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Pharmacological Evaluation for the Anti-rheumatoid Arthritis in Albino Rat

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ABSTRACT

Backgrounds & Objectives :- The aim of present study was to evaluate the anti-rheumatoid arthritis activity of Ficus racemosa linn. (family :Mareaceae). Literature survey revealed that Ficus racemosa has potent anti-inflamatory activity. Thus providing us the background to evaluate the anti-arthritis activity.

Methods :- The ethanol extract of the leaves of the ficus racemosa was extracted by soxhlet extraction method. The extract was then subjected to phytochemical tests and the carbohydrates, phenols, tannins, alkaloids, flavonoids, steroids and tritrepenoids were found. The acute toxicity of the ethanolic extract was examined according to the OECD guidelines. The extract was then evaluated for the anti-rheumatoid arthritis by using formaldehyde induced arthritis in rats experimental model. Paw volume was then calculated.

Results:- The ethanolic extract of leaves of Ficus racemosa produced a dose dependent activity in all experimental models. The anti-arthritis activity efficacy was significantly comparable to standard (Diclofenac sodium 13.5 mg/kg) and showed reduced paw volume om the 10th day in a dose dependent manner. The ethanolic extract o the leaves of the Ficus racemosa was used at a dose of 100 mg/kg and 200 mg/kg. also the acute toxic studies revealed No observable Adverse Effect Level (NOVEL) at the dose of 5000 mg/kg.

Conclussions:- Result of the present study suggest that the anti-arithritc activity of ethanolic was due to the interplay between its anti-inflamatory and disease modifying activities, thus supporting its therapeutic use.

I. INTRODUCTION

India has in ancient heritage of traditional medicine. The Materia Medica of India provides a great deal of information of the folklore practices and traditional aspects of therapeutically important natural products. Indian traditional medicine is based on various systems including ayurveda, Siddha, Unani and Homeopathy. The evaluation of these drugs is primarily based on phytochemical, pharmacological and allied approaches including various instrumental techniques such as chromatography, microscopy and others. With the emerging worldwide interest in adopting and studying traditional systems and exploiting their potential based on different health care systems, the evaluation of the rich heritage of traditional medicine is essential.

According to Ventakamaran **(Ventakamaran et al., 1972)**, the taxonomy treatment of the Moraceae family constitutes large taxa of over fifty enera and nearly 1400 species, including some important groups like Artocarpus , Morus and Ficus. The The genus Ficus constitutes an important group of **(Shiksharthi et al., 2011)** trees with immense medicinal value. It is a sacred tree of Hindus and Buddhists. Several species belonging to the genera of Ficus were reported to contain furano coumarins which is an important plant phototoxins **(Swain et al., 1990) .** Ventakamaran also claimed that Moraceae family contains phytochemistry related to flavonoids, flavonoids with insoprenoid substituents and stilbenes. Antioxidants from figs can protect lipoproteins in plasma from oxidation and produce a significant increase in plasma antioxidant capacity **(Duenas et at., 2008)**.

It is found throughout the year, grows in evergreen forests, moist localities and bank of streams, deciduous forests, to the elevation of 1800m above sea level, often cultivated in villages for shade and its edible fruits **(Indian Medicinal Plants, 1996, Chopra et al., 1992 Chopra et al., 1958 and Medicinal Plants of india, 1956)**. It is commonly known as Gular fig, Cluster fig in English, Gular in Hindi and as Udumbara in Sanskrit **(Chopra et al., 1986 and Atal et al., 1982)**.

The literature survey reveals that no reports were found on the anti arthritic activity of the leaves extract of Ficus racemosa. This prompted us to investigate the anti-arthritic and anti-ulcer activity of Ficus racemosa leaves.

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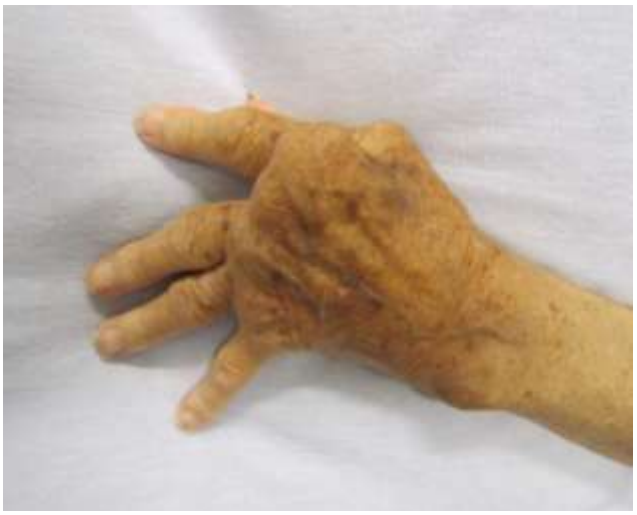
Fig: Plant of Ficus racemosa

For the anti arthritics activity formaldehyde induced ulcer rat model was utilized to evaluate the anti arthritic effect. Rheumatoid arthritis is a systemic auto-immune disease. Symmetrical inflammatory polyarthritis is the primary clinical manifestation. The arthritis usually begins in the small joints of the hands and the feet, spreading later to the larger joints the inflamed joint lining or synovium extends and then erodes the articular cartilage and bone, causing joint deformity and progressive physical disability. Extra-articular features include nodules, pericarditis, pilmonary fibrosis, peripheral neuropathy and amyloidosis.

It may be define as "Rheumatoid arthritis is a systemic, chronic inflammatory disease affecting multiple tissues but principally attacking the joints to produce a non supportive proliferative synovitis that frequently progresses to destroy auricular cartilage and underlying bone with resulting disabling arthritis.



1.1 Pathogenesis:-

There is little doubt that there is a genetic predisposition to rheumatoid arthritis and that the joint inflammation is immunologically mediated.

It is proposed that the disease is initiated- in a genetically predisposed individual-by activation of helper T cells responding to some arthritogenic agent, possibly microbial.

In turn, the activated CD4+ cells produce cytokines that will.

1. Activate macrophages and other cells in the joint space, releasing degradative enzymes and other factors that perpetuate inflammation and
2. Activate B cells, resulting in the production of antibodies, some of which are directed against self-constituents.

The rheumatoid synovium is rich in both lymphocyte- and microphage-derived cytokines. The activity of these cytokines accounts for many features of rheumatoid synovitis; not only are they pro-inflammatory, some, such as IL-1 and TGF-a, cause synovial cell and fibroblast proliferation. They also stimulate synovial cell and chondrocyte

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secretion of proteolytic and matrix-degrading enzymes.

1.2 Diagnosis of Rheumatoid Arthritis:-

Blood Tests:- Various blood tests may be used to help diagnose rheumatoid arthritis, determine its severity, and detect complications of the disease.

Rheumatoid Factor:- In rheumatoid arthritis, antibodies in the blood that collect in the synovium of the joint are known as rheumatoid factor**.** In about 80% of cases of rheumatoid arthritis, blood tests reveal rheumatoid factor. It can also show up in blood tests of people with other diseases.

Erythrocyte Sedimentation Rate:- An erythrocyte sedimentation rate (ESR or sedimentation rate) measures how fast red blood cells (erythrocyte) fall to the botton of a fine glass tube that is filled with the patient's blood. The higher the sedimentation rate the greater the inflammation.

C-Reactive Protein:- High level of C-reactive protein (CRP) are also indicators of active inflammation. Like the ESR, a high result does not indicate what part of the body is inflamed, or what is causing the inflammation.

Anti-CCP Antibody:- The presence of antibodies to cyclic citrullinated peptides (CCP) can identify rheumatoid arthritis years before symptoms develop. In combination with test for rheumatoid factor, the CCP antibody test is the predictor of which patients will go on to develop severe rheumatoid arthritis.

Tests for Anemia:- Anemia is a common complication. blood tests determine the amount of red blood cells (hemoglobin and hematocrit) and iron (soluble transferrin receptor and serum ferritin) in the blood.

Imaging Tests:-

X-rays generally have not been helpful to detect the presence of early rheumatoid arthritis because they cannot show images of soft tissue. However, x-rays can help track the progression of joint damage over time. The doctor may also order other imaging tests, such as ultrasound, or magnetic resonance imaging (MRI).

II. EXPERIMENTAL WORK

2.1Collection of Plant Material:-

The leaves were collected, identified and then air dried. The leaves were collected from the Local garden at Lucknow, U.P. (India). The leaves were shade dried and air until a constant weight was obtained which took approx 20 days and then were processed for size reduction by using cutter mill (portable mixer). Then crushed material was passed through 40# sieve (coarse powder) for uniform size.

The leaves were taxonomically identified and authenticated by Dr. D. C. Saini at Birbal Sahini Institute of Plant botany, Lucknow, UP, India with a reference number 13395 also the leaves were stored in herbarium and submitted for any future reference.

2.2Extraction of Plant Material:-

The techniques for separation of active substance from crude drug is called as extraction. (Kulkarni et al., 2006).

2.3 Preparation of Leaf Extract:-

Dried leaves were pulverized into coarse powder the powder weighed about 7.5kg. followed by extraction of about 30 gm of drug with a soxhlet apparatus with 250 ml of 95% ethanol (solvent) for about 10 hours. The obtained extract was concentrated by slow evaporation process. **(Harbone et al., 1973).** The obtained extract was then kept in moisture free container and used for phytochemcial analysis thereafter.

2.4 Qualitative Phytochemical Analysis:-

2.4.1Test for Carbohydrates:-

Fehling's Test (For Reducing Sugars):-

Test solutions were treated with few drops of Fehling's reagent A and B [Dissolve 34.66 g of Copper sulphate in distilled ater and make upto 500ml (solution A).

Dissolve 173 g of potassium sodium tartarate and 50 g of sodium hydroxide in distilled water and make volume upto 500 ml (solution B)]. Mix two solutions in equal volume prior to use for detection of reducing sugars. It gives brick red color on warning with the test sample.

Molisch's Test:-

Test solution treated with few drops of Molisch's reagent (10 g a-naphthol in 100 ml of 95% ethanol). Then 2 ml of conc. sulphuric acid is added slowly from sides of the test tube shows purple ring at the junction of two layers.

Barfoed's Test:-

One ml of a sample solution is placed in a test tube. 3 ml of Barfoed's reagent (a solution of cupric acetate and acetic acid) is added. The solution is then heated in a boiling water bath for three minutes, formation of a reddish precipitate within three minutes.

2.4.2Test for Proteins:-

Millons Test:-

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Test solutions treated with Millon's reagent [Dissolve 1 g of mercury in 9 ml of fuming nitric acid, after cooling; add equal volume of distilled water]. Protein is stained red on warming.

Biuret Test:-

Add 1 cm3 of sodium hydroxide solution (40% or bench solution) and 1% copper (II) sulphate solution drop wise - drop by drop - to the sample skake well and allow the mixture to stand for 5 minutes. The solution turns from blue to violet.

2.4.3Test for Alkaloids:-

5 ml of the prepared extracts were evaporated to dryness. The residue was taken in 5 ml of hydrochloric acid, saturated with sodium chloride and filtered. The filtrate was separately tested with following reagents:

Dragendorff's Test:-

The acidic solution treated with Dragendorff's reagent (potassium bismuth iodide) gives orange precipitate.

Mayer's Test:-

Test solution with Mayer's reagent (potassium mercuric iodide) gives cream colored precipitate.

Hager's Test:-

The acidic solution treated with Hager's reagent (saturated picric acid solution) gives yellow precipitate.

Wagner's Test:-

Test solution treated with Wagner's reagent (iodic-potassium iodide solution) gives reddish brown precipitate.

2.4.4Test for Steroids (Libermann Burchard Test):-

To the test solution few drops of acetic anhydride were added and conc. sulphuric acid added from sides of test tube, shaken and allowed to stand. Lower layer turns bluish green indicating the presence of sterols.

2.4.5Test for Saponins (Foam Test):-

Test solution on shaking shows foam formation, which is stable for at least 15-20 minutes.

2.4.6Test for Tennins:-

Gelatin Test:-

Test solution when treated with lead acetate solution gives a white precipitate, when a 1 % solution of gelatin containing 10% sodium chloride is added.

Lead Acetate Test:-

The test residue of each extract was taken separately in water, warmed and filtered. Tests were carried out with the filtrate using a 10 % w/v solution of basic lead acetate in distilled water was added to the teat filtrate. If precipitate is obtained , tannins are present.

$Fecl_3$ Test:-

The test residue of each extract was taken separately in water, warmed and filtered. tests were carried out with the filtrate using A 5 % solution of ferric chloride in % alcohol was prepared. Few drops of this solution was added to a little of the above filtrate. If dark green or deep blue color is obtained , tannins are present.

2.4.7Test for Flavonoids:-

Shinoda Test:-

One ml of extract , 5-10 drops of dilute HCL was added followed by a small amount Mg (magnesium) and the solution was boiled in a water- Bath for a few minutes. Majenta colour shows the presence of Flavonoids.

Aqueous NAOH Test:-

To 2-3 ml of extract , few drops of sodium hydroxide solution were added in a test tube. Formation of intense yellow colour that became colourless on addition of few drops of dilute HCI indicated the presence of flavonoids.

Conc. Sulphuric Acid Test:-

A fraction of the extract was treated withconcentrated H2SO4 and observed for the formation of orange color.

2.4.8Test for Triterpenoids (Noller's Test):-

One ml of extract with tin and thionyl Chloride[1 ml] were added. Heat it on a water-bath purple colour shows the presence of triterpenoids.

2.4.9Test for Amino Acids:-

Ninhydrin Test:-

The ninhydrin reagent is 0.1 %w/v solution of ninhydrin in n-butanol. A little of this reagent was added to the test extract. A violet or purple color is developed , if amino acids are present.

Millons Test:-

Test solutions treated with Millon;s reagent (Dissolve 1 g of mercury in 9 ml of fuming nitric acid, after cooling; and equal volume of distilled water . Protein is stained red on warming).

III. EXPERIMENTAL ANIMAL MODEL EMPLOYED:-

Pharmacological Methods for the Evaluation of Anti-rheumatoid Arthritis Activity:-

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General :-

Different types of animal models have been devised to evaluation the Antiulcer activity some of them are as follows:-

Complete Freumd's Adjuvant Induced Arthritis:-

Arthritis was induced by a single intra-dermal injection (0.1 ml) of Complete Freun's adjuvant containing 1.0 mg dry heat-killed Mycobacterium tuberculosis per milliliter sterile paraffin oil into a foot pad of the left hind paw of male rats. **(Mizushima et al., 1972),** a glass syringe (1 ml) with the locking hubs and a 26G needle was used for injection. The rats were anesthetized with ether inhalation prior to and during adjuvant injection, as the very viscous nature of the adjuvant exerts difficulty while injecting. The swelling paws were periodically examined (up to 21 days) in each paw from the ankle using Digital Plethysmometer. **(Winter et al., 1962).**

Formaldehyde Induced Arthritis:-

The anti-arthritis activity can also be evaluation by using formaldehyde induced arthritis model in Wistar albino rats. On the 0^{th} day, the basal paw volume of left hind paw of each animal will measured using Plethysmometer. On day 1 and day 3, they will be injected into the sub-plantar region of the left hind paw with 0.1 ml of 2 % v/v formaldehyde in normal saline. Paw volume of injected paw will be measured daily. **(Brownlee, 1950)**

Animals:-

Wistar swiss albino rats of either sex weighing 150-200 gm and of 8-10 weeks of age were procured from animal house of Azad Institute of Pharmacy and Research, Lucknow , U.P., India. **CPSCEA** registration number 1146/ac/07 cpsc. They were housed in polypropylene cages, 3 animal per cage. The animals were acclimatized to standard laboratory conditions i.e., maintained in a constant temperature 25±2 °C and humidity 50-55% , 12 h of light /dark cycle and allowed access to water and food ad libitum. All experimental procedures were carried out in accordance wth the CPCSEA Guidelines and were approved by the Institutional Animal Ethical Committee at Azad Institute of Pharmacy and Research , Lucknow , U.P., India.

Experimental Animal Model Employed:-

Formaldehyde Induced Arthritis in Experimental Animals:-

Wistar rats of either sex weighing between 150-200 g. will be randomly selected. They will be grouped in a group of 6 animals each into 4groups. On the 0^{th} day 1 and day 3, they will be injected into the sub-planter region of the left hind paw with 0.1 ml of 2 % v/v formaldehyde in normal saline solution. Dosing with standard drug, Diclofenac sodium and extract will be started on same day and continued for 10 days. Groups I served as –Arthritis control, Group II – Diclofenac Sodium (standard drug) treated. Group III & IV – Ficus racemosa treated 100mg/kg & 200 mg/kg body eight respectivity. Paw volume of injected paw was measured daily.

Animal study protocol

- **Dose selection.** Dose selection was done on the basis of previous literature study and acute toxicity studies.
- **Standard drug** Dicloenac Sodium

Table 3.2 Animal study protocol for formaldehyde induced Arthritis Experimental Model

GROUP	TREATMENT	DOSE AND ROUTE OF ADMINIDTRATION
1.	Normal control	10 ml/kg, oral +0.1 ml of 2% v/v formaldehyde in normal saline solution, injection in subplanter region.
2.	Standard (Diclofenac)	13.5mg/kg, oral daily for 10 days +0.1 ml of 2% v/v formaldehyde in normal saline solution , injected in subplanter region on first and third day.
3.	Test (Treated)	100 mg/kg, oral daily for 10 days +0.1 ml of % v/v Formaldehyde in normal saline solution , injected in subplanter region on first and third day.
4.	Test (Treated)	200 mg/kg, oral daily for 10days +0.1 ml of 2% v/v formaldehyde in normal saline solution , injected in subplanter region on first and third day.

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Acute Toxicity Study:-

The highest attainable dose 5000 mg/kg was used in Organization for Economic Cooperation Development **(OECD)** guideline 423. Three female rats, each sequentially dosed at intervals of 48 hrs, were used for the test. Once daily cage side observations included changes in skin, fur eyes, mucous membrane (nasal), autonomic (salivation, lacrimation, perspiration , piloerection, urinary incontinence, and defecation) and central nervous system (drowsiness, gait, tremors and convulsion) changes. Mortality, if any , was determined over a period of 2 weeks

IV. RESULTS AND DISSCUSSIONS

Preliminary Phytochemical Screening:

The preliminary phytochemical screening results are showed the presence of the following constituent as shown in the table:-

Table 4.1 Preliminary Phytochemical Screening of Ethanolic extract of Leaf (F. racemosa)

S.NO	CONSTIUENTS	TESTS	OBSERVATION
1.	Carbohydrates	Molish's Test	+
		Fehling's Test	+
		Barfoed"s Test	+
2.	Proteins	Millon's Test	-
		Biuret Test	-
3.	Amino Acids	Ninhydrin Test	-
		Millon's Test	-
4.	Fixed oil and Fats	Saponification Test	-
5.	Saponins	Foam Test	+
6.	Phenolics and Tannins	$Fecl_3$ Test	+
		Gelatin Test	+
		Lead acetate Test	+
7.	Alkaloids	Dragondroff's Test	+
		Mayer's Test	+
		Hager's Test	+

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		Wagner's Test	+
8.	Flavonoids	Aqueous NaOH test	+
		Conc. H_2SO_4 Test	+
		Shinoda's Test	+
9.	Steroids	Libermann Burchard's Test	+
10.	Tritrepenoids	Noller's Test	+

Acute Toxicity Study:-

In acute toxicity study, ethanolic extract of leaves at a dose of 5000 mg/kg caused neither visible signs of toxicity nor mortality. Generally , a very slight reduction in body weight gain and internal organ weight is simple and sensitive index of toxicity after exposure to toxic substance . Furthermore, gross examination of internal organs of all rat revealed no detectable abnormalities. Thus it can be concluded that ethanolic extract of leaves is virtually non toxic.

S.No.	Group	Ulcer Index (mean ±S.E.M)	Percentage Inhibition
1.	Control (Ethanol 1 ml/200g)	22.8 ±0.237	
2.	Treated 100 mg/kg (FGLE)	12.7 ± 0.753**	44.29
3.	Treated 200 mg/kg (FGLE)	8.867±0.524**	61.10
4.	Standard (Ranitidine 50 mg/kg)	4.867±0.575**	78.65

Gross apprences of the Rat stomach of the different animal groups have been showed through the following figures:-

Histopathological Analysis:-

The Microscopy histopathology of rat stomach revealed sub mucosa showed lymphocytic collections. The mucosal layer is unremarkable. All

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the tissue showed a part of mucosa replaced with stratified squamous epithelium showing kertain formation at the surface in a dose dependent manner.

Anti-Rheumatoidarithritc Activity:-

The anti-arthritic activity was evaluation by using formaldehyde induced arthritis model in Wistar albino rats. The assessment made on the 10th day showed that, treatment with Diclofenac sodium treated group, FGLE 100 mg/kg and 200 mg/kg significantly reduced (P<0.01) the swelling in the injected (left) hind paw as compared to the control animal group.

On the 10th day FGLE treated animals showed inhibition of paw edema while Diclofenac sodium treated animals showed maximum inhibition of paw edema. The result are shown in Mean paw volume of formaldehyde induced arthritis rat model. Data are expressed as means ±S.E.M. (n = 6). P<0.01 FGLE (100 mg/kg, 200mg/kg) and Diclofenac sodium (13.5 mg/kg) for versus control group using ANOVA followed by Dunnett's test.

S.NO	Group	Day0	Day 8	Day 9	Day 10
1.	Control	0.935± 0.0076	1.975± 0.0084	1.951± 0.0094	1.948± 0.0079
2.	Standard	0.895± 0.0088	1.178± 0.0119**	1.158± 0.0094**	1.156± 0.0136**
3.	Treated 100 mg/kg	0.898± 0.0094	1.445±0.0115**	1.421± 0.0174**	1.40± 0.0136**
4.	Treated 200 mg/kg	0.900± 0.0096**	1.253± 0.0088**	1.241± 0.0104**	1.238± 0.0101**

Discussion for the Acute Toxicity Study:-

Ficus racemosa is a plant used worldwide in traditional medicine for the treatment of various ailments. The present work evaluation the acute toxicity of the ethanolic extract of its leaves. The results demonstrate a lack of toxicity following oral administration of the ethanolic extract at a dose as high as 5000 mg/kg in the acute toxicity study. In the acute toxicity study, extract caused neither treatment-related signs of toxicity nor mortality during the course of study. Therefore it is safe to state that its oral LD_{50} is greater than 5000 mg/kg. This resulted in classifying the extract as unclassified in the acute toxicity hazard categories according to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) (OECD, 2001). The substances that present LD_{50} higher than 5000 mg/kg by oral route can be considered practically non toxic. Therefore, it can be suggested that ethanolic extract of Leaves of Ficus racemosa is devoid of oral toxicity **(Kennedy et al., 1996).**

Discussion for Anti-rheumatoid Arthritis Activity:-

Formaldehyde is a phlogistic agent which shows signs and symptoms of inflammation, which can be assessed as increase in, paw thickness in mouse as a result of increased inflammation, edema and increased vascular permeation. Formaldehyde administered at a low dose induces an oedema which mainly results from a oedema which mainly depends on the released of neuropeptides, prostanoids, -hydroxytryptamine and histamine. Here in this study, rats treated with FGLE at two doses level showed decrease in total paw volume to their control group and is significantly comparable to Standard (Diclofenac sodium) mg/kg treated animals.

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