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Development, Standardization and Evaluation of an Antiarthritic Polyherbal Formulation

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Abstract: The objective of this study was to make an ayurvedic pill that can be used to treat gout. The capsules are tested according to WHO standards and also have pharmacological action done on them. The study's goals were: (i) Analysis of raw materials by doing the preliminary raw materials study, we can learn more about the formulation's raw materials or ingredients, and (ii) To use preformulation studies to make a pill with three herbs. The *Asparagus racemosus* extract could stop the protenase enzyme, protein denaturation and membrane lysis, but the effect depend on the amount. At a concentration of 0.8 mg, the enzymes that break down proteins, protenase, and membranes were most active. The standard medication, diclofenac sodium 0.2 mg contains more than this. *Lippia nodiflora* extract (0.8 mg) showed the most protenase enzyme, activity protein denaturation and membrane stability. This was less than the standard medication which is diclofenac sodium 0.2 mg. The extract from *Oldenlandia heynei* could stop protenase enzyme activity, protein denaturation and membrane lysis, but the effect depended on the amount. When the concentration was 0.8 mg the enzymes that break down proteins, protenase, and membranes were at their strongest. This was lower than the usual drug, diclofenac sodium 0.2 mg. The swelling in the paws went down in both the groups that were given the polyherbal mixture and the groups that were given diclofenac sodium. When paw edema was examined between the groups treated with the polyherbal mixture and the arthritic control group, there was a significant decrease. This shows that the polyherbal mixture stopped the changes in inflammation that come with arthritis, just like diclofenac sodium. This shows that the polyherbal mixture stopped the changes in inflammation that come with arthritis, just like diclofenac sodium.

Keywords: Rheumatoid arthritis, Herbal, Polyherbal, Antiarthritic, Inflammation

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Introduction

In rheumatoid arthritis, an autoimmune disease, the joints become inflamed, synovial cells grow, and articular cartilage breaks down (Chimagave *et al.*, 2020). It is a painful and disabling inflammatory condition that can make it very hard to move around because of the pain and damage to the joints. Inflammation is the body's reaction to damage, infection, or injury. It shows up as heat, redness, pain, swelling, and problems with how the body works (Singh *et al.*, 2015). Inflammation is a normal, defensive reaction to tissue damage caused by an impact, a harmful chemical, or a microbe. It is the body's way of getting rid of the irritation and stopping or killing the invading organisms. It also sets the stage for tissue repair (Surana and Mahajan, 2022). It starts when chemical messengers are released from damaged tissue and cells that have moved (Petchi *et al.*, 2015). It is a common disease that most often affects people in their 30s to 40s, with women being more likely to get it than men. Fingers and toes, wrists, knees, and ankles are the parts that get hurt the most (Ahire *et al.*, 2023). Extraarticular symptoms can happen and often do in people with serious disease. These can be in the eyes, lungs, blood vessels, heart, nerves, and mucosal tissue. The earliest known type of medicine is herbal medicine, often known as botanical medicine or herbalism (Singh *et al.*, 2011). In the past, people from all over the world used herbs for their healing or medicinal properties. Herbs are plants or parts of plants that are used for their flavor, smell, or health benefits. Chemicals that are found in herbal plants have healing effects on the body. Herbal drugs are used in both developed and developing countries for health care (Barua *et al.*, 2017). They are made from complicated chemical mixtures of plants, but they are not very effective because the body does not absorb them well when they are eaten (Shani and Jayachandran, 2020). Many people now use herbal mixtures to treat diabetes, arthritis, liver disease, coughs, improve memory, and help the body adapt to new situations. People take herbal medicine remedies to improve their health. They can be found as pills, capsules, beverages, powders, extracts, or as dried or fresh plants (Keservani and Sharma, 2014). According to WHO data, about 80% of people on the planet still get their main medical care from plants and other traditional remedies. (Ahire *et al.*, 2022). Herbal medicine is an important part of all traditional medicine from native people, and it is also a part of Ayurvedic, Homeopathic, and Naturopathic medicine. According to the WHO, around 74% of the 119 chemical medicines derived from plants are being utilized in contemporary medicine in a manner that is comparable to how the plants were traditionally used as medicines by the local communities (Supalkar *et al.*, 2023). At the moment, big drug companies are doing a lot of study on plants found in rain forests and other places to see if they could be used as medicine. A lot of what scientists know about medicines today came from what native peoples knew about herbs in the 20th century. Herbs are the source of many drugs that people use today (Aswathy *et al.*, 2021). Approximately 25% of prescription drugs in the United States have at least one active ingredient originating from plants. Some are synthetically created to mimic natural plant products, while others are derived from plant oils. It was crucial to the development and evolution of contemporary civilization (Ahire *et al.*, 2023). The use of herbs evolved with the centuries. Man-made medications are produced in laboratories, yet these drugs may be harmful to the body. This is a result of the many chemicals they contain. Chemists have dissected plants to extract their medicinal properties. Modern labs have produced

Table 1: F2 batch formulation

S. No	Formulation Ingredient	Taken Quantity
1.	*Lippia nodiflora*	100 mg
2.	*Asparagus racemosus*	30 mg
3.	*Olden landia heynaii*	110 mg
4.	Talc	100 mg
5.	Aerosil	1 mg
6.	Magnesium sterate	1.25 mg
7.	Dicalcium phasphate	50 mg
8.	Sodium benzoate	0.50 mg
9.	Sodium Methyl Paraben	0.50 mg

the chemical component needed to make pharmaceuticals function. Numerous plant-based products are formed into capsules, tablets, and pills. These continue to offer the same health advantages as genuine herbs (Behera *et al.,* 2010).

The study's goals were: (i) Analysis of raw materials by doing the preliminary raw materials study, we can learn more about the formulation's raw materials or ingredients, and (ii) To use preformulation studies to make a pill with three herbs.

Materials and Methods

Identification of Herbal Materials:

Preparation of granules:

Each individual herb plant material was cleaned, followed by three to four rounds of washing in demineralized water and drying in the shade. After being ground up, the dry plant material was run through a sieve with 30 slots made of stainless steel mesh. Each plant component was weighed separately, ground in a stainless steel pulverizer to a reasonably fine powder, and combined with the binder and other excipients (Patel and Shah, 2013). The granules were placed into red capsules measuring "0", with an average content weight of 520 mg, after QA clearance. Out of all the testing batches, batch 2 was determined to be the ideal batch and was chosen for future large-scale production considerations (Talele *et al*., 2022).

Evaluation of antiarthritic activity:

Preparation of extract:

The extraction of polyherbal capsule granules was accomplished with efficacy by employing the Soxhlet technique and a hydro-alcoholic solution (3:2) for a duration of ten hours. After that, the hydroalcoholic extract was centrifuged twice for 5 min at 1500 rpm. The extract was then allowed to evaporate on a water bath until it was completely dry. The dried extract that was produced was utilized to test the antioxidant and anti-arthritic properties *in vitro* (Aher *et al*., 2023).

In vitro evalution of antiarthritic activity:

Evalution of inhibition of proteinase enzyme:

Neutrophils are known to contain large amounts of proteinase. They have a lot of neutral serine proteinase in their lysosomal granules. Leucocyte proteinase has been associated with the formation of tissue injury during inflammatory responses**.** Many animals' digestive systems include trypsin, a serine protease that hydrolyzes proteins. Trypsin is the protease enzyme and casein is the substrate in this experiment (Bhatt *et al.,* 2022).

Protocol:

It took 5 min at 37ºC to process the 2 ml of mixture, which had 0.06 mg of trypsin, 1 ml of 25 mM Tris-HCl buffer (pH 7.4), and 1 ml of a water-based solution of the test sample (100, 200, 400, and 800 mcg/ml). The mixture was kept warm for 20 min after 1.0 ml of 0.8% (w/v) casein was added. Two milliliters of 70% (v/v) perchloric acid

were added to stop the process. It was done to centrifuge the cloudy solution. A blank buffer was used to measure the optical density of the supernatant at 280 nm (Kumari and Satyanarayana, 2019).

Evalution of Protein Denaturation:

During this procedure, exogenous stimuli or chemicals, such as heat, an organic solvent, a strong acid or base, or a concentrated inorganic salt, are applied to proteins. This results in the loss of the third and fourth conformations of proteins. When altered, the majority of biological proteins lose their biological function. Protein denaturation is a widely recognized etiology of inflammation in rheumatoid arthritis. In this investigation, heat was utilized to facilitate protein degradation (Soni *et al*., 2013).

Protocol:

This reaction mixture has 0.05 ml of test material and 4.5 ml of egg albumin (5% water solution). A small amount of 1N HCl was used to bring the pH of the reaction mixture up to 6.3. The mixture was kept at 37°C for 20 min, and then it was cooked to 51°C for 20 min. The samples were cooled down, and at 660 nm, the haze was found. The experiment was done by three different people. The word "control" stands for "protein denaturation to 100%". The results were compared to a reference sample that had 0.2 mg of diclofenac sodium in it (Keservani *et al*., 2017).

Evaluation of Membrane stabilizing assay:

Due to the similarity between the erythrocyte and lysosomal membranes, medication that affect erythrocyte stability may also affect lysosomal membrane stability. As a result, when the membrane stabilizes, it can obstruct the release or function of mediators such as leukotrienes, prostaglandins, histamine, and serotonin. The assay's underlying idea is to stabilize the rat red blood cell membrane against lysis caused by hypotonicity (Khare and Shukla 2022).

Protocol:

One ml of 0.15 M phosphate buffer (pH 7.4), 2 ml of hypotonic saline (0.25% NaCl), and 1 ml of the test sample in normal saline was made up to 4.5 ml reaction mixture. It was then filled with 0.5 ml of standard water and 10% rat red blood cells. There was no RBC in the sample solution, which was used as a reference, and 1 ml of isotonic saltwater was used as the test solution. The mixture was kept at 56°C for 30 min. The tubes were cooled with running water for 20 min. The brightness of the supernatant was recorded at 560 nm after the mixtures were centrifuged. The result was compared to a control sample that had 0.2 mg of diclofenac sodium in it (Kumar, 2022).

In vivo antiarthritic evaluation:

Acute Oral Toxicity Evaluation:

The design of the acute toxicity investigation followed OECD standards 423. Acute toxicity testing evaluates a substance's toxicity following a single dosage of a chemical or medication. Acute toxicity studies are primarily conducted to assess the level of toxicity quantitatively and qualitatively in order to compare it to other medication substances. More acute toxicity testing provides quantitative data on the effects of a chemical on acute toxicity tests; in other words, it provides details about the acute toxicity mechanism (Rane *et al.*, 2023). The primary goal of acute toxicity testing is no longer to produce animal death in order to estimate LD_{50}, as this technique of determination has altered over the past three decades mostly for animal welfare reasons. The test follows a step-by-step protocol that uses the fewest possible animals for each phase. Enough data is gathered on the substance's acute toxicity to allow for its classification. A set of test animals were given the drug orally at one of the specified dosages. Three animals of one sex (usually female) are used in each phase of the methodical testing process for the drug. It will be determined by whether or not the animals dosed at one phase exhibit compound- related mortality (Satyanarayana, 2019).

Experimental animals:

For the study, 140–200 g mature female wistar albino rats in good health who were not pregnant were chosen. *Ad libitum* water was given to all three animals, and food was withheld the night before the dose (Rana, *et al.*, 2023).

Dose Selection:

Since this was a conventional herbal remedy, the fatality was improbable even at the maximum initial dosage. Therefore, a limit test was performed on all three animals at a single dosage level of 2000 mg/kg body weight (Tamilselvi, 2021).

Observation:

After the dose, each animal was monitored separately for the first 30 min, then once a day for the next 24 h, and then every day for the next 14 days. During the first 4 h, the animals received extra attention (Sonawane *et al*., 2023).

In vivo evaluation of antiarthritic activity:

Male albino Wistar rats were given a single sub-planter injection of 0.1 ml of Complete Freund's adjuvant, which included 1.0 mg of dry heat-killed Mycobacterium TB per milliliter of sterile paraffin oil, to induce arthritis. The vehicle control group did not receive this injection. Using a vernier caliper, the swelling in each hind paw was periodically assessed from the ankle up. Oral administration of Polyherbal capsules and Diclofenac sodium was done as a newly made solution in distilled water (Keservani *et al*., 2016).

Statistical Analysis of pharmacological study:

The findings were presented as Mean ± SEM. One-way analysis of variance (ANOVA) was used to assess the data, and Dennett's test was then conducted. P values less than 0.01 were regarded as noteworthy (Rane *et al.,* 2023).

Results and Discussion

Formulation Development and Pre-formulation Studies:

Three formulation trials were conducted with varying excipient selections, taking into account various aspects of manufacturing issues and quality flaws. Each of the resulting formulations was assessed based on its disintegration time, moisture content, flow quality, and uniformity of weight and filling.

The three experimental flow characteristics fell between the specified limits and the excellent range. Thus, the third experiment was selected for more research. The statistics showed that the last trial batch (F2) was the most successful. This batch was used to test a high batch size (5,000 capsules as compared to 500 capsules) in order to optimize the formula and conduct pilot scale-up studies.

Accelerated stability studies:

Table 3 illustrates the capsule organoleptic properties during the stability phase. Quality Control Parameters are shown in Table 4.

Pharmacological Evaluation of Antiarthritic Activity:

In-vitro anti arthritic activity:

Asparagus racemosus extract inhibited membrane lysis, protenase enzyme, and protein denaturation in a dose-dependent manner. At 0.8 mg the highest concentration for protenase enzyme, protein denaturation and membrane stabilization (85.30±0.90, 81.10±0.20, 81.90±0.36) (Table 5), was achieved. This dosage was lower than that of the conventional medication, diclofenac sodium, which was 0.2 mg (86.80±0.80, 80.90±0.16, 85.17±1.14).

Lippia nodiflora extract inhibited membrane lysis, protenase enzyme, and protein denaturation in a dose-dependent manner. At 0.8 mg the highest concentration for protenase enzyme, protein denaturation, and membrane stabilization (86.15±0.80, 80.50±0.67, 70.80±0.81) (Table 6) was achieved. This dosage was lower than that of the conventional medication, diclofenac sodium, which was 0.2 mg (85.30±0.46, 84.62±0.41, 75.23±1.15).

Oldenlandia heynei extract demonstrated dose-dependent inhibitory action on membrane lysis, protenase enzyme, and protein denaturation. The

Table 2: Evaluation of formulation batches

Parameters	F1	F2	F3
Bulk density(g/cm^2)	0.36±0.024	0.42±0.02	0.39±0.017
Tapped density(g/cm^2)	0.55±0.027	0.57±0.02	0.59±0.04
Compressibility index (%w/w)	40.15±1.25	26.9±2.03	31.98±2.58
Hausner ratio	1.39±0.35	1.39±0.03	1.39±0.05
Angle of repose(degrees)	34.90±3.36	35.4±3.61	41.88±1.2

Table 3: Capsule organoleptic properties during the stability phase

Parameters	Observations
Nature	Solid Powder
Color	Brownish
Odor	Slightly aromatic
Taste	Odorless

Table 4: Quality Control Parameters

Parameters	Stability period		
	After 30 Day	After 60 Days	After 90 Days
Weight Uniformity	512.2±2.86mg	516.1±1.36mg	516.4±0.55mg
Loss on drying (LOD)	3.11± 0.22% w/w	3.70±0.13% w/w	3.6±0.04% w/w
Disintegration test (DT)	9'26"±0.24	8'55"±0.36	8'16"±0.70
pH	5.4±0.50	5.60±0.30	5.90±0.41

Table 5: The anti-arthritic properties of *Asparagus racemosus* extract *in vitro*

Assay	Percentage inhibition				
	0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.2 mg (std)
Protein denaturation	61.11±0.12	75.80±0.06	81.32±0.44	85.30±0.90	86.80±0.80
Inhibition of protenase enzyme	60.10±0.29	73.10±0.42	75.50±0.17	81.10±0.20	80.90±0.16
Membrane stabilization	60.12±0.17	66.40±0.60	75.81±0.14	81.90±0.36	85.17±1.14

Table 6: The anti-arthritic properties of *Lippia nodiflora* extract *in vitro*

Assay	Percentage inhibition at different concentrations				
	0.1 mg	**0.2 mg**	**0.4 mg**	**0.8 mg**	**0.2 mg (std)**
Protein denaturation	75.60±0.33	80.10±0.36	80.18±0.36	86.15±0.80	85.30±0.46
Inhibition of protenase enzyme	70.11±0.40	70.30±0.66	76.80±0.20	80.50±0.67	84.62±0.41
Membrane stabilization	56.82±0.48	59.90±0.30	65.71±0.35	70.80±0.81	75.23±1.15

Table 7: The anti-arthritic properties of *Oldenlandia heynei* extract *in vitro*

Assay	Percentage inhibition				
	0.1 mg	**0.2 mg**	**0.4 mg**	**0.8 mg**	**0.2 mg (std)**
Protein denaturation	71.13±0.17	76.40±0.13	80.11±0.41	83.11±0.41	86.11±0.06
Inhibition of protenase enzyme	69.41±0.41	73.41±0.55	75.49±0.66	81.50±0.83	81.23±0.19
Membrane stabilization	60.85±0.05	66.39±0.31	71.36±0.05	73.49±0.30	72.31±0.21

Table 8: Variations in the size of the paws (measured in millimeters)

Dose treatment	I Group	II Group	III Group	IV Group	V Group
0th day	0.33±0.016	0.34±0.021	0.46±0.03	0.49±0.05	0.53±0.027
4th day	0.31±0.005	0.50±0.015	0.36±0.03	0.47±0.019	0.47±0.04
8th day	0.32±0.005	0.49±0.016	0.29±0.04	0.36±0.034	0.36±0.028
14th day	0.31±0.002	0.53±0.016	0.24±0.03	0.31±0.04	0.24±0.03
21st day	0.33±0.02	0.54±0.015	0.16±0.03	0.22±0.028	0.20±0.042

ANOVA was used to assess the data, and Dennett's test was then conducted. P values less than 0.01 were regarded as noteworthy.

highest concentration for protenase enzyme, protein denaturation, and membrane stabilization was 0.8 mg (83.11±0.41, 81.50±0.83, 73.49±0.30), which was lower than the 0.2 mg of diclofenac sodium, the usual medication (86.11±0.06, 81.23±0.19, 72.31±0.21) (Table 7).

Oral acute toxicity study:

Rats administered a polyherbal formulation (2000 mg/kg body weight) were observed both physically and behaviorally. The table displays the findings of the acute toxicity investigation. Animals treated with polyherbal formulations up to 2000 mg/kg showed no signs of morbidity or death.

In vivo antiarthritic activity:

Tables 8 shows the antiarthritic activity.

Conclusion

The goal of the current study was to design, standardize, and evaluate the pharmacological efficacy of a polyherbal anti-arthritic formulation. The manufactured capsules were standardized utilizing many criteria, such as phytoconstituent quantitation, HPTLC, and heavy metals, in accordance with WHO recommendations. The capsules' stability tests were conducted in accordance with ICH norms. The effectiveness of the formulation in treating rheumatoid arthritis was investigated through pharmacological experiments conducted *in vitro* and *in vivo*. The designed capsule's antioxidant activity was also assessed. In accordance with OECD criteria, acute toxicity tests were carried out, and *in vivo* study protocols were defined. Rats receiving both a polyherbal formulation and a diclofenac treatment showed increases in body weight. When comparing the treatment groups with the arthritic control group, there was a statistically significant rise in body weight in the polyherbal formulation groups. Both the diclofenac sodium-treated group and the polyherbal formulation-treated group had less paw edema. There was a statistically significant decrease in paw edema between the groups treated with the polyherbal formulation and the arthritic control group. Clinical studies and the specific mechanism of action creating this anti-arthritic benefit can be the subject of future study, which can also be expanded upon.

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