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A Review on Antirheumatoid Activity of Alpinia Calcarata

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ABSTRACT:
Inflammatory arthritis is a common problem observed in elderly people. Nearly one fifth of the world population suffers from this debilitating disease. Traditional medicines like Siddha, Ayurveda, Unani and Chinese medicineshave mentioned few herbal drug remedies for arthritis but lack in providing scientific evidence of therapeuticbenefits. However, past few decades showed great achievements in the herbal drug standardization due to thedevelopment in modern chromatographic techniques. Experimentally, rhizomes of Alpinia calcarata are shown to possess antirheumatic activity. As well as antibacterial,antifungal, anthelmintic, antinociceptive, anti-inflammatory,antioxidant, aphrodisiac, gastroprotective, and antidiabetic activities. Phytochemical screening revealed the presence of polyphenols, tannins, flavonoids, steroid glycosides and alkaloids in the extract and essential oil of this plant. Essential oil and extracts from this plant have been found to possess wide range pharmacological and biological activities.

Keywords: Alpinia calcarata ,Rheumatoid Arthritis, Pharmacological activity, traditional use.

I. INTRODUCTION

1.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic, systemic inflammatory disorder or a long term auto immune multisystem illness in which the body's immune system attacks the body's tissues and joints mistakenly causing an inflammatory synovitis which often progresses the destruction of joint ankylosis and articular cartilage.[1] It arise more frequently in females than males, being predominantly observed in the elderly. An autoimmune disease is a condition which arises from an abnormal response to our normal immune system. The immune system is a host defense mechanism comprising complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body. The synovium (inside of joints) is a thin delicate lining serves as an important source of nutrients for cartilage which thickens during RA resulting in inflammation and pain in and around the joint. [2] RA primarily affects the lining of the synovial joints and can cause progressive disability, premature death, and socioeconomic burdens. Additionally, synovial cells synthesize joint lubricants and helps them move smoothly such as collagens, as well as fibronectin and hyaluronic acid that constitute the structural framework of the synovial interstitium.[3]Rheumatoid arthritis is influenced by the following factors such as gender, age, environmental factors and reproductive status, various studies demonstrate that genetic factors also play a major role on an individual's susceptibility to RA[4]

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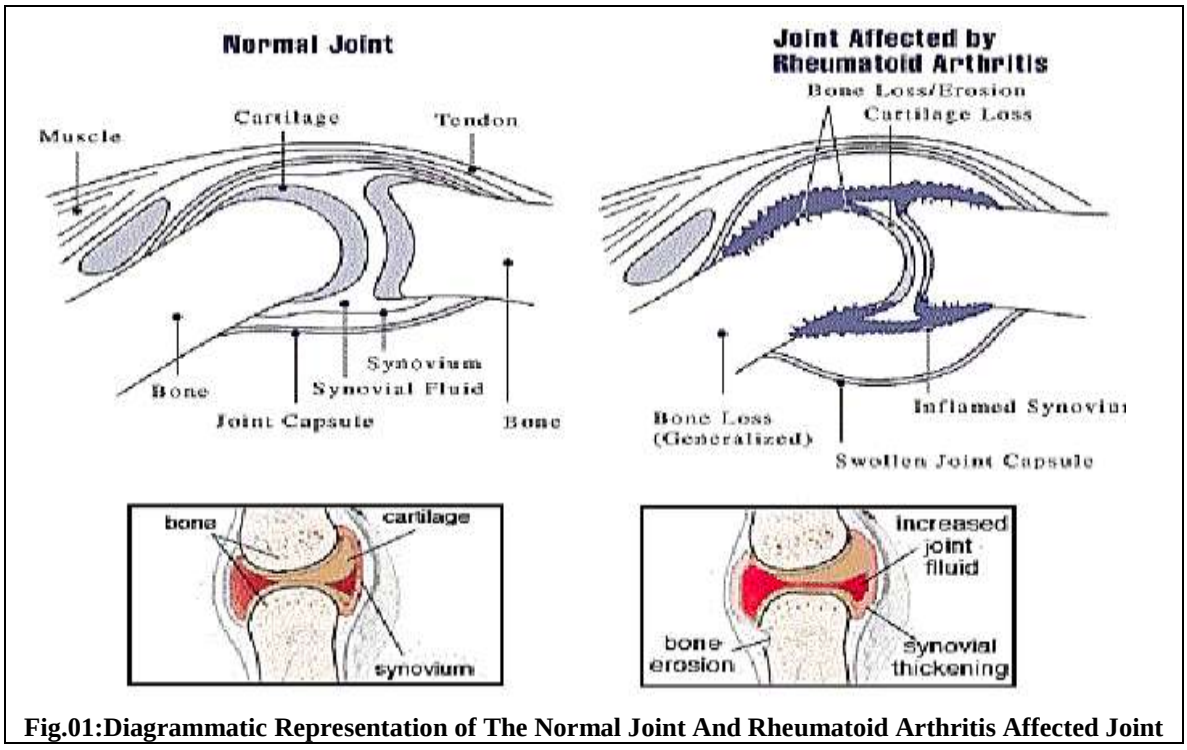

Fig.01:Diagrammatic Representation of The Normal Joint And Rheumatoid Arthritis Affected Joint

It is characterized by periods of disease flares and remissions. Chronic inflammation of rheumatoid arthritis can cause permanent joint destruction and deformity. It leads to warm, swollen, painful and stiff joints which gets worsened following restUsually, multiple joints of the fingers and hands, wrists, feet and knees typically gets affected in a symmetrical distribution (affecting both sides of the body). It may also affect other parts of the body and this may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart[5]

The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion. Early diagnosis is considered as the key improvement index for the most desirable outcomes (i.e., reduced joint destruction, less radiologic progression, no functional disability, and disease modifying antirheumatic drugs (DMARD)-free remission) as well as cost effectiveness as the first 12 weeks after early symptoms occur is regarded as the optimal therapeuticwindow. However, early diagnosis remains challenging as it relies heavily on the clinical information gathered from the patient's history and physical examination supported by blood tests, and imaging analysis. The reasons for a delayed diagnosis vary markedly between countries with differing healthcare systems, while the reasons for a delay in initiating DMARD therapy in RA patients appear to be both patient- and physician-dependent.[6]

Disease Activity Score using 28joints (DAS-28), Simplified Disease Activity Assessment Index (SDAI), and Clinical Disease Assessment Index (CDAI). To achieve full suppression of the activity of the disease (clinical remission), rheumatologists need to monitor disease activity continuously and accurately and to accurately and to adjust the treatment regimen accordingly.[7]

1.2 HISTORY

The first recognized description of Rheumatoid Arthritis was in 1800 by the French physician Dr Augustin Jacob Landré-Beauvais (1772 1840), worked at Salpetriere Hospital in Paris. The disease, "Rheumatoid Arthritis" was named so in 1859 by British Rheumatologist Dr Alfred Baring Garrod[8]

The hallmark feature of rheumatoid arthritis (RA) is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, although any joint lined by a synovial membrane may be involved[9]

The severity of RA may fluctuate over time, but chronic RA most commonly results in the progressive development of various degrees of joint destruction, deformity, and a significant

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decline in functional status.Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can also be significantadjust the treatment regimen accordingly.[10]

1.3 EPIDEMIOLOGY

Worldwide, the annual incidence of RA is approximately 3 cases per 10, 000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (eg, 5-6% in some Native American groups) and much less prevalent in others (eg, black persons from the Caribbean region)[11]

1.4 SIGNS AND SYMPTOMS

The onset of rheumatoid arthritis in most patients is insidious, often beginning with fever, malaise, arthralgias, and muscle weakness before progressing to inflammation and swelling of the joints.

- Joint pain, stiffness and swelling are the most common symptoms of arthritis.
- Redness and warm joint which is lasts for 6 weeks.
- Sudden high fever.
- Rheumatoid factor presents and red blood cell decreased in blood testing.

Many people with arthritis notice their symptoms are worse in the morning [12]

1.5 ETIOLOGY OF RHEUMATOID ARTHRITIS

Despite the intensive work, the cause of RA remains unclear. The synovial cells have a unique feature to exhibit characteristics of a localized tumor which invades the adjacent articular cartilage, subchondral bones, tendons and ligaments. Many inflammatory mediators have been proposed to play a significant role in the pathogenesis of RA[13]

1) ROLE OF INNATE AND ADAPTIVE IMMUNITY

Innate immunity has been implicated through the engagement of Fc receptor by immune complexes and Toll like receptors by bacterial products. Antigen driven T cell and B cell response may also participate as a result of xeno antigen reactivity and cytokine activity participates with autocrine and paracrine network. In addition to this, many other factors like smoking, environmental factors and microbial proteins play a role. This mechanism is often self-limited in normal individuals. [14]

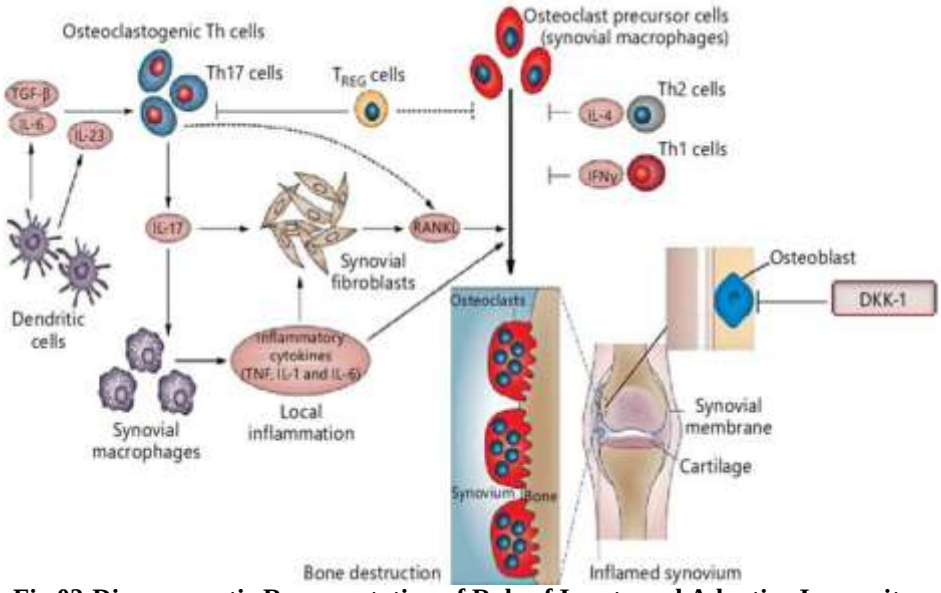

Fig.02:Diagrammatic Representation of Role of Innate and Adaptive Immunity

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2)ROLE OF HLA-DR IN RA

The structure of MHC class II plays an important role in the susceptibility and severity of RA. The role of HLA-DR 4 was found to be a major contributory factor in the pathogenesis of RA. The third hypervariable region of DR (beta) chain is the site involved in the pathogenesis. The epitope is found to be Glutamine-Leucine-Arginine Alanine-alanine (QKRAA)[15]

3) Gender -As of any autoimmune diseases, the prevalence of RA is found to be high in Women gender.

4) Tobacco - Although several environmental factors are studied in the pathogenesis, nothing stands much in thecontributory effect than smoking. Smoking could cause the activation of innate immune systemthereby leading on to the development of the disease.

5) Autoimmunity- The role of autoimmunity is firmly established by the presence of the Rheumatoid Factor in the patient's blood with RA. However, the auto antibody titre doesn't correlate well with the disease activity. The improvement of clinical features can be associated with modest decreasein the RA andAnti citrullinated antibody level[16]

1.6 DIFFERENT STAGES OF RHEUMATOID ARTHRITIS

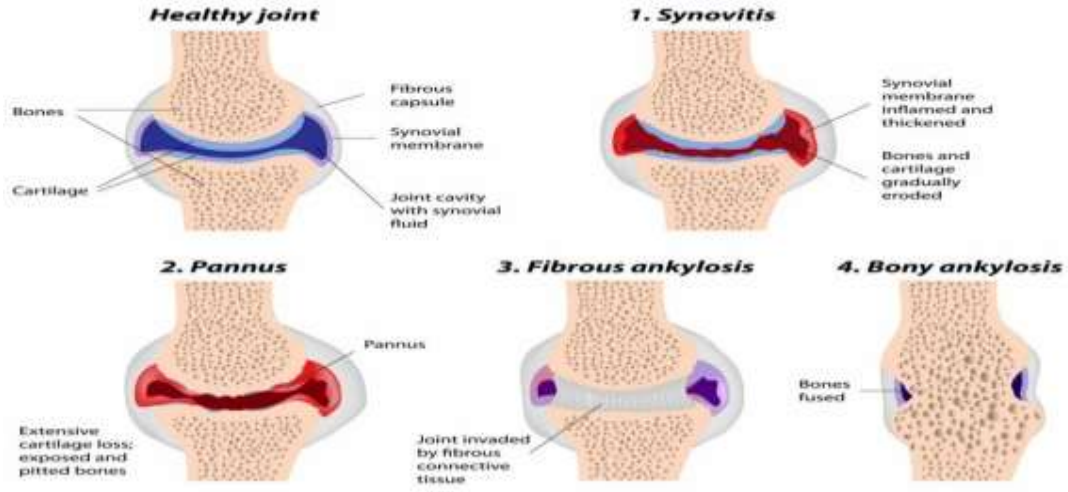
Three identified stages of rheumatoid arthritis, characterized by differing pathogenesis and physical changes.

Stage I: Early-stage RA is notable by the presence of synovial membrane inflammation, which results in joint swelling and pain on motion. Immune cells move to the inflammation site, leading to high cell counts in synovial fluid; however, x-rays are typically negative, other than showing the possible presence of some osteoporosis and soft tissue swelling. Treatment of early-stage RA focuses on joint protection and inflammation control.

Stage II: In moderate stage RA, there is T and B cell proliferation and angiogenesis in the synovium. Synovial tissue starts to grow into the joint cavity, across cartilage, which will be gradually destroyed. The joint begins to narrow because of cartilage loss. There are typically no joint deformities at this stage, though mobility may become limited with adjacent muscle atrophy. There may be mild malaise as well as the presence of nodules

Stage III: End-stage or advanced RA disease results in a cessation of inflammatory processes. The formation of fibrous tissue and/or bone ankylosing (fusing of bone) results in ceased joint function. MRI will show proliferative pannus (a membrane of granulation tissue). Patient symptoms are much the same as in stage III, i.e. joint pain, swelling, stiffness, weakness and malaise. At this point, treatment goals focus on reduction of pain and halting additional joint damage. Patients with end-stage RA may undergo joint replacement surgery[17]

Fig.03:Diagrammatic Representation of Steps Involved In Inflammation Of RA



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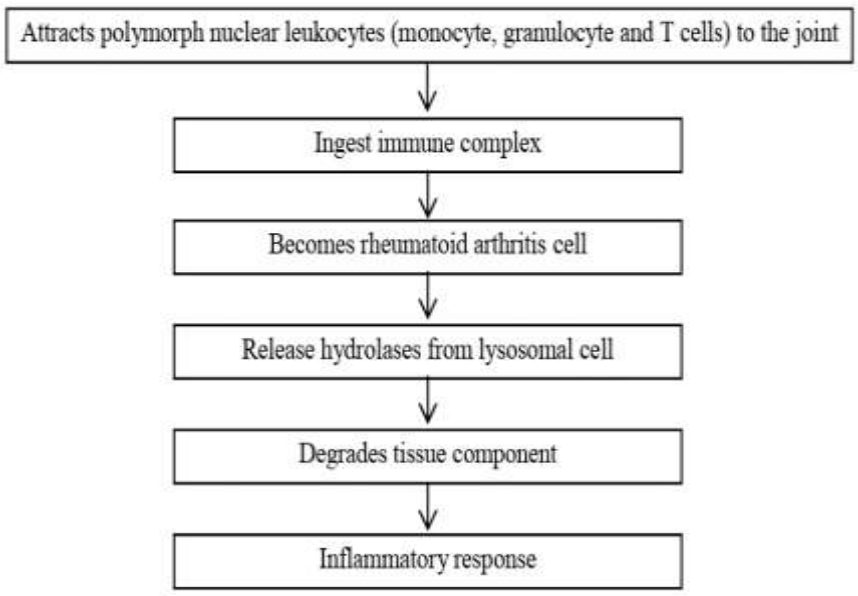

Fig.04:Diagrammatic Representation of Pathophysiology of Rheumatoid Arthritis

II. PLANT PROFILE

Fig.05: Plant And Rhizome of Alpinia Calcarata

II. TAXONOMICAL CLASSIFICATION

Kingdom: Plantae
Division: Mangnoliphyta
Class: Liliopsida
Order: Zingiberales
Family: Zingiberaceae
Genus: Alpinia
Species: calcarata

Synonyms: Alpinia calcarata Rosk., Alpinia erectaLodd. and Steud., Alpinia bracheataRosk., Alpinia cerrnta Sims., Renealmiacalcarata[18]

III. PLANT DESCRIPTION

Rhizomatous perennial herb with a nontuberous rootstock, stems slender, about 75 cm tall; leaves simple, alternate, 25-32 cm long and 2.5-5 broad, lanceolate, acuminate, long-pointed, glabrous on both surfaces and shining on the upper

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surface, scantily hairy along the margin, petioles sheathing; flowers pinkish white, irregular, bisexual, in pendunculate, terminal, dense flowered panicles 8.5 cm long [5]There are pink calcarata rhizomes and whitish yellow galangal rhizomes. Pink galangal rhizomes have a diameter of 8–10 cm, with a pseudo-stem length of 3.5 m. The yellowish white calcarata rhizome has a smaller diameter of 1–2 cm, and the length of the pseudo-stem is 1–1.5 m. Alpinia calcarta is easy to grow in various regions of Indonesia, especially on the islands of Kalimantan and Java [19]

IV. TRADITIONAL USE

According to traditional systems of medicine, rhizomes of A. calcarata of this plant is used to treat rheumatoid arthritis. It is a major constituents of herbal formulations used against rheumatoid arthritis used as a fomentation on rheumatic joints. Rhizomes are said to possess diuretic, aphrodisiacand antitoxic properties. It is used in polyuria, coughs, stomachic diseases, diabetes, colds, bronchial asthma, respiratory ailments and heart diseases. They are also used to treat snake bites. It improves the voice, prevents bad breathand strengthens the nerves[20]

V. PHARMACOLOGICAL ACTIVITY

Anti-Inflammatory Activity

The use of A. calcarata to cure the inflammation of joints has been investigated and it was shown that the water extract of A. calcarata rhizomes has cured the formaldehyde induced joint inflammations in rats. This was further experimented by clinical studies using human patients and confirmatory results were observed hot water and hot ethanol extracts of A. calcarata possess significant and marked dose dependant anti-inflammatory activity. It was observed that the activity is due to prostaglandin inhibition and anti-histamine activities[21]

Anti-Oxidant Activity

Ethanol extract, hot water extract and essential oil of A. calcarata possess anti-oxidant activity [22]

Analgesic Activity

The ethanol and hot water extracts of A, calcarata rhizomes are shown to possess analgesic activity.. Rhizomes of A. calcarata containing polyherbal preparation called "MaharasnadhiQuatha" was shown to possess anti-inflammatory, anti-oxidant and analgesic activities'Studies have shown that A. calcarata may be the main component responsible for these properties'[23]

Anti-Microbial Activity

Number of in vitro studies have been carried out to investigate the anti-microbial activity of A. calcarata. Ethanol and water extracts of the plant have been shown to possess antibacterial activity against Escherichia coli and Staphylococcus aureus. Studies revealed that the essential oil of A. calcaratarhizome was active against the following fungal species- Fusarium sps., Curvulariasps., and Colletotrichum sps. The essential oil of A. calcarata has inhibited the growth of Mycobacterium tuberculosis[24]

Anthelmintic Activity

The alcoholic extract of A. calcarata showed moderate activity against human Ascaris lumbricoides in vitrostudies[25]

Anti-Diabetes Activity

Anti-diabetes activity of hot water and hot ethanol extracts of A. calcarata rhizomes was studied using experimental rats. These two extracts significantly reduced the blood glucose levels and inhibitedthe glucose absorption by the lumen of the intestine in animal experiments [26]

Gastroprotective Activity

It was demonstrated that hot water and hot ethanol extracts of A. calcarataarhizomepossessmarked gastroprotective properties as evidenced by its significant inhibition of gastric lesions (in terms of length and number) induced by ethanol [27]

Antinociceptive effect

Hot water extract and hot ethanol extract of A. calcarata rhizome were carried out for antinociceptive activity in three models of nociception (tail flick, hot plate and formalin tests) in albino rats.[10,29] hot water extract at the doses of 100, 250, 500, 750, 1000 mg/kg) and hot ethanol extract at the doses of 100, 250, 500, 750, 1000 mg/kg were orally administrated to the experimental rats and the reaction time was counted. A strong and dose dependent antinociceptive activity was observed in the hot plate and the formalin tests. But no significant antinociceptive effect was recorded in the tail flick test. The antinociceptive effect in hot ethanol extract was slightly higher than that in hot water

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extract. Finally, the result remarked an opioid mediated antinociceptive effect of A. calcarata[28]

Anti inflammatory effect

Alpinia calcarata Roscoe rhizomes are used in traditional medicines as a remedy for bronchitis, cough, respiratory ailments, diabetics, asthma and arthritis. Generally the antiarthritic drugs have antiinflammatory and antinociceptive properties. The antiinflammatory activity of hot water extract and hot ethanol extract of A. calcaratarhizomes in carrageenan induced inflammatory model. The findings concluded that the inhibitions of histamine and prostaglandin synthesis are the probable mechanisms by which A. calcarata mediates its antiinflammatory action[29]

Enzymatic effect of A. calcarata

Fungal strain of A. calcarata has been identified for amylase production. Among thirty isolates of endophytic fungi of A. calcarata, isolate number seven identified as Cylindrocephalumsp. showed highest amylolytic activity and was taken for further study. Influence of various physical and chemical factors such as pH, temperature, carbon and nitrogen sources on amylase production in liquid media were studied. The maximal amylase production was found to be at 30°C and at pH 7.0 of the growth medium. Among the various carbon and nitrogen sources tested, maltose at 1.5% and Sodium nitrate at 0.3% respectively gave optimum amylase production [30]

Anti-ulcer Activity

An Alpinia Calcarata ethanolic extract has anti-ulcer, antigastric secretion, and cytoprotective properties in rats. The Calcarata rhizome is also widely used to treat stomach disorders. An Alpinia galanga ethanolic extract showed significant results in reducing gastric secretion and was cytoprotective; therefore, Alpinia galanga also had antiulcer activity . It was reported that the calcarata rhizome ethanolic extracts caused cytological and biochemical changes in rats induced by cyclophosphamide. The calcarata rhizome, in addition to being a spice, is also used in medicine to treat stomach aches, gastralgia, dyspepsia, digestive disorders, sea ailments, tonics, and ulcers[30]There are also anti-feedants and lethal substances in the calcarata rhizome extract. An active compound in the calcarata rhizome extract shows insecticidal activity; the compound is acetate 1'-acetoxicaviol, which has the molecular formula: C13H14O4. Some other galangal species also contain compounds that are anti-feedants[31]

VI. CONCLUSION

Alpinia calcarata roscoe is an important plant for its various pharmacological activity and it would be worthwhile in continuing research to isolate the active compounds. The plant has been traditionaly used in the tratment of rheumatoid arthritis. It is used in polyuria, coughs, stomachic diseases, diabetes, colds, bronchial disease, asthma and heart disease. Alpiniacalcarata contains a variety of chemical compounds that have pharmacological properties as herbal medicines. The future aspects of the plant can be anti asthmatic as it contains many of the phytochemicals and work has not been performed yet.

VII. REFERENCES

[1]. Arambewela, L. S. R., Arawwawala, L. D. A. M., &Ratnasooriya, W. D. (2004). Antinociceptive activities of aqueous and ethanolic extracts of Alpinia calcarata rhizomes in rats.Journal of
[2]. Ethnopharmacology, 95(2–3), 311–316. https://doi.org/10.1016/j.jep.2004.07.015
[3]. Di Carlo, M., Smerilli, G., &Salaffi, F. (2021). Mechanisms and Mediators of Pain in Chronic Inflammatory Arthritis. Current Treatment Options in Rheumatology, 7(3), 194–207.
[4]. Cheng, Q., Wu, H., & Du, Y. (2021). The roles of small-molecule inflammatory mediators in rheumatoid arthritis. In Scandinavian Journal of Immunology (Vol. 93, Issue 3).
[5]. Islam, F., Rowshanul Habib, M., Islam, M., Yesmin, R., Ali, H., Chandra Karmakar, P., Rowshanul Habib, M., & Yeasmin, T. (2017). Antioxidant activity of ethanolic extract of Alpinia calcarataRosc. Rhizome. Journal of Pharmacognosy and Phytochemistry, 6(4), 469–474.
[6]. Kore KJ, Shete RV, & Desai NV. (2011). Anti-Arthritic activity of Hydroalcoholic extract of LawsoniaInnermis. In Int. J. Drug Dev. & Res (Vol. 3, Issue 4). http://www.ijddr.in
[7]. Choubey, J., Patel, A., & Verma, M. K. (2013). PHYTOTHERAPY IN THE TREATMENT OF ARTHRITIS: A REVIEW. International Journal of Pharmaceutical Sciences and Research

2853 IJPSR, 4(8), 2853–2865. https://doi.org/10.13040/IJPSR.0975-8232.4(8).2853-65

[8]. Cheng, Q., Wu, H., & Du, Y. (2021). The roles of small-molecule inflammatory mediators in rheumatoid arthritis. In Scandinavian Journal of Immunology (Vol. 93, Issue 3). John Wiley and Sons Inc. https://doi.org/10.1111/sji.12982

[9]. Jaijesh, P., Kaitheri, S. K., Potu, B. K., Govindan, S., Kumar, R. S., Narayanan, S. N., &Moorkoth, S. (2009). Anti-Arthritic potential of the plant Justicia gendarussa Burm F. Clinics, 64(4), 357–360. https://doi.org/10.1590/S1807-59322009000400015

[10]. Fatima, N. (2021). Determination of Pharmacological Screening for Anti-arthritic Potential of Moringa oleifera in Rats Challenged with Formalin. In Technological Innovation in Pharmaceutical Research Vol. 9 (pp. 44–56). Book Publisher International (a part of SCIENCEDOMAIN International). https://doi.org/10.9734/bpi/tipr/v9/10831d

[11]. Cheng, Q., Wu, H., & Du, Y. (2021). The roles of small-molecule inflammatory mediators in rheumatoid arthritis. In Scandinavian Journal of Immunology (Vol. 93, Issue 3). John Wiley and Sons Inc. https://doi.org/10.1111/sji.12982

[12]. Chinnasamy, V., Subramaniyan, V., Chandiran, S., Kayarohanam, S., Kanniyan, D. C., Velaga, V. S. S. R., & Muhammad, S. (2019). Antiarthritic activity of achyranthes aspera on formaldehyde-induced arthritis in rats. Open Access Macedonian Journal of Medical Sciences, 7(17), 2709–2714. https://doi.org/10.3889/oamjms.2019.559

[13]. Kumar, V. L., & Roy, S. (2007). Calotropis procera latex extract affords protection against inflammation and oxidative stress in Freund's complete adjuvant-induced monoarthritis in rats. Mediators of Inflammation, 2007. https://doi.org/10.1155/2007/47523

[14]. DjuichouNguemnang, S. F., Tsafack, E. G., Mbiantcha, M., Gilbert, A., Atsamo, A. D., Yousseu Nana, W., MatahMartheMba, V., &Adjouzem, C. F. (2019). In Vitro Anti-Inflammatory and in Vivo Antiarthritic Activities of Aqueous and Ethanolic Extracts of DissotistholloniiCogn. (Melastomataceae) in Rats. Evidence-Based Complementary and Alternative Medicine, 2019. https://doi.org/10.1155/2019/3612481

[15]. Gaffo, A., Saag, K. G., & Curtis, J. R. (2006). Treatment of rheumatoid arthritis. In American Journal of Health-System Pharmacy (Vol. 63, Issue 24, pp. 2451–2465). American Society of Health-Systems Pharmacy. https://doi.org/10.2146/ajhp050514

[16]. Felson, D. T., Smolen, J. S., Wells, G., Zhang, B., Van Tuyl, L. H. D., Funovits, J., Aletaha, D., Allaart, C. F., Bathon, J., Bombardieri, S., Brooks, P., Brown, A., Matucci-Cerinic, M., Choi, H., Combe, B., De Wit, M., Dougados, M., Emery, P., Furst, D., … Boers, M. (2011). American college of rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis and Rheumatism, 63(3), 573–586. https://doi.org/10.1002/art.30129

[17]. Gabriel, S. E., & Michaud, K. (2009). Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. In Arthritis Research and Therapy (Vol. 11, Issue 3). https://doi.org/10.1186/ar2669

[18]. Jaijesh, P., Kaitheri, S. K., Potu, B. K., Govindan, S., Kumar, R. S., Narayanan, S. N., &Moorkoth, S. (2009). Anti-Arthritic potential of the plant Justicia gendarussa Burm F. Clinics, 64(4), 357–360. https://doi.org/10.1590/S1807-59322009000400015

[19]. Chandrakanthan, M., Handunnetti, S. M., Premakumara, G. S. A., &Kathirgamanathar, S. (2020). Topical Anti-Inflammatory Activity of Essential Oils of Alpinia calcarataRosc., Its Main Constituents, and Possible Mechanism of Action. Evidence-Based Complementary and Alternative Medicine, 2020. https://doi.org/10.1155/2020/2035671

[20]. Scheffer J. Monoterpenes in the essential rhizome oil of Alpinia galanga (L.) Willd. Sci Pharm. 1981; 49: 337-46.

[21]. Kong, L.Y., Qin, M.J. andNiwa, M. (2000). Diterpenoids from rhizomes of Alpinia calcarata. Journal of Natural Product 63 (7): 939-942.

[22]. ThalpathaOsumahhna, (2002). Department of Ayurveda, Bandaranaikc Memorial Ayurveda Research Institute. Vol. I.
[23]. Pushpangadan, P. and Atal, C.K. (1984). Ethno-medico-Bolanicalinvestigations in Kerala I,Some primitive tribals of Western Ghats and their herbal medicine. Journal of Ethno-pharmacology 11(1): 59-77.
[24]. Senarathna, D.W.J. (1987). OsupalasahaAtbehet, Bandaranaikc Memorial Ayurveda Research Institute.
[25]. Medicine (Vol. 43, Issue 4, pp. 148–155). Taylor and Francis Ltd. https://doi.org/10.1080/25785826.2020.1770948
[26]. Manan, M., Saleem, U., Ahmad, B., Aslam, N., Anwar, A., & Zafar, A. (2022). Anti-arthritic and toxicological evaluation of ethanolic extract of Alternanthera bettzickiana in rats. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.1002037
[27]. Kumar, V. L., & Roy, S. (2007). Calotropis procera latex extract affords protection against inflammation and oxidative stress in Freund's complete adjuvant-induced monoarthritis in rats. Mediators of Inflammation, 2007. https://doi.org/10.1155/2007/47523
[28]. Arambcwela, L.S.R., etal. (2005). Report submitted to NSF on the Development of therapeutic products based on plant derived immunomodulatory and other bioactive compounds / extracts.
[29]. Kore KJ, Shete RV, & Desai NV. (2011). Anti-Arthritic activity of Hydroalcoholic extract of LawsoniaInnermis. In Int. J. Drug Dev. & Res (Vol. 3, Issue 4). http://www.ijddr.in
[30]. Ambewela LS, Arawwawala LD, Ratnasooriya WD. Gastroprotective activity of hot ethanolic extract of Alpinia calcarata rhizomes in rats. Ceylon J Med Sci 2005;48:1‑ 11.
[31]. Dadang RS, Ohsawa K. An important medicinal plant: A review. J Pestic Sci. 1998. 23(3): 304-7.
[32]. Qureshi S, Shah AH, Ahmed MM, Rafatullah S, Bibi F, Al-Bekairi AM. Alternative treatment of reduced semen quality with plant extracts. Int J Pharmacogn.1994; 32(2): 171-7.