuca longifolia* between receptors responsible for gout. The study was done by using Patchdock server for docking and the docked files were visualized and analyzed by using Pymol software. MSU has caused abnormalities in renal enzyme markers, antioxidant assays and histopathology. The rats treated with *Madhuca longifolia* were able normalize the toxicity caused by MSU which is similar to Indomethacin. The rats treated with *Madhuca longifolia* were able normalize the toxicity caused by MSU which is similar to indomethacin. The *in-silico* docking analysis has shown best binding affinity with Myricetin-3-O-arabinose with 9 bonds.

Keywords: *Madhuca longifolia*, *in-silico* docking, gouty arthritis, MSU crystal, anti-arthritic activity.

INTRODUCTION

Gout is an inflammatory arthritis which is also referred as common crystal arthropathy. This arthropathy is caused mainly due to accumulation of serum urate on joints forming monosodium urate (MSU) crystals in a symptomatic joint leading to tophus formation which is the main criterion for to be classified as Gout with patients[1]. Uric acid is ionized into urate in the body and they deposit on the tissues when the serum uric acid level rise beyond the threshold level. Normal pathological threshold of hyperuricemia is found to be 6.8 mg/dL beyond this levels are considered to be risk for humans leading to Gout[2]. Even though, Increased production of uric acid is found to be a main reason for GOUT but it is responsible for only 10% of cases of while the remaining 90% is due to renal under-excretion which is why it is important to study kidney parameters also while dealing with Gout[3]. Men due to higher levels of serum uric acid content than their gender counterpart are more susceptible for the MSU accumulation leading to gout[4].Worldwide prevalence of gout got gradually increased due to higher intake of fast foods, lack of physical activities and metabolic syndromes[5].

Gout can be diagnosed by using Ultrasonography which helps in visualization of deposited MSU crystals along the articular cartilage surface[6]. Non-steroidal anti-inflammatory drugs (NSAID) are widely used for relief of pain and inflammation. Gout can be primarily treated by using NSAID Indomethacin which helps in relieving pain[7]. NSAIDs mechanism for suppression works with inhibition of cyclooxygenase (COX)-1 and (COX)-2 enzymes which in turn suppress prostranoid production[8]. The use of NSAIDs frequently for gout management can contribute to wide variety of problems including kidney disease[9]. Indomethacin is a tested treatment for acute and chronic exposure with clinically relevant doses, which in turn suppressed the production of COX-1- and COX-2-derived prostaglandins and but still it caused small intestinal damage as well as a reduction in bacterial β-glucuronidase activity[10]. So, instead of using synthetic drugs we can use Plant sources are considered to be alternatively cost effective and protective than synthetic drugs. Plants that protect liver contains an assortment of constituents which are chemical in nature like monoterpenes, phenols, lignans, coumarins, carotenoids, fundamental oil, natural acids, xanthenes, glycosides, flavonoids, lipids and alkaloids[11].

Madhuca longifolia, a family of Sapotaceae is a folk medicinal plant. Tribal people commonly use this for the treatment of snakebite as an antidote in the southern part of Tamil Nadu, India. It's a medium-large sized tree distribution mostly found in Nepal, India and Sri Lanka[12]. *M. longifolia* leaves are used in the treatment of Cushing's disease and chronic bronchitis[13]. Oleic acid (46.3%), palmitic acid (17.8%), stearic acid (14.0%) and linoleic acid (17.9%) are reported as the major component fatty acid in *M. longifolia*[14].

In the current state of drug discovery process the bio informatics tools play a great role in making the process easier for scientists which they use in finding the binding site of a molecule exactly[15]. *In-silico* docking is found to be a great tool used for the prediction of the lead compounds which were involved in the production of drugs which is used in the treatment of various disorders and diseases even though the molecules are smaller by size[16]. The tools were used to predict the properties of molecules in a relatively shorter period with greater accuracy. It also predicts the geometrical structure of a molecule, nature of the bond, length of the bond, charge of the compounds, binding affinity, interaction mode, names of atoms and residues involved[17]. The aim of our

study is to evaluate the Anti-arthritic activity on female Wistar albino rats by using aqueous extract of *Madhuca longifolia* leaf.

MATERIAL AND METHODS

Preparation of plant extract and chemicals

The fresh leaves of *M. longifolia* were obtained which was authenticated and identified by Prof. Jayaraman, Director of Institute of Herbal Botany, Plant Anatomy Research Centre, Chennai, Tamil Nadu, India. The authentication number of the specimen is PARC/ 2016 /3322. The fresh leaves of *M. longifolia* were collected and the samples were powdered by using mortar and pestle. The powdered sample was macerated in distilled water (dH_2O) in the ratio of 1:2 (w/v) and were soaked for 24 h and filtrated by using Whatman filter paper number 1. The filtrate was dried to yield extract which was later used for the study. Indomethacin (IND) tablet was obtained from Micro lab Pvt, Ltd, Solan, Himachal Pradesh, India which was administered by dissolving in sterile water.

Animal house conditioning

Female Wistar albino rats of 160-190 g were used for the experiment, which was obtained from the VIT Animal house, Vellore, Tamil Nadu, India. Experiment on animals was approved by the institutional animal ethical committee, VIT, Vellore (Reg no: VIT/IAEC/13/Feb13/21). Animals have housed six rats per cage and maintained in standard conditions. The animals were acclimatized for a week before starting the experiment. Rats were provided freely accessed water and pellet diet purchased from Hindustan Lever Ltd, Mumbai, India.

Experiment design

- **Group-I:** Used as the control rats.
- **Group-II:** Utilized as MSU induced rats (4 mg/kg. b.w. /day, i.v) MSU was induced at day 1.
- **Group-III:** Utilized as treatment group for gout administrated with Aqueous Leaf Extract of *Madhuca longifolia* (ALEML) (500 mg/kg. b. w./day) orally for 3 consecutive days and MSU was induced at day 1 (4 mg/kg. b. w./day, i.v)
- **Group-IV:** Utilized as standard group administrated with Indomethacin (25 mg/kg. b. w. /day) orally for 3 consecutive days and MSU (4 mg/kg. b. w. /day, i.v) on day 1.
- **Group-V:** Served as drug alone group administrated with ALEML (500 mg/kg. b. w. /day).

At the end of this experiment, the rats were euthanized by ether anesthesia and the blood was collected from trunk to prepare serum. Serum was used for biochemical marker analysis. Liver, kidney, paw and spleen were retrieved from the rat.

Wight assessment, Biochemical and Antioxidant analysis of the tissues

Body weight of the rats was estimated on each day of the treatment period till euthanasia. The renal enzyme markers like uric acid, urea, creatinine and acid phosphatase were estimated on serum to evaluate functioning of kidney on different groups. A few portions of the kidney, stomach, intestine and liver tissue were used to analyze the antioxidant activities such as superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH). Serum urea, uric acid, and creatinine were measured using commercial diagnostic kits obtained from Auto Span Diagnostics Ltd., India.

Histological evaluation

The kidney, paw and liver tissue were washed with 0.1 M ice-cold phosphate buffered saline (PBS) and were stored in 10% formalin for histopathology processing. Tissue portion was fixed by haematoxylin and eosin staining and was visualized for histopathological morphology.

Docking analysis

Interleukin-1β (1TWM), PRPSAP-1 (2C4K), Xanthine dehydrogenase (2CKJ), PDZK-1 (2EEI), NLR Family Pyrin Domain Containing 3 (2NAQ), Nuclear receptor corepressor-2 (2R5T), Toll like receptor-4 (2Z62), Glucokinase regulator (4BB9), ABCG-2 (5NJ3) were found to be the receptors for gout and the docking was done with them. The compounds of *M. longifolia* are Propanoic acid, N-Methoxy-N-methylacetamide, Furfural, Butanoic acid, 2-Furancarboxaldehyde, 5-methyl, Phenol, 2-Hydroxy-gamma-butyrolactone, 1-Amino-2,6-dimethylpiperidine, 4-Hydroxy-2,5-dimethyl-3(2H)-furanone, 3H-Pyrazol-3-one, 2,4-dihydro-2,4,5-trimethyl, Cyclohexanecarboxylic acid 2-methyl, D-Allose, 1-Methyl-2-pyrrolidone-4-carboxamide, a-D-Mannopyranoside, methyl, β-carotene, Xanthophylls, Erythrodiol, palmitic acid, Myricetin, myricetin 3- O-arabinoside, Myricetin 3-O-L-rhamnoside, 3-Hexanone, 2,5-dimethyl, 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl, Benzenecarboxylic acid, 2-Furancarboxaldehyde, 5-(hydroxymethyl), Hydroquinone, Quercetin, Quercetin 3-galactoside, oleanolic acid, β-sitosterol, Stigmasterol, β-sitosterol- β-Dglucoside, n-hexacosanol, n-octacosanol, and (3Z)-Phycocyanobilin were used as ligand for docking analysis.

Statistical analysis

The data were calculated for the minimum six rats for all the parameters. Then the results were validated using one-way ANOVA followed by Student Newman-Keuls test. The results were represented by mean (±) standard deviation which was considered as the significant value at $P < 0.05$.

RESULTS

Effect of ALEML on weight assessment in MSU-induced rats

The weight of each rats were calculated to notice the *M. longifolia* weight gaining effect in the treatment of Gout while there is an increase in weight of rats in Group-5 but there is a decrease in weight of the Group-2 rats which has shown weight loss due to the accumulation of MSU coupled with the low intake of food by the rats when they are affected by Gout (Table 1).

Table 1: Weight assessment of rats during study period

Day	Group 1 NORMAL	Group 2 MSU	Group 3 MSU + ALEML	Group 4 MSU + IND	Group 5 ALEML
Day-1	239.66 ± 1.63	240.5 ± 1.87	259 ± 2.16 a*b*	245.5 ± 1.8 a*b*c*	250.5 ± 1.87 a*b*c*d*
Day-2	239.66 ± 1.63	235.16 ± 1.47 a*	259.33 ± 2.16 a*b*	245.53 ± 1.86 a*b*c*	252.5 ± 1.87 a*b*c*
Day-3	239.66 ± 1.63	233.33 ± 1.86 a*	259.5 ± 1.87 a*b*	245.53 ± 1.87 a*b*c*	253.5 ± 1.87 a*b*c*

Each value represents the mean ± SD of six rats. Comparisons were made as follows: a-Group-I vs Groups 2, 3, 4, 5; b- Group-II vs Group-III, 4, 5; c-Group-III vs Group-IV, 5; d-Group-IV vs Group-V. The symbols represent statistical significance at *p < 0.05. Statistical analysis was calculated by one-way ANOVA followed by the Student Newman–Keul's test.

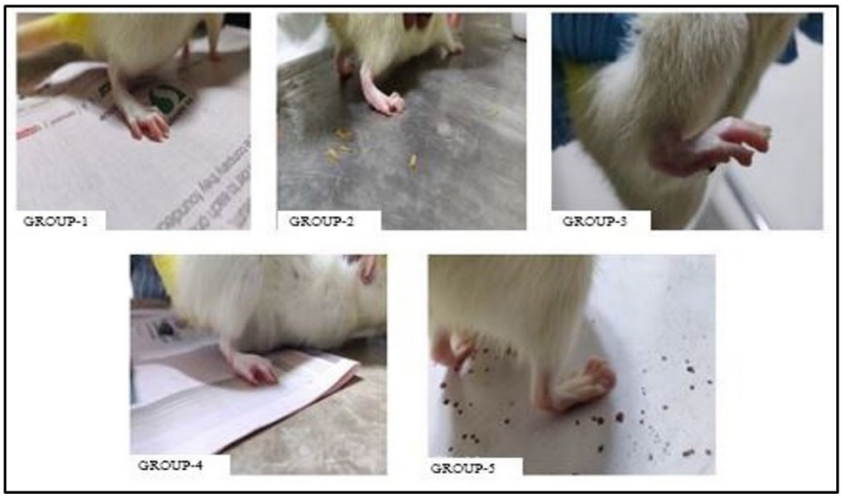


Figure 1: Paw volume analysis

Table 2: Effect of *M. longifolia* on acid phosphatase levels

Group	Liver	Spleen	Kidney
Group 1 NORMAL	1.61 ± 0.16	1.89 ± 0.12	3.12 ± 0.13
Group 2 MSU	3.60 ± 0.22 a*	3.34 ± 0.15 a*	4.17 ± 0.14 a*
Group 3 MSU + ALEML	2.18 ± 0.13 a*b*	2.21 ± 0.12 a*b*	3.32 ± 0.15 b*
Group 4 MSU + IND	2.26 ± 0.09 a*b*c*	2.13 ± 0.05 b*	3.5 ± 0.14 a*b*
Group 5 ALEML	1.81 ± 0.14 b*d*	2.05 ± 0.67 b*	3.08 ± 0.10 b*d*

Each value represents the mean ± SD of six rats. Comparisons were made as follows: a-Group-I vs Groups 2, 3, 4, 5; b- Group-II vs Group-III, 4, 5; c-Group-III vs Group-IV, 5; d-Group-IV vs Group-V. The symbols represent statistical significance at *p < 0.05. Statistical analysis was calculated by one-way ANOVA followed by the Student Newman–Keul's test.

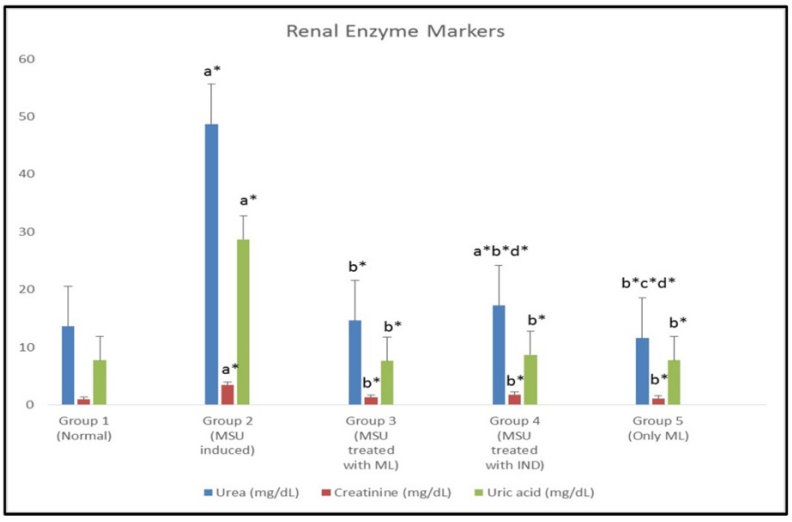


Figure 2: Effect of MSU on renal markers on study groups

Each value represents the mean ± SD of six rats. Comparisons were made as follows: a-Group-I vs Groups 2, 3, 4, 5; b- Group-II vs Group-III, 4, 5; c-Group-III vs Group-IV, 5; d-Group-IV vs Group-V. The symbols represent statistical significance at *p < 0.05. Statistical analysis was calculated by one-way ANOVA followed by the Student Newman–Keul's test.

Effect of ALEML on Paw volume study

The paw volume on MSU rats shows inflammation. Paw volume on other groups was represented in Figure 1. ALEML treated rats have shown no inflammation which is similar to normal control group.

Effect of ALEML on acid phosphatase levels

The Control rats were found to have a normal range of acid phosphatase while the MSU induced Group-2 rats it showed a higher level of acid phosphatase indicating the damage of system leading to a rise in of these marker levels in the organ which indicates the hyper-accumulation of MSU in the system (Table 2). The treated groups displayed positive but varying results, but mostly being in a controllable level. While comparing both the Group-3 and Group-4 the former showing a better control over this marker. The acid phosphatase level of liver, spleen and kidney were represented in Table 2 that was denoted by μmoles×10^−2.

Effect of ALEML on renal enzyme markers

Urea, Creatinine and Uric acid are the renal enzyme markers that are found to be in higher level when a person has Gout or when the person has higher risk for Gout. The Control rats displayed normal range of Urea, Uric acid and Creatinine while the MSU induced rats showed a higher release of these markers in serum which indicates the hyper-accumulation of MSU in the system (Figure 2). The treated groups displayed positive but varying results, on comparison the Group-3 rats treated with ALEML showed better curative effect than the Group-4 which was treated with Indomethacin but showed a significant increase in the release of all the renal enzyme markers. The Group-5 rats were given ALEML only and it maintained the level of these renal enzyme markers.

Effect of ALEML on antioxidants

The antioxidant assays like SOD, CAT and GSH were carried out on liver, kidney and spleen (Figure 3). The Control rats displayed was found to have a normal range of antioxidant in liver while the MSU induced rats showed a lower level of antioxidant indicating the damage of liver tissues leading to degeneration of these marker levels in the organ which indicates the hyper-accumulation of MSU in the system. The treated groups displayed positive but varying results, on comparison the Group-3 rats treated with ALEML showed better antioxidant effect than the Group-4 which was treated with Indomethacin but showed a significant decrease in the release of all the antioxidant markers. The Group-5 rats were given ALEML only and it maintained the level of these antioxidant markers.

Effect of ALEML on histopathology analysis of kidney in Gout-induced rats

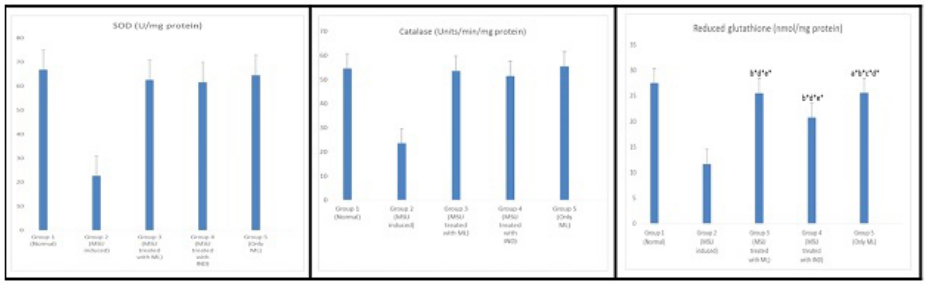
The kidney histopathology shows the effect of MSU in group-2 as it was compared with the control rats and group-5 shows normal renal tissue (Figure 4). The ALEML treated group also shows normal glomerular indicating that the drug protected kidney as well as it prevented the damage caused because of MSU. The group-4 rats also showed tubular necrosis which indicates the fact that indomethacin damages the kidney.

Effect of ALEML on histopathology analysis of Paw in Gout-induced rats

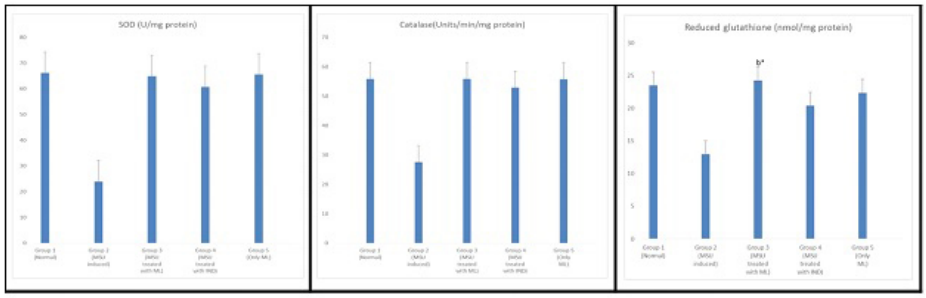
The paw histopathology shows the effect of MSU in group-2 as it was compared with the control rats and group-5 shows normal paw collagen (Figure 5). The ALEML treated group also shows normal collagen indicating that the drug protected paw as well as it prevented the damage caused because of MSU. The group-4 rats also showed normal paw collagen which indicates the fact that indomethacin also works as a good drug for Gout.

Effect of ALEML on docking analysis

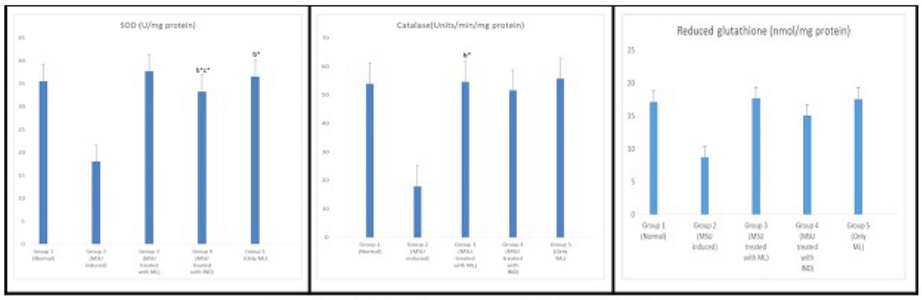
Score, Area and ACE of the ligand with highest affinity towards each of the receptors were represented in Table 3. The interaction between IL-1 β receptor and Quercetin molecule is after docking. This interaction involved GLU-64, GLU-64, SER-40, SER-40, TYR-68, TYR-90 bonds between ligands and receptor (Figure 6a). The interaction between PRPSAP-1 receptor and Myricetin molecule is after docking. This interaction involved GLN-141, GLN-141, LYS-85, LYS-116, LYS-124, LYS-124, THR-82, SER-120 bonds between ligands and receptor (Figure 6b). The interaction between Xanthine dehydrogenase receptor and Quercetin molecule after docking. This interaction involved ARG-79, ASN-1070, ASN-1070, ARG-791, GLU-762, ARG-791 bonds between ligands and receptor (Figure 6c). The interaction between PDZK-1 receptor and Myricetin molecule is after docking. This interaction involved LYS-16, LYS-16, LEU-25, HIS-69, LYS-77, LYS-16 between ligands and receptor (Figure 6d). The interaction between NLR Family Pyrin Domain Containing 3 receptor and Myricetin-3-O-arabinoside molecule is after docking. This interaction involved ARG-79, ASN-1070, ASN-1070, ARG-791, GLU-762, ARG-791 bonds between ligands and receptor (Figure 6e). The interaction between nuclear receptor corepressor-2receptor and Myricetin-3-O-arabinoside molecule is after docking. The interaction involved GLU-62, GLU-63, GLU-63, LYS-86 bonds between ligands and receptor (Figure 7f). The interaction between Toll like receptor-4 and Myricetin-3-O-arabinoside molecule after docking. The interaction involved ASP-50, LYS-47, ILE-48, ILE-48, SER-76, SER-71, SER-73, SER-73, GLY-70 bonds between ligands and receptor (Figure 7g). The interaction between Glucokinase regulator receptor and Quercetin 3-galactoside molecule is after docking. The interaction involved HIS-9, GLU-32, GLU-32, ARG-525, ARG-525, ILE-11bonds between ligands and receptor (Figure 6h). The interaction between ABCG-2 gene receptor and Quercetin 3-galactoside molecule after is docking. The interaction involved LYS-616, TYR-613, TYR-613, ASN-604, GLN-424, GLN-424, LYS-616 bonds between ligands and receptor (Figure 6i).



Effect of MSU on liver antioxidant



Effect of MSU on kidney antioxidant



Effect of MSU on spleen antioxidant

Figure 3: Effect of MSU on antioxidant assay on study groups

Each value represents the mean ± SD of six rats. Comparisons were made as follows: a-Group-I vs Groups 2, 3, 4, 5; b- Group-II vs Group-III, 4, 5; c-Group-III vs Group-IV, 5; d-Group-IV vs Group-V. The symbols represent statistical significance at *p < 0.05. Statistical analysis was calculated by one-way ANOVA followed by the Student Newman–Keul's test.

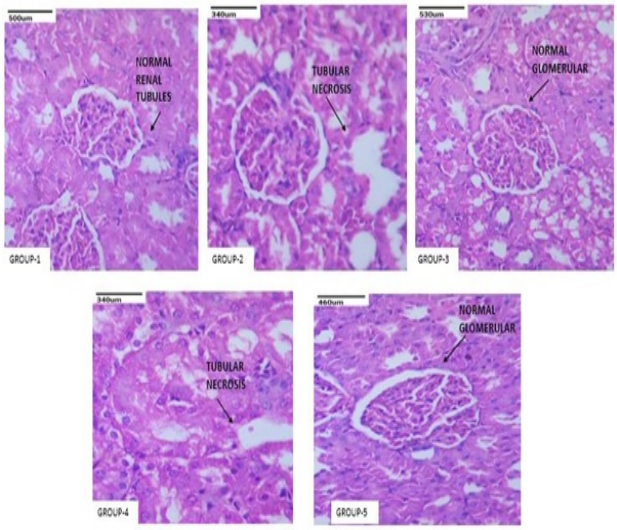


Figure 4: Effect of MSU on kidney histopathology on study groups

The kidney histopathology shows the effect of MSU in group-2 as it was compared with the control rats and group-5 shows normal renal tissue. The ALEML treated group also shows normal glomerular indicating that the drug protected kidney as well as it prevented the damage caused because of MSU. The group-4 rats also showed tubular necrosis which indicates the fact that indomethacin damages the kidney.

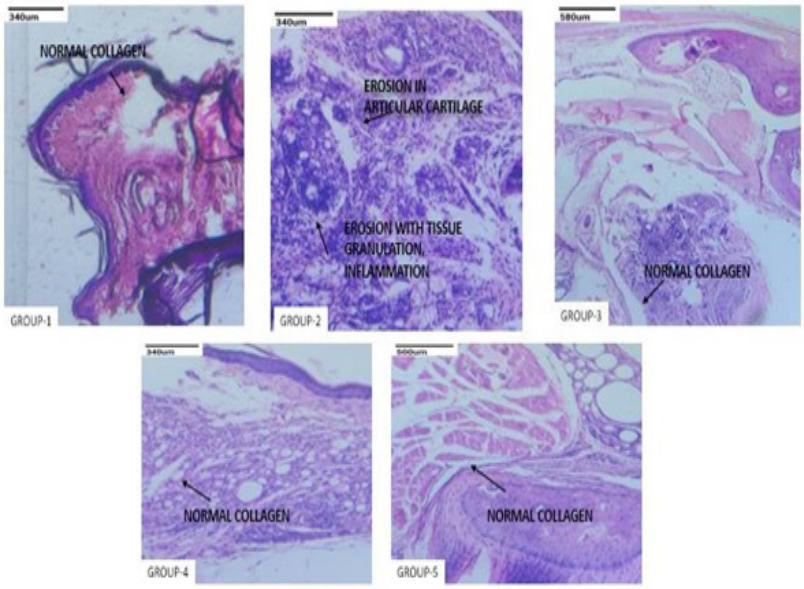


Figure 5: Effect of MSU on paw histopathology on study groups

The paw histopathology shows the effect of MSU in group-2 as it was compared with the control rats and group-5 shows normal paw collagen. The ALEML treated group also shows normal collagen indicating that the drug protected paw as well as it prevented the damage caused because of MSU. The group-4 rats also showed normal paw collagen which indicates the fact that indomethacin also works as a good drug for Gout.

Table 3: Score, Area and ACE of best docked complex

S. No.	Receptor	Ligand	Score	Area	Ace
1	Interleukin-1 β	Quercetin	2354	258.20	-119.46
2	PRPSAP-1	Myricetin	4498	496.10	-136.31
3	Xanthine dehydrogenase	Quercetin	5744	660.70	-116.28
4	PDZK-1	Myricetin	3566	382.80	-112.98
5	NLR Family Pyrin Domain Containing 3	Myricetin-3-O-arabinoside	5422	660.30	-99.45
6	Nuclear receptor corepressor-2	Myricetin-3-O-arabinoside	4282	574.80	-222.97
7	Toll like receptor-4	Myricetin-3-O-arabinoside	5674	667.30	-248.66
8	Glucokinase regulator	Quercetin-3-Galactoside	5688	655.20	-229.78
9	ABCG-2	Quercetin-3-Galactoside	5712	602.10	-153.44

DISCUSSION

Elevated uric acid level is the important risk factor of Gout which is a multifactorial disease which can affect 73% of the offspring's genetically[17]. URAT1 plays a vital role in maintenance of uric acid levels in the body[18]. Chromosome 4q25 has been found to be the genomic region which is involved with gout which was found evident due to a study done in male Chinese Han population. The intake of ALEML leads to weight gain which was evident from the Table 5 that the rats which were given only ALEML that is group-5 which gained a significant amount of weight ranging from 2-5 grams individually. When the rats were subjected to MSU through IP on their joints they acquired Gout which led to swollen paw. When untreated the swelling increased which can be seen in group-2 from the Figure 3. The rats treated with ALEML showed a significant reduction in swelling which can be seen in group-3 from the Figure 4. The paw size reduced up to 0.2 cm in group-3 when compared with the other groups with gout which proves ALEML is a better cure for gouty arthritis.

The renal markers Urea, Uric acid and Creatinine were assessed in the study in which the results show increased levels of all these markers in Group-2 and there was a significant increase from the normal levels in group-4 which shows that the kidney may got damaged due to the intake of Indomethacin. But, group-3 rats which were treated with ALEML showed no damage to the kidney which is assessed by the level of the kidney markers. This shows that kidney was restored the damages[19]. The Acid phosphatase (ACP) levels in the liver, kidney and spleen were assessed in the study in which the results show increased levels of this ACP in group-2 and there was a significant increase from the normal levels in group-4 liver and spleen which shows that the system got damaged due to the intake of Indomethacin[20]. But, group-3 rats which were treated with ALEML showed no increase in the levels of ACP in liver and spleen but in kidney there was a slight increase in the levels of ACP, group-5 also didn't show an increase in levels of ACP at all the three organs[21].

The Antioxidant markers SOD, CAT and Reduced Glutathione were assessed in the study on kidney, spleen and liver in which the results show decreased levels of all these antioxidants in Group-2 and there was a significant decrease from the normal levels in group-4. And, group-3 rats which were treated with ALEML showed similar levels of antioxidants which like Control group and group-5. This proves that ALEML can be a good antioxidant rich drug[22]. The histopathology analysis of kidney shows clearly that there was tubular necrosis in group-2 and group-4 rats which means the kidneys were damaged in these groups but not in group-3 or group-5. This proves that ALEML even though increases the level of ACP in a small range it doesn't affect kidney while taken as a curative drug for gout[23]. The histopathology analysis of paw shows clearly that there was erosion in articular cartilage coupled with tissue granulation and inflammation in group-2 which has been affected from gout but in group-4 and group-3 rats has normal collagen and articular cartilage. This proves that ALEML can be used as a curative drug

for gout[1]. From the *In-silico* docking analysis done it was evident that the Toll like receptor-4 has been docked strongly to Myricetin-3-O-arabinose with 9 bonds in number. The receptor was found to be bonded at the following residual sites H-41,O-32,O-18,O-7,O-20,H-47,O-27,O-28,O-28 present on the ligands they were docked with the following sites ASP-50,LYS-47,ILE-48,ILE-48,SER-76,SER-71,SER-73,SER-73,GLY-70 of the receptor.

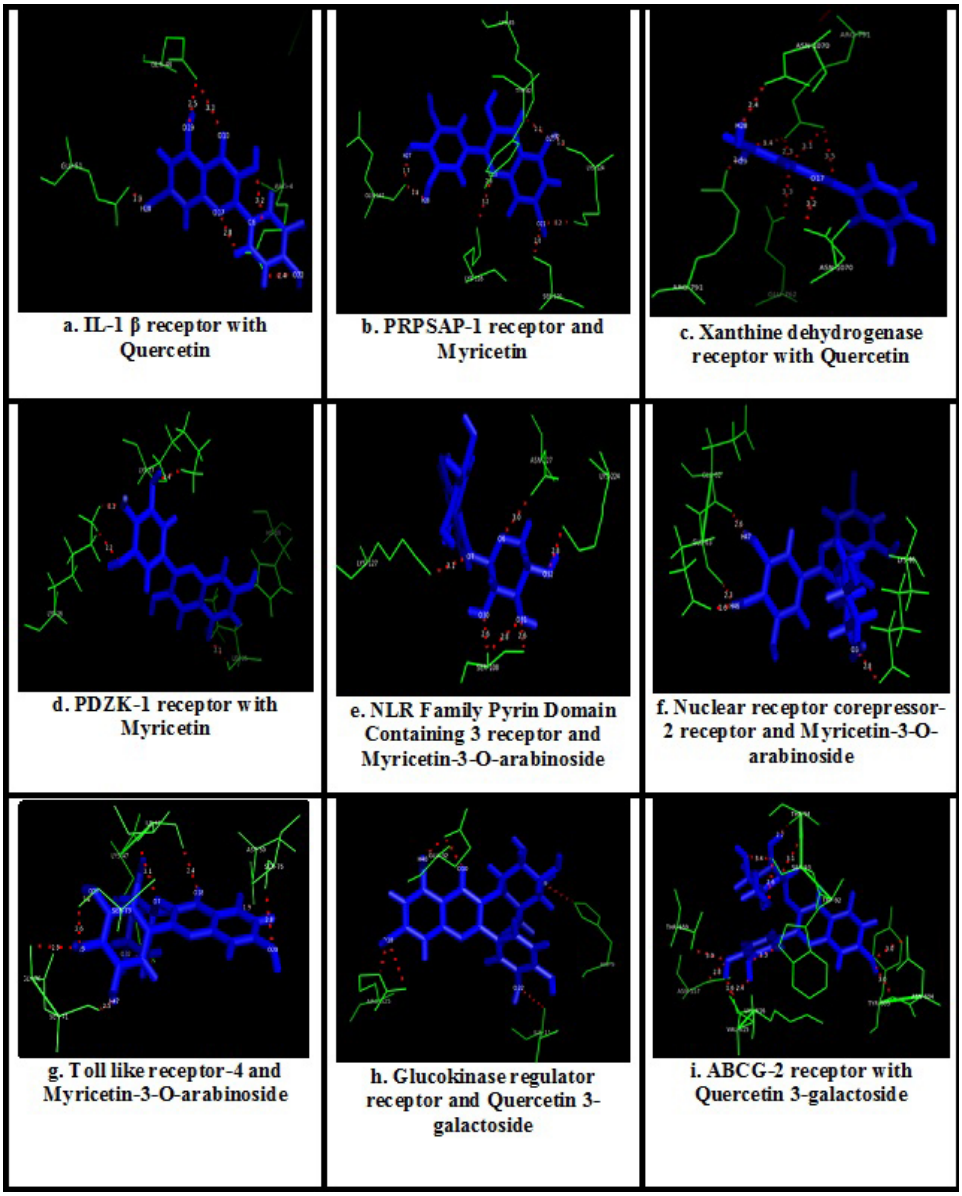


Figure 6: Docking analysis

Docked complex of Receptor (Orange) and Ligand (Gray) with bonding (Yellow)

CONCLUSION

The current study has shown the anti-arthritic potential of ALEML against MSU-induced rats through antioxidant assay, renal enzyme activity and histopathology analysis. The treatment has confirmed ALEML potential activity as an antioxidant, anti-inflammatory and anti-arthritic agent. Also, from the *In-silico* docking analysis done it is evident that different receptors have different ligand with greater affinity to bind. Based on the interaction pattern one can target these genes and design effective curative drugs for gout.

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