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REVIEW ARTICLE **OPEN ACCESS**

Potential of Neoteric Phytoactives and Herbs for Targeting Pathophysiological Modules of Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is debilitating, progressive autoimmune diseases of unknown cause. It affects joints by destructing bone and cartilage, leading to pain, inflammation, and restricted movement of joints. Many conventional antiarthritic agents are available, most of them are immunosuppressive and commonly associated with severe side effects. In recent years, numerous plant actives and herbs have been investigated for their anti-arthritic efficacy in order to overcome the therapeutic shortcomings of these conventional therapies. The finding of these researches revealed that herbs and their bioactives can modulate the major inflammatory cytokine expression in synovial cells and the regulation of the inflammatory immune process by targeting various cellular targets including PGE2 and COX-2. The present review is an endeavour to gather the therapeutic insight of some potential plant based actives and herbs for aiming pathophysiological targets in arthritis and their effective management. It also reports the medicinal value of herbs as novel clinical pharmaceutical agents for the management of arthritic conditions with the least side effects.

Keywords: *Arthritis, herb, plant actives, autoimmune disease, cytokines.*

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INTRODUCTION

Arthritis is an inflammational disease that is distinguished and begins largely in proportion to its age. Its prominent symptoms include joint pain, rigidity, decreased joint movement and redness, and joint swelling. Rheumatoid arthritis (RA) is a catastrophic type of inflammatory joint diseases that threaten people globally amongst many forms of arthritis[1,2,3]. Rheumatoid arthritis is a debilitating autoimmune condition due to the hyperproliferation of synovial fibroblast and massive invasion of inflammatory cells in the joints comprising CD4+T cells and innate immune cells such as macrophages. Numerous different pro-inflammatory cytokines such as IL-1β, TNF-α, IL- 6, IL-10, and IL-18 facilitate self-immunity, systemic inflammation, and degradation of the tissue [4,1].

A variety of prescribed medications have been used to regulate joint inflammation and pain in RA. These affordable drugs relieve joint inflammation, mitigate pain, minimize joint deterioration, and reduce disability. Non-Steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are most commonly utilized as the first line of therapy with fast responses to regulate inflammation and pain in RA [4]. Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, sulfasalazine, antimalarial medications, and other medicinal products that can modulate the functioning of the immune system by inhibiting radiographic growth and fatality. These medications used for the management of RA can squelch inflammatory targets and produce numerous therapeutic effects by suppressing the activation and creation of different enzymes (for example cyclooxygenase [COX]-1 and COX-2), cytokines (for example TNF-α and IL-1β), or transcription factors (for example, nuclear factor-kB [NF-kβ], c-Jun N-terminal kinases and p38 kinases). Though these therapies have ameliorating activity on the joint injury, physical mobility, and quality of life, their myriad side effects is still a curse to human health [**5**]. The side effects of these drugs include Cushing habitus, elevated blood pressure, hyperglycemia, stomach ulceration, and bleeding [4,5].

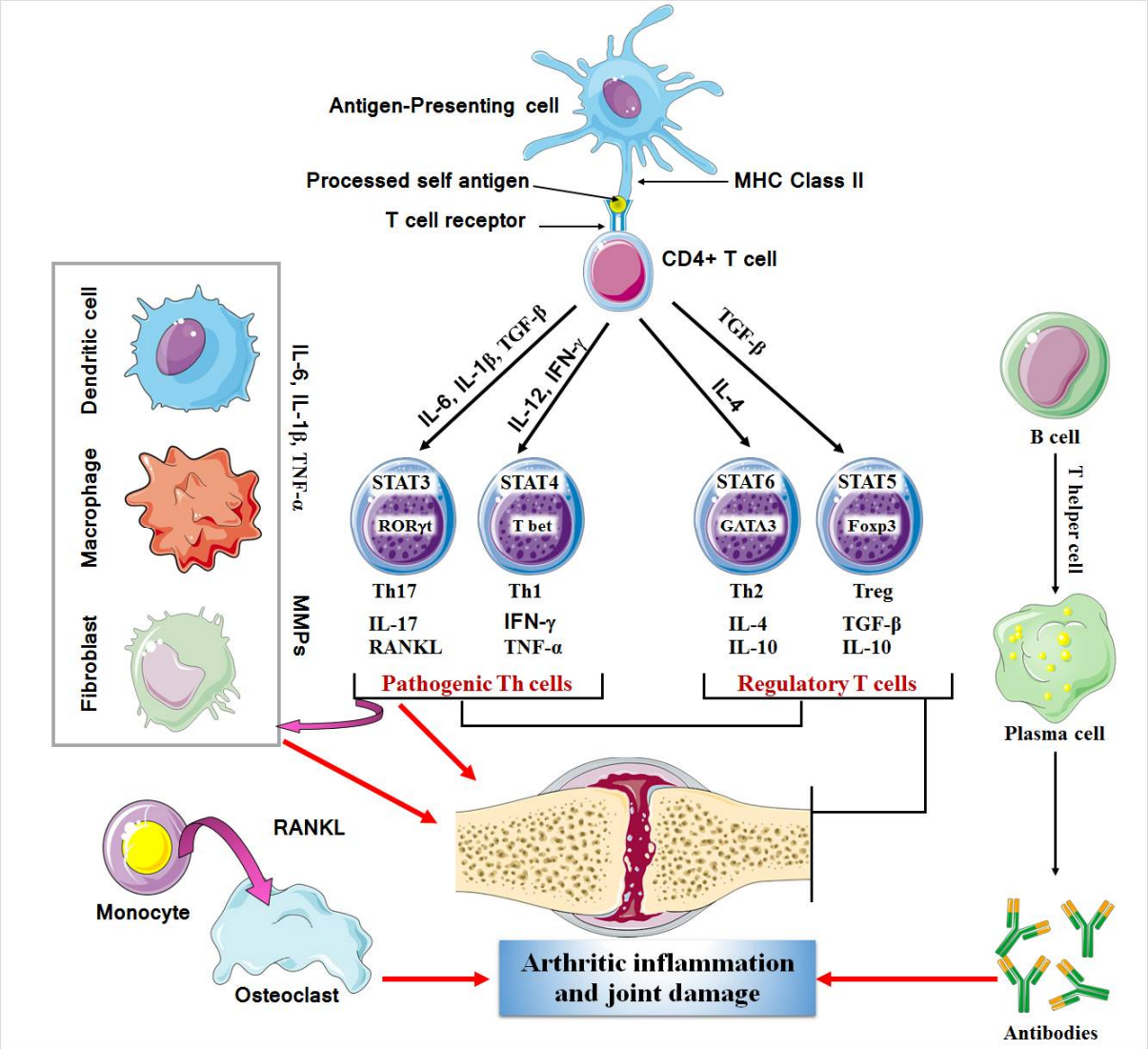

Figure1. An illustration of pathological mechanism and role of biochemical markers in the progression of RA.

On the other hand, the use of biologics in various autoimmune disorders is emerging. Numerous biologics have been currently been utilizing in these days that include Tocilizumab, certolizumab, etanercept, adalimumab, etc., for successful management of rheumatoid pain, inflammation, and other symptoms [6,7]. Despite their effective nature biologics are not very acceptable by a large patient's population due to their associated limitations. The use of such biologics suffers due to their generalized immunosuppression that made the body defending system weak against surrounding invades. They needed a skilled person to be administered as most of them can only be given parenterally. It also involves a huge amount of money to spend on getting these treatment options [6].

Therefore to overcome such associated issues with synthetic drugs and biologics there is an urgent need for the therapeutic option for effective and reliable management of RA [4, 8]. The bioactives from the herbal origin is now gaining huge attention nowadays due to the power of overcoming all the limitation of the above stated therapeutic options [9]. Alternatives to these medications are traditional medicines and natural resources that offer tremendous potential as promising medicinal candidates by their increased efficacy and minimum side effects[10, 11, 12, 13]. This further encourages the discovery and production of new bioactive substances to treat the inflammatory condition of RA [9]. Phytochemical studies by advanced analytical techniques revealed that various terpenoids, polyphenolic compounds, and alkaloids are renowned for their important in-vivo and in-vitro anti-inflammatory action [14]. Many of these prevent signs of arthritis, reinforce the histology of the joints involved in reducing lipid peroxidation, and increasing the number of antioxidants (e.g. superoxide dismutase, catalase, glutathione, glutathione peroxidase) and hemoxygenase-1 levels of expression [15, 16]. Therefore, exploring and insight of these

natural plant based actives and herbs would be a breakthrough in effective management of RA and other autoimmune conditions.

HERBS AND ACTIVES WITH ANTARTHRITIC POTENTIAL

Gomphrena celosioides Mart.

Gomphrena celosioides Mart. (Amaranthaceae) has been used traditionally to alleviate pain. It is belonging to the genus ***Gomphrena***, which is well known for the treatment of rheumatism in Brazil. Due to its traditional use, it has been screened for the antiarthritic on mice. The ethanolic extract of aerial parts was investigated for antiarthritic activity at the doses of 300, 700, and 1000 mg/kg by paw inflammation, mechanical hyperalgesia, cold allodynia, carrageenan-induced leukocyte migration, zymosan-induced peritonitis, carrageenan-induced adhesion, and rolling experiment models. All doses of ***G. celosioides*** significantly reduced paw inflammation, and mechanical hyperalgesia. The cold hyperalgesia was significantly diminished in 3-4 hours after the carrageenan injection. It has been also found that extract of ***G. celosioides*** prominently diminished leukocyte migration (at 1000 mg/kg, 300 mg/kg) in the carrageenan-induced pleurisy model and also minimize zymosan-induced articular edema. The extract has also shown prominent reduction in edema and mechanical hyperalgesia in Freund's complete adjuvant-induced inflammation screening on day 22, whereas the cold allodynia was decreased on day 6. Findings revealed that ethanolic extract of ***G. celosioides*** has some precious actives that may responsible for the antihyperalgesic effect and antiarthritic effect [17].

Moringa oleifera

Moringa oleifera is a miracle tree, having numerous of therapeutic potential to cure a variety of diseases. Scientific data reported that ***Moringa oleifera*** has some precious active principles like essential amino acids, carotenoids, ascorbic acid, flavonoids, and phenolics that may responsible for its therapeutic and nutritional values [**18].** Recently, Different solvents extracts of leaves were analyzed for phytochemicals by HPLC and also investigated for antiarthritic activity. HPLC analysis revealed considerable content of quercetin and kaempferol in leaves. Moreover, different extracts (Methanolic, aqueous, and ethyl acetate) were significantly decreased albumin denaturation and inhibition of proteinase activity. Results of antioxidant activity of extracts were significant, which may support the amelioration of clinical manifestation of RA. The antiarthritic effect was screened by formaldehyde induced paw inflammation, results showed that extracts produced the highest percent inhibition (82%) of paw inflammation at 600mg/kg. Leaf extract has also improved RBC count and weight loss in arthritic rats. This finding supports the antiarthritic activity of ***Moringa oleifera*** [19].

Olaxsubs corpioidea

Olaxsubs corpioidea is a miraculous plant of Nigeria, which is traditionally used to treat joint pain, rheumatism, liver diseases, and as an antidote [**20].** Its root extracts have been screened for anti-arthritic potential on Wistar albino rats by using chicken type II-Complete Freund's adjuvant (CFA) induced arthritis rat method. Findings reported that ethanol and aqueous root extracts effectively reduced the paw inflammation and triggered a marked decrease in C-reactive protein levels. Extracts have also normalized the rate of erythrocyte sedimentation and Significantly decrease the cytokine level such as TNF-α, IL-1B, and IL-6 in extract-treated arthritic rats[21].

Copaiferasalikounda (Heckel)

Seedpod Extracts of ***Copaiferasalikounda*** was tested for its antiarthritic efficacy by using chicken collagen/complete Freund's adjuvant-induced arthritis screening method. Different doses (400, 600, and 800 mg/kg body weight) of ethanol and aqueous extracts of seed pod were administrated after intradermal injection chicken collagen/complete Freund's adjuvant during the study. Observation demonstrated the marked inhibition in paw edema and improvement in the weight of experimental animals. The elevated level of the pro-inflammatory mediators (I L-1β, IL-6, TNF-α) were normalized in the arthritic animal of the extract-treated group. It has been also found that extract normalized the RBC count, erythrocyte sedimentation rate, and reduced C-reactive protein levels. Results of anti-arthritic screening were significant and dose-dependent manner, which indicates ***Copaiferasalikounda*** has some precious active that may reason behind its therapeutic potential **[22**].

Bauhinia purpurea

It is belonging to the family of *Caesalpiniaceae*, having a variety of medicinal properties to treat many diseases. Its ethnomedicinal use includes the treatment of wounds and diarrhoea [**23]**. In recent years, its antiarthritic screening reports revealed that hydroalcoholic extract from the stem bark has produced a prominent antiarthritic effect by reducing paw edema in complete Freund's adjuvant induced arthritis. Additionally, extracts have significantly decreased the level of cytokines (Tumour necrosis factor alpha [TNF-α], interleukin-6 [IL-6], IL-10, and IL-1 β) in arthritic rat but increase in the level of IL-10. Results have supported the antiarthritic activity of *Bauhinia purpurea*[**24**].

Dissotisthollonii Cogn.

Dissotisthollonii Cogn. (Melastomataceae) has been used by various communities to treat typhoid fever, gastrointestinal disorders, and inflammatory diseases. Its extracts of the leaves were tested for its potential to alleviate the pathological condition of arthritis. Aqueous and ethanolic extracts showed significant inhibition on cyclooxygenase, 5-lipoxygenase, protein denaturation, and ROS production. Both the extracts (Aqueous and ethanolic) significantly reduced paw inflammation induced by zymosan A (69.30% and 81.80%) and CFA (71.85% and 79.03%) at a dose of 500 mg/kg. Additionally, Both extracts produced a protective effect against mechanical hyperalgesia. This study demonstrated that DissotistholloniiCogn. has the potential to cure arthritis [**25**].

Tapinanthus globiferus

Joint arthritis is a known as one of the common autoimmune disorders, its safe and effective therapy stays a big challenge before pharmacy researchers, because of antagonistic impacts brought about by allopathic medications. Raceline et al. conducted a clinical examination for the evaluation of pharmacological impact of hydro-concentrate of Tapinanthus globiferus (HTG) leaves (at doses of 50, 100 and 200 mg/kg) on complete Freund's adjuvant (CFA)- instigated arthritis rat model. The HTG evidently eased physiological impedance by decreasing paw volume, shielding against anaemia, leukocytosis, transaminases action expanding, alkaline phosphatase and hyper-creatininemia. The extract has improved the cell anti- oxidant status and the structural complication at joint level. Such clinical impacts imposed by the HTG against the physiological dysfunctions, legitimize its present use in the customary treatment of rheumatoid joint inflammation **[26].**

Buddleja cordata Kunth

Buddleja cordata Kunth plant is utilized in customary natural medication in Mexico for the treatment of rheumatic agonies and ailments identified with fiery processes, as joint inflammation. Gutiérrez-Rebolledo et al. assessed the anti- arthritic potential and toxic impact of methanolic extricates from wild plant leaves (Bc-Wp), and cell culture (Bc-Cc) of *B. cordata*. applying complete Freund's adjuvant animal model. The best desired effect was discovered to be at the dose of 250 mg/kg; which was assessed to evaluate its effect over various physiological parameters associated with arthritis. Histological examination of po-pliteal ganglion indicated reducing rate of lytic sores, lipid inclusions and leukocyte invasion. In addition, both concentrates revealed anti-oedematous activity, protection against the oxidation of lipid and proteins, positive alteration on anti- oxidant enzymatic response, down-regulation on lymphocytes CD4+ makers of IL-1β and TNF-α, an expansion in IL-10 levels, which caused a lessening in leukocyte invasion in ganglionic tissue during exploratory joint inflammation. **[27].**

Glycine tabacina

The entire plant of *Glycine tabacina* (Labill.) Benth has been utilized as a customary home grown medication to treat rheumatism, ostealgia and nephritis in China. Just as a local natural medication 'I-Tiao-Gung' in Taiwan. Tu et al. led a clinical study to research the counter arthritic impact of ethanol concentrate of G. tabacina (GTE) in a collagen-induced joint inflammation (CIA) rodent model. GTE successfully ensured the bone and ligament of joints from disintegration, sore and deformation as well as strong anti CIA activity through hindering pro-incendiary cytokines and oxidation in rats, recommending its expected preventive and remedial impacts on rheumatoid joint inflammation (RI). **[28].**

Cleistopholis patens

Aloke et al. examination pointed toward assessing the counter ligament potentials of ethanol and aqueous concentrates of stem bark of *Cleistopholis patens* (SBCP) in complete Freund's adjuvant (CFA) actuated rheumatoid joint inflammation in rats. Rheumatoid joint pain induction caused noticeable increment in paw size, fiery makers and malondi-aldehyde (MDA) while critical decrease was seen in body weight comparatively with normal control. Treatment with test extract closely resembling indomethacin in markedly diminished the paw size and caused weight gain while the altered incendiary parameters and MDA were turned around comparative with negative control. The discoveries propose that SBCP have great anti-arthritic effect practically identical to indomethacin and subsequently could be utilized in rheumatoid joint pain. **[29].**

Nimbolide

Bloom of neem tree (*Azadirachta Indica*) contains nimbolide; a triterpenoid has different restorative properties. Cui et al. surveyed the counter ligament action of nimbolide in Complete Freund's Adjuvant - joint pain instigated rodent model. Rats treated with nimbolide showed stamped decrease in ligament score, organ records, volume of paw, edema arrangement, alongside significant up gradation in body weight. Histopathological discoveries demonstrated critical decrease in devastation of joints following nimbolide treatment. Such treatment has extraordinarily improved wellbeing and diminished aggravation through decreasing the pro-inflammatory cytokines articulation in arthritic rodents **[30].**

Achyranthes aspera

Chinnasamy et al evaluated the ameliorative capability of aqueous concentrate of Achyranthes aspera (AEAA) against joint inflammation utilizing formaldehyde (0.1 ml of 2% v/v) initiated swiss albino mice and Wistar rat model. Oral application of AEAA indicated a critical dose- dependent hindrance of paw volume; where the dosages of 250 mg/kg and 500 mg/kg were discovered to be 30% and, 38.33% successful individually. At fourteenth day the joint oedema was discovered to be 27.2% and 36.36 individually**[31].**

Physcion 8-O-β-glucopyranoside

Physcion 8-O-β-glucopyranoside (POGD), one of the major bio-actives present in the *Polygonum cuspidatum*, is an anthraquinones. Geng et al. examined the anti-ligament impact of POGD and its potential mechanism. A type II collagen-actuated arthritis (CIA) rodent model was set up to assess the anti-ligament impact of POGD in vivo. The anti- proliferative impacts of POGD on MH7A cells were recognized utilizing a CC K-8 test, and the arrival of pro fiery cytokines, interleukin (IL)- 1β, IL-6, IL-8, IL-12 and IL-17A, were investigated by ELISA. The outcomes showed that POGD fundamentally repressed MH7A cell development. POGD extraordinarily restrained paw oedema and the joint pain indices of the CIA rodents; it might likewise hinder the arrival of pro fiery cytokines. Moreover, POGD down regulated the articulation levels of TGF-β1, Smad4, NF-κB p65 (N), p38, p-p38, p-ERK1/2, JNK, p-JNK, TGF-β1, Smad4, p-JNK, JNK, p-P38, P38, p-ERK1/2, ERK1/2 and NF-κB p65 (N), and up-controlled the Smad7, NF-κB p65 (C) and IκB in TNF-α actuated MH7A cells. Taking everything into account, POGD is stated to be a promising potential anti- inflammatory moiety[32].

Alhagipseudalhagi

The plant *Alhagipseudalhagi* has for quite some time been utilized conventionally for the treatment of arthritis and gout in Ayurveda system. Singh et al investigated the phytochemical screening and impact of the crude concentrate of the ethereal part of A. pseudalhagi and its fraction in Formaldehyde incited, Turpentine instigated and complete freund's adjuvant (CFA) actuated exploratory models of joint pain in wistar albino rodents. The 95% ethanolic extract (APEE) was fractionated in four portions including chloroform division (APC), ethyl acetic acid derivation part (APEA), methanolic part (APM) and aqueous part (APA). These were exposed to clinical examination. Haematological and biochemical protocols viz. estimation of paw volume, joint breadth, body weight, RBC, WBC, Platelets, CRP, Hb, ALT, AST, ALP and total protein were resolved on APEE and APEA and supported by histopathological and radiological examination. The plant displayed dose dependent anti-arthritic impact. The ethyl acetic acid derived fraction demonstrated more critical impact when contrasted with the 95% ethanolic extricate at 400 mg/kg body weight dose.[33].

Eupatorium japonicum

Rheumatoid joint pain fibroblast-like synovial cells (RJFLS) are known to assume a significant part in rheumatoid joint pain (RJ) propagation, show resistance to immune-suppressants through carcinoma like properties. Shin et al distinguished a novel remedial compound for RJ, which diminished aggravation and the irregular multiplication of RJFLS of herbal family from Korean local plants named *Eupatorium japonicum Tunb.* (EJT). It was most adequately diminished viability through the activation of ROS-intervened apoptosis in a dose- dependent way. Moreover, the expanded ROS incited the expression of ATF4 and CHOP, central factors in ER stress-interceded apoptosis. Strikingly, EJT treatment diminished the activity of IL-1α and the transcription of MMP-9 on altered dose, which were instigated by TNF-α treatment, through the restraint of NF-α B and p38 enactment. All such parameters emphasized that EJT exhibited anti- inflammatory impacts clinically.[34]

Momordica charantia

Momordica charantia (Cucurbitaceae) is a plant, announced for its assortment of ethnic medicinal qualities. Kola et al. screened anti-arthritic action of the Ethanolic and aqueous concentrate of plant fruit. This activity was evaluated utilizing formaldehyde, Freund's adjuvant initiated joint pain in rats and Collagen incited joint pain model in mice. In Formaldehyde prompted joint pain model the rate of decrease in paw volume was 30.69% and 42.81% for hydro concentrate though for ethanolic extricate it was 25.23% and 39.5%. In Freund's adjuvant model, the level of decrease in paw volume was 56.1% and 66.51% for ethanolic extract and 52.6% and 63.83% for hydro concentrate, individually. In collagen prompted arthritis model, the joint pain index was discovered 6.02 and 3.68 for ethanolic extract at medium and high dosage. The joint pain index of hydro concentrate was discovered 5.66 and 4.03 at medium and high dosage. This trial gave a positive outcome in controlling inflammation in adjuvant initiated arthritic and collagen instigated joint inflammation model in rats and mice **[35].**

Table 1: Herbs and phytoactives with antiarthritic potential

S. No.	Name of Plant or actives	Family/type of actives	Part used/ source	Dose	Reported Active principles of herb	Reference
1.	*Gomphrena celosioides Mart.*	*Amaranthaceae*	Aerial parts	300, 700, and 1000 mg/kg	Aurantiamide and Aurantiamide acetate	[17,36]
2.	*Moringa oleifera*	*Moringaceae*	Leaf	50, 300 and 600 mg/kg	rutin, quercetin, and gallic acid	[19,37]
3.	*Olaxsubscorpioidea*	*Olacaceae*	Root	400, 600 and 800 mg/kg	Rutin, morin, quercetin and caffeic acid.	[21, 38]
4.	*Copaiferasalikounda (Heckel)*	*Leguminosae*	Seed pod	400, 600, and 800 mg/kg	-	[22]
5.	*Bauhinia purpurea*	*Fabaceae*	Stem bark	50, 100, and 200 mg/kg	Coumarin, Vitamin C, thiamine, Pantothenic acid	[24,39, 40]
6.	*Dissotisthollonii*	*Malastomataceae*	Leaf	500 mg/kg	β-sitosterol, β-sitosterol-3-O-β-D-glucopyranoside and arjunolic acid	[25, 41]
7.	*Tapinanthusglobiferus*	*Loranthaceae*	Leaf	50, 100 and 200 mg/kg	Alkaloids, flavonoids, polyphenols, tannins, steroids and saponins	[26, 42]
8.	*Buddleja cordata*	*Scrophulariaceae*	Leaf	250mg/kg	Vb, polyphenols, Cycloclorinone, 2[4`hydroxyphenyl]-ethyl hexacosanoate	[27, 43]
9.	*Glycine tabacina*	*Leguminosae*	Whole Plant	1.11, 2.22 and 4.44 mg/kg	Genistin, daidzein, genistein, pratensein, glytabastan A-H, coumestans 1–6 and 8–10	[28, 44, 45]
10.	*Cleistopholis patens*	*Annonaceae*	Stem Bark	400, 600 and 800 mg/kg	Eupolaurine, 3 methoxy champangine, glycosides, alkaloids, steroids, saponins, terpenoids, favonoids and carbohydrates	[29, 46]
11.	Nimbolide	*Triterpene*	*Azadirachta Indica*	20 mg/kg	-	[47, 48]
12.	*Achyranthes aspera*	*Amaranthaceae*	Leaf	250 and 500 mg/kg	Alkaloids, Carbohydrates, glycosides, phenolic compound, flavonoids, tannin and proteins	[31, 49]
13.	Physcion 8-O-β-glucopyranoside	*Anthraquinone*	*Polygonum cuspidatum*	20, 40 and 60 mg/kg	-	[32, 50, 51]
14.	*Alhagipseudalhagi*	***Papilionaceae***	Areal part	400 mg/kg	Tannins, coumarin derivatives, alkaloid, Quercetin, gum resin, Two new flavanone glycosides, alhagitin and alhagidin	[33, 52, 53]
15.	*Eupatorium japonicum*Thunb.	*Asteraceae*	Whole Plant	25 and 37.5 µg/ml	Thymol, pyrrolizidine Alkaloids, tindicine, amabiline,viridiforine, echinatine, rinderine	[34, 54]
16.	*Momordica charantia*	*Cucurbitaceae*	Fruit	200 and 400 mg/kg	alkaloid, glycoside, terpenoids, tannins, saponins, and flavonoids	[35, 55]

CONCLUSION

Earth germinates some miraculous herbs that showed their significant antiarthritic potential in pharmacological screenings. This review throws light on herbs and plant actives, which are recently reported for their antiarthritic efficacy. Some herbs such as *Gomphrena celosioides*, *Moringa oleifera, Olaxsubs copioidea* Mart., *Copaiferas alikounda (Heckel), Bauhinia purpurea, Dissotisthollonii, Tapinanthus globiferus, Buddleja cordata, Glycine tabacina, Cleistopholis patens,Achyranthes Aspera, Alhagipseudalhagi, Eupatorium japonicum thunb., Momordica charantia,* and few actives like Nimbolide, Physcion 8-O-β-glucopyranoside were investigated for their antiarthritic activity[**56**]. These herbs and actives were screened through various pharmacological screening methods such as collagen-induced arthritis, formaldehyde induced paw inflammation,Freund's adjuvant (CFA) induced arthritis, paw inflammation induced by zymosan A, and *in-vitro* Protein denaturation method. These pharmacological studies revealed that mentioned herbs and actives were potentially modulatemajor biochemical mediators include phospholipase A2 (PLA2), cyclooxygenase (COX), lipoxgenase (LOX), prostaglandins (PG), leukotrienes

(LT) and also modulate pro-inflammatory cytokines level (TNF)-α, IL-1β, IL-6, IL-8, IL-10, IL-17A. Additionally, these herbs and active have also showed prominent inhibitory effect on chronic inflammation during *in-vivo* pharmacological evaluation. These outcomes of recent studies indicate that mentioned herbs and actives may effective to modulate the pathophysiology of arthritis and may provide better alternative for conventional therapies.

ABBREVIATIONS

MMP-matrix metalloproteinase, NF-κB-nuclear factor-κB, RA-Rheumatoid arthritis, RANKL-receptor activator of nuclear factor kappa-B ligand, MHCII-major histocompatibility complex class II, CD4-cluster of differentiation 4, ALP -alkaline phosphatase, ALT-alanine transaminase, AST-aspartate aminotransferase, WBC-White Blood Cell, RBC- Red Blood Cell, CRP-C-reactive protein, Hb-hemoglobin, ATF4, activating transcription factor 4, NF-κB p65 -Nuclear factor kappa B p65, IκBα-inhibitor of nuclear factor kappa B, ERK1/2-extracellular signal-regulated protein kinase ½, JNK-c-Jun N-terminal kinases, TNF-α- Tumor necrosis factor-α, IL-12- interleukin-12, IFN-γ -Interferon-γ, MHC-II- Major histocompatibility complex II, TGF-β- Transforming growth factor beta, IL-1β- interleukin-1 beta, IL-6- interleukin-6, IL-8- interleukin-8, IL-10- interleukin-10, IL-17A- interleukin-17A, CFA- complete Freund's adjuvant.

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Potential of Neoteric Phytoactives and Herbs for Targeting Pathophysiological Modules of Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is debilitating, progressive autoimmune diseases of unknown cause. It affects joints by destructing bone and cartilage, leading to pain, inflammation, and restricted movement of joints. Many conventional antiarthritic agents are available, most of them are immunosuppressive and commonly associated with severe side effects. In recent years, numerous plant actives and herbs have been investigated for their anti-arthritic efficacy in order to overcome the therapeutic shortcomings of these conventional therapies. The finding of these researches revealed that herbs and their bioactives can modulate the major inflammatory cytokine expression in synovial cells and the regulation of the inflammatory immune process by targeting various cellular targets including PGE2 and COX-2. The present review is an endeavour to gather the therapeutic insight of some potential plant based actives and herbs for aiming pathophysiological targets in arthritis and their effective management. It also reports the medicinal value of herbs as novel clinical pharmaceutical agents for the management of arthritic conditions with the least side effects.

Keywords: *Arthritis, herb, plant actives, autoimmune disease, cytokines.*

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INTRODUCTION

Arthritis is an inflammational disease that is distinguished and begins largely in proportion to its age. Its prominent symptoms include joint pain, rigidity, decreased joint movement and redness, and joint swelling. Rheumatoid arthritis (RA) is a catastrophic type of inflammatory joint diseases that threaten people globally amongst many forms of arthritis[1,2,3]. Rheumatoid arthritis is a debilitating autoimmune condition due to the hyperproliferation of synovial fibroblast and massive invasion of inflammatory cells in the joints comprising CD4+T cells and innate immune cells such as macrophages. Numerous different pro-inflammatory cytokines such as IL-1β, TNF-α, IL- 6, IL-10, and IL-18 facilitate self-immunity, systemic inflammation, and degradation of the tissue [4,1].

A variety of prescribed medications have been used to regulate joint inflammation and pain in RA. These affordable drugs relieve joint inflammation, mitigate pain, minimize joint deterioration, and reduce disability. Non-Steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are most commonly utilized as the first line of therapy with fast responses to regulate inflammation and pain in RA [4]. Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, sulfasalazine, antimalarial medications, and other medicinal products that can modulate the functioning of the immune system by inhibiting radiographic growth and fatality. These medications used for the management of RA can squelch inflammatory targets and produce numerous therapeutic effects by suppressing the activation and creation of different enzymes (for example cyclooxygenase [COX]-1 and COX-2), cytokines (for example TNF-α and IL-1β), or transcription factors (for example, nuclear factor-kB [NF-kβ], c-Jun N-terminal kinases and p38 kinases). Though these therapies have ameliorating activity on the joint injury, physical mobility, and quality of life, their myriad side effects is still a curse to human health [**5**]. The side effects of these drugs include Cushing habitus, elevated blood pressure, hyperglycemia, stomach ulceration, and bleeding [4,5].

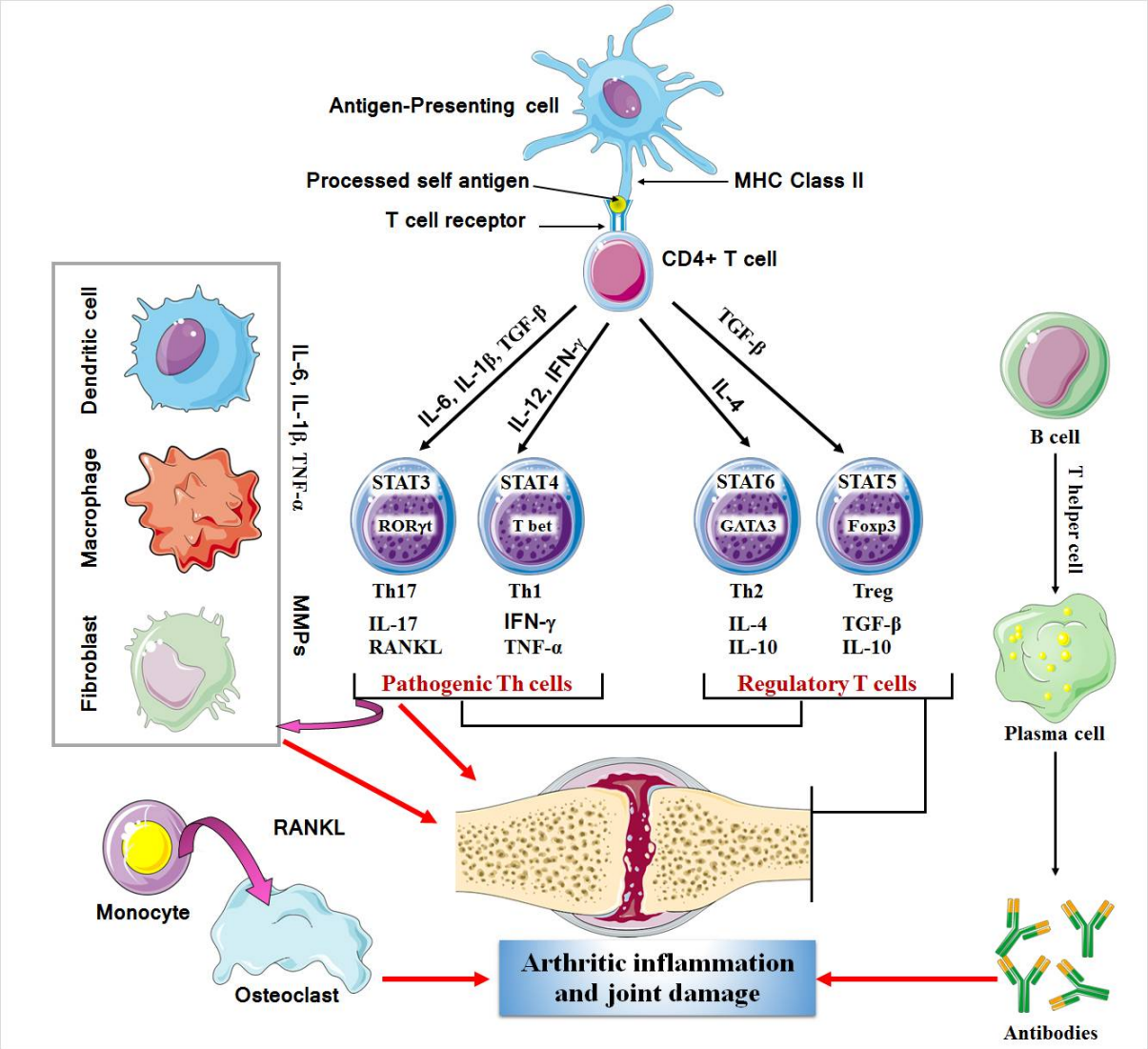

Figure1. An illustration of pathological mechanism and role of biochemical markers in the progression of RA.

On the other hand, the use of biologics in various autoimmune disorders is emerging. Numerous biologics have been currently been utilizing in these days that include Tocilizumab, certolizumab, etanercept, adalimumab, etc., for successful management of rheumatoid pain, inflammation, and other symptoms [6,7]. Despite their effective nature biologics are not very acceptable by a large patient's population due to their associated limitations. The use of such biologics suffers due to their generalized immunosuppression that made the body defending system weak against surrounding invades. They needed a skilled person to be administered as most of them can only be given parenterally. It also involves a huge amount of money to spend on getting these treatment options [6].

Therefore to overcome such associated issues with synthetic drugs and biologics there is an urgent need for the therapeutic option for effective and reliable management of RA [4, 8]. The bioactives from the herbal origin is now gaining huge attention nowadays due to the power of overcoming all the limitation of the above stated therapeutic options [9]. Alternatives to these medications are traditional medicines and natural resources that offer tremendous potential as promising medicinal candidates by their increased efficacy and minimum side effects[10, 11, 12, 13]. This further encourages the discovery and production of new bioactive substances to treat the inflammatory condition of RA [9]. Phytochemical studies by advanced analytical techniques revealed that various terpenoids, polyphenolic compounds, and alkaloids are renowned for their important in-vivo and in-vitro anti-inflammatory action [14]. Many of these prevent signs of arthritis, reinforce the histology of the joints involved in reducing lipid peroxidation, and increasing the number of antioxidants (e.g. superoxide dismutase, catalase, glutathione, glutathione peroxidase) and hemoxygenase-1 levels of expression [15, 16]. Therefore, exploring and insight of these

natural plant based actives and herbs would be a breakthrough in effective management of RA and other autoimmune conditions.

HERBS AND ACTIVES WITH ANTARTHRITIC POTENTIAL

Gomphrena celosioides Mart.

Gomphrena celosioides Mart. (Amaranthaceae) has been used traditionally to alleviate pain. It is belonging to the genus ***Gomphrena***, which is well known for the treatment of rheumatism in Brazil. Due to its traditional use, it has been screened for the antiarthritic on mice. The ethanolic extract of aerial parts was investigated for antiarthritic activity at the doses of 300, 700, and 1000 mg/kg by paw inflammation, mechanical hyperalgesia, cold allodynia, carrageenan-induced leukocyte migration, zymosan-induced peritonitis, carrageenan-induced adhesion, and rolling experiment models. All doses of ***G. celosioides*** significantly reduced paw inflammation, and mechanical hyperalgesia. The cold hyperalgesia was significantly diminished in 3-4 hours after the carrageenan injection. It has been also found that extract of ***G. celosioides*** prominently diminished leukocyte migration (at 1000 mg/kg, 300 mg/kg) in the carrageenan-induced pleurisy model and also minimize zymosan-induced articular edema. The extract has also shown prominent reduction in edema and mechanical hyperalgesia in Freund's complete adjuvant-induced inflammation screening on day 22, whereas the cold allodynia was decreased on day 6. Findings revealed that ethanolic extract of ***G. celosioides*** has some precious actives that may responsible for the antihyperalgesic effect and antiarthritic effect [17].

Moringa oleifera

Moringa oleifera is a miracle tree, having numerous of therapeutic potential to cure a variety of diseases. Scientific data reported that ***Moringa oleifera*** has some precious active principles like essential amino acids, carotenoids, ascorbic acid, flavonoids, and phenolics that may responsible for its therapeutic and nutritional values [**18].** Recently, Different solvents extracts of leaves were analyzed for phytochemicals by HPLC and also investigated for antiarthritic activity. HPLC analysis revealed considerable content of quercetin and kaempferol in leaves. Moreover, different extracts (Methanolic, aqueous, and ethyl acetate) were significantly decreased albumin denaturation and inhibition of proteinase activity. Results of antioxidant activity of extracts were significant, which may support the amelioration of clinical manifestation of RA. The antiarthritic effect was screened by formaldehyde induced paw inflammation, results showed that extracts produced the highest percent inhibition (82%) of paw inflammation at 600mg/kg. Leaf extract has also improved RBC count and weight loss in arthritic rats. This finding supports the antiarthritic activity of ***Moringa oleifera*** [19].

Olaxsubs corpioidea

Olaxsubs corpioidea is a miraculous plant of Nigeria, which is traditionally used to treat joint pain, rheumatism, liver diseases, and as an antidote [**20].** Its root extracts have been screened for anti-arthritic potential on Wistar albino rats by using chicken type II-Complete Freund's adjuvant (CFA) induced arthritis rat method. Findings reported that ethanol and aqueous root extracts effectively reduced the paw inflammation and triggered a marked decrease in C-reactive protein levels. Extracts have also normalized the rate of erythrocyte sedimentation and Significantly decrease the cytokine level such as TNF-α, IL-1B, and IL-6 in extract-treated arthritic rats[21].

Copaiferasalikounda (Heckel)

Seedpod Extracts of ***Copaiferasalikounda*** was tested for its antiarthritic efficacy by using chicken collagen/complete Freund's adjuvant-induced arthritis screening method. Different doses (400, 600, and 800 mg/kg body weight) of ethanol and aqueous extracts of seed pod were administrated after intradermal injection chicken collagen/complete Freund's adjuvant during the study. Observation demonstrated the marked inhibition in paw edema and improvement in the weight of experimental animals. The elevated level of the pro-inflammatory mediators (I L-1β, IL-6, TNF-α) were normalized in the arthritic animal of the extract-treated group. It has been also found that extract normalized the RBC count, erythrocyte sedimentation rate, and reduced C-reactive protein levels. Results of anti-arthritic screening were significant and dose-dependent manner, which indicates ***Copaiferasalikounda*** has some precious active that may reason behind its therapeutic potential **[22**].

Bauhinia purpurea

It is belonging to the family of *Caesalpiniaceae*, having a variety of medicinal properties to treat many diseases. Its ethnomedicinal use includes the treatment of wounds and diarrhoea [**23]**. In recent years, its antiarthritic screening reports revealed that hydroalcoholic extract from the stem bark has produced a prominent antiarthritic effect by reducing paw edema in complete Freund's adjuvant induced arthritis. Additionally, extracts have significantly decreased the level of cytokines (Tumour necrosis factor alpha [TNF-α], interleukin-6 [IL-6], IL-10, and IL-1 β) in arthritic rat but increase in the level of IL-10. Results have supported the antiarthritic activity of *Bauhinia purpurea*[**24**].

Dissotisthollonii Cogn.

Dissotisthollonii Cogn. (Melastomataceae) has been used by various communities to treat typhoid fever, gastrointestinal disorders, and inflammatory diseases. Its extracts of the leaves were tested for its potential to alleviate the pathological condition of arthritis. Aqueous and ethanolic extracts showed significant inhibition on cyclooxygenase, 5-lipoxygenase, protein denaturation, and ROS production. Both the extracts (Aqueous and ethanolic) significantly reduced paw inflammation induced by zymosan A (69.30% and 81.80%) and CFA (71.85% and 79.03%) at a dose of 500 mg/kg. Additionally, Both extracts produced a protective effect against mechanical hyperalgesia. This study demonstrated that DissotistholloniiCogn. has the potential to cure arthritis [**25**].

Tapinanthus globiferus

Joint arthritis is a known as one of the common autoimmune disorders, its safe and effective therapy stays a big challenge before pharmacy researchers, because of antagonistic impacts brought about by allopathic medications. Raceline et al. conducted a clinical examination for the evaluation of pharmacological impact of hydro-concentrate of Tapinanthus globiferus (HTG) leaves (at doses of 50, 100 and 200 mg/kg) on complete Freund's adjuvant (CFA)- instigated arthritis rat model. The HTG evidently eased physiological impedance by decreasing paw volume, shielding against anaemia, leukocytosis, transaminases action expanding, alkaline phosphatase and hyper-creatininemia. The extract has improved the cell anti- oxidant status and the structural complication at joint level. Such clinical impacts imposed by the HTG against the physiological dysfunctions, legitimize its present use in the customary treatment of rheumatoid joint inflammation **[26].**

Buddleja cordata Kunth

Buddleja cordata Kunth plant is utilized in customary natural medication in Mexico for the treatment of rheumatic agonies and ailments identified with fiery processes, as joint inflammation. Gutiérrez-Rebolledo et al. assessed the anti- arthritic potential and toxic impact of methanolic extricates from wild plant leaves (Bc-Wp), and cell culture (Bc-Cc) of *B. cordata*. applying complete Freund's adjuvant animal model. The best desired effect was discovered to be at the dose of 250 mg/kg; which was assessed to evaluate its effect over various physiological parameters associated with arthritis. Histological examination of po-pliteal ganglion indicated reducing rate of lytic sores, lipid inclusions and leukocyte invasion. In addition, both concentrates revealed anti-oedematous activity, protection against the oxidation of lipid and proteins, positive alteration on anti- oxidant enzymatic response, down-regulation on lymphocytes CD4+ makers of IL-1β and TNF-α, an expansion in IL-10 levels, which caused a lessening in leukocyte invasion in ganglionic tissue during exploratory joint inflammation. **[27].**

Glycine tabacina

The entire plant of *Glycine tabacina* (Labill.) Benth has been utilized as a customary home grown medication to treat rheumatism, ostealgia and nephritis in China. Just as a local natural medication 'I-Tiao-Gung' in Taiwan. Tu et al. led a clinical study to research the counter arthritic impact of ethanol concentrate of G. tabacina (GTE) in a collagen-induced joint inflammation (CIA) rodent model. GTE successfully ensured the bone and ligament of joints from disintegration, sore and deformation as well as strong anti CIA activity through hindering pro-incendiary cytokines and oxidation in rats, recommending its expected preventive and remedial impacts on rheumatoid joint inflammation (RI). **[28].**

Cleistopholis patens

Aloke et al. examination pointed toward assessing the counter ligament potentials of ethanol and aqueous concentrates of stem bark of *Cleistopholis patens* (SBCP) in complete Freund's adjuvant (CFA) actuated rheumatoid joint inflammation in rats. Rheumatoid joint pain induction caused noticeable increment in paw size, fiery makers and malondi-aldehyde (MDA) while critical decrease was seen in body weight comparatively with normal control. Treatment with test extract closely resembling indomethacin in markedly diminished the paw size and caused weight gain while the altered incendiary parameters and MDA were turned around comparative with negative control. The discoveries propose that SBCP have great anti-arthritic effect practically identical to indomethacin and subsequently could be utilized in rheumatoid joint pain. **[29].**

Nimbolide

Bloom of neem tree (*Azadirachta Indica*) contains nimbolide; a triterpenoid has different restorative properties. Cui et al. surveyed the counter ligament action of nimbolide in Complete Freund's Adjuvant - joint pain instigated rodent model. Rats treated with nimbolide showed stamped decrease in ligament score, organ records, volume of paw, edema arrangement, alongside significant up gradation in body weight. Histopathological discoveries demonstrated critical decrease in devastation of joints following nimbolide treatment. Such treatment has extraordinarily improved wellbeing and diminished aggravation through decreasing the pro-inflammatory cytokines articulation in arthritic rodents **[30].**

Achyranthes aspera

Chinnasamy et al evaluated the ameliorative capability of aqueous concentrate of Achyranthes aspera (AEAA) against joint inflammation utilizing formaldehyde (0.1 ml of 2% v/v) initiated swiss albino mice and Wistar rat model. Oral application of AEAA indicated a critical dose- dependent hindrance of paw volume; where the dosages of 250 mg/kg and 500 mg/kg were discovered to be 30% and, 38.33% successful individually. At fourteenth day the joint oedema was discovered to be 27.2% and 36.36 individually**[31].**

Physcion 8-O-β-glucopyranoside

Physcion 8-O-β-glucopyranoside (POGD), one of the major bio-actives present in the *Polygonum cuspidatum*, is an anthraquinones. Geng et al. examined the anti-ligament impact of POGD and its potential mechanism. A type II collagen-actuated arthritis (CIA) rodent model was set up to assess the anti-ligament impact of POGD in vivo. The anti- proliferative impacts of POGD on MH7A cells were recognized utilizing a CC K-8 test, and the arrival of pro fiery cytokines, interleukin (IL)- 1β, IL-6, IL-8, IL-12 and IL-17A, were investigated by ELISA. The outcomes showed that POGD fundamentally repressed MH7A cell development. POGD extraordinarily restrained paw oedema and the joint pain indices of the CIA rodents; it might likewise hinder the arrival of pro fiery cytokines. Moreover, POGD down regulated the articulation levels of TGF-β1, Smad4, NF-κB p65 (N), p38, p-p38, p-ERK1/2, JNK, p-JNK, TGF-β1, Smad4, p-JNK, JNK, p-P38, P38, p-ERK1/2, ERK1/2 and NF-κB p65 (N), and up-controlled the Smad7, NF-κB p65 (C) and IκB in TNF-α actuated MH7A cells. Taking everything into account, POGD is stated to be a promising potential anti- inflammatory moiety[32].

Alhagipseudalhagi

The plant *Alhagipseudalhagi* has for quite some time been utilized conventionally for the treatment of arthritis and gout in Ayurveda system. Singh et al investigated the phytochemical screening and impact of the crude concentrate of the ethereal part of A. pseudalhagi and its fraction in Formaldehyde incited, Turpentine instigated and complete freund's adjuvant (CFA) actuated exploratory models of joint pain in wistar albino rodents. The 95% ethanolic extract (APEE) was fractionated in four portions including chloroform division (APC), ethyl acetic acid derivation part (APEA), methanolic part (APM) and aqueous part (APA). These were exposed to clinical examination. Haematological and biochemical protocols viz. estimation of paw volume, joint breadth, body weight, RBC, WBC, Platelets, CRP, Hb, ALT, AST, ALP and total protein were resolved on APEE and APEA and supported by histopathological and radiological examination. The plant displayed dose dependent anti-arthritic impact. The ethyl acetic acid derived fraction demonstrated more critical impact when contrasted with the 95% ethanolic extricate at 400 mg/kg body weight dose.[33].

Eupatorium japonicum

Rheumatoid joint pain fibroblast-like synovial cells (RJFLS) are known to assume a significant part in rheumatoid joint pain (RJ) propagation, show resistance to immune-suppressants through carcinoma like properties. Shin et al distinguished a novel remedial compound for RJ, which diminished aggravation and the irregular multiplication of RJFLS of herbal family from Korean local plants named *Eupatorium japonicum Tunb.* (EJT). It was most adequately diminished viability through the activation of ROS-intervened apoptosis in a dose- dependent way. Moreover, the expanded ROS incited the expression of ATF4 and CHOP, central factors in ER stress-interceded apoptosis. Strikingly, EJT treatment diminished the activity of IL-1α and the transcription of MMP-9 on altered dose, which were instigated by TNF-α treatment, through the restraint of NF-α B and p38 enactment. All such parameters emphasized that EJT exhibited anti- inflammatory impacts clinically.[34]

Momordica charantia

Momordica charantia (Cucurbitaceae) is a plant, announced for its assortment of ethnic medicinal qualities. Kola et al. screened anti-arthritic action of the Ethanolic and aqueous concentrate of plant fruit. This activity was evaluated utilizing formaldehyde, Freund's adjuvant initiated joint pain in rats and Collagen incited joint pain model in mice. In Formaldehyde prompted joint pain model the rate of decrease in paw volume was 30.69% and 42.81% for hydro concentrate though for ethanolic extricate it was 25.23% and 39.5%. In Freund's adjuvant model, the level of decrease in paw volume was 56.1% and 66.51% for ethanolic extract and 52.6% and 63.83% for hydro concentrate, individually. In collagen prompted arthritis model, the joint pain index was discovered 6.02 and 3.68 for ethanolic extract at medium and high dosage. The joint pain index of hydro concentrate was discovered 5.66 and 4.03 at medium and high dosage. This trial gave a positive outcome in controlling inflammation in adjuvant initiated arthritic and collagen instigated joint inflammation model in rats and mice **[35].**

Table 1: Herbs and phytoactives with antiarthritic potential

S. No.	Name of Plant or actives	Family/type of actives	Part used/ source	Dose	Reported Active principles of herb	Reference
1.	*Gomphrena celosioides Mart.*	*Amaranthaceae*	Aerial parts	300, 700, and 1000 mg/kg	Aurantiamide and Aurantiamide acetate	[17,36]
2.	*Moringa oleifera*	*Moringaceae*	Leaf	50, 300 and 600 mg/kg	rutin, quercetin, and gallic acid	[19,37]
3.	*Olaxsubscorpioidea*	*Olacaceae*	Root	400, 600 and 800 mg/kg	Rutin, morin, quercetin and caffeic acid.	[21, 38]
4.	*Copaiferasalikounda (Heckel)*	*Leguminosae*	Seed pod	400, 600, and 800 mg/kg	-	[22]
5.	*Bauhinia purpurea*	*Fabaceae*	Stem bark	50, 100, and 200 mg/kg	Coumarin, Vitamin C, thiamine, Pantothenic acid	[24,39, 40]
6.	*Dissotisthollonii*	*Malastomataceae*	Leaf	500 mg/kg	β-sitosterol, β-sitosterol-3-O-β-D-glucopyranoside and arjunolic acid	[25, 41]
7.	*Tapinanthusglobiferus*	*Loranthaceae*	Leaf	50, 100 and 200 mg/kg	Alkaloids, flavonoids, polyphenols, tannins, steroids and saponins	[26, 42]
8.	*Buddleja cordata*	*Scrophulariaceae*	Leaf	250mg/kg	Vb, polyphenols, Cycloclorinone, 2[4`hydroxyphenyl]-ethyl hexacosanoate	[27, 43]
9.	*Glycine tabacina*	*Leguminosae*	Whole Plant	1.11, 2.22 and 4.44 mg/kg	Genistin, daidzein, genistein, pratensein, glytabastan A-H, coumestans 1–6 and 8–10	[28, 44, 45]
10.	*Cleistopholis patens*	*Annonaceae*	Stem Bark	400, 600 and 800 mg/kg	Eupolaurine, 3 methoxy champangine, glycosides, alkaloids, steroids, saponins, terpenoids, favonoids and carbohydrates	[29, 46]
11.	Nimbolide	*Triterpene*	*Azadirachta Indica*	20 mg/kg	-	[47, 48]
12.	*Achyranthes aspera*	*Amaranthaceae*	Leaf	250 and 500 mg/kg	Alkaloids, Carbohydrates, glycosides, phenolic compound, flavonoids, tannin and proteins	[31, 49]
13.	Physcion 8-O-β-glucopyranoside	*Anthraquinone*	*Polygonum cuspidatum*	20, 40 and 60 mg/kg	-	[32, 50, 51]
14.	*Alhagipseudalhagi*	***Papilionaceae***	Areal part	400 mg/kg	Tannins, coumarin derivatives, alkaloid, Quercetin, gum resin, Two new flavanone glycosides, alhagitin and alhagidin	[33, 52, 53]
15.	*Eupatorium japonicum*Thunb.	*Asteraceae*	Whole Plant	25 and 37.5 µg/ml	Thymol, pyrrolizidine Alkaloids, tindicine, amabiline,viridiforine, echinatine, rinderine	[34, 54]
16.	*Momordica charantia*	*Cucurbitaceae*	Fruit	200 and 400 mg/kg	alkaloid, glycoside, terpenoids, tannins, saponins, and flavonoids	[35, 55]

CONCLUSION

Earth germinates some miraculous herbs that showed their significant antiarthritic potential in pharmacological screenings. This review throws light on herbs and plant actives, which are recently reported for their antiarthritic efficacy. Some herbs such as *Gomphrena celosioides*, *Moringa oleifera, Olaxsubs copioidea* Mart., *Copaiferas alikounda (Heckel), Bauhinia purpurea, Dissotisthollonii, Tapinanthus globiferus, Buddleja cordata, Glycine tabacina, Cleistopholis patens,Achyranthes Aspera, Alhagipseudalhagi, Eupatorium japonicum thunb., Momordica charantia,* and few actives like Nimbolide, Physcion 8-O-β-glucopyranoside were investigated for their antiarthritic activity[**56**]. These herbs and actives were screened through various pharmacological screening methods such as collagen-induced arthritis, formaldehyde induced paw inflammation,Freund's adjuvant (CFA) induced arthritis, paw inflammation induced by zymosan A, and *in-vitro* Protein denaturation method. These pharmacological studies revealed that mentioned herbs and actives were potentially modulatemajor biochemical mediators include phospholipase A2 (PLA2), cyclooxygenase (COX), lipoxgenase (LOX), prostaglandins (PG), leukotrienes

(LT) and also modulate pro-inflammatory cytokines level (TNF)-α, IL-1β, IL-6, IL-8, IL-10, IL-17A. Additionally, these herbs and active have also showed prominent inhibitory effect on chronic inflammation during *in-vivo* pharmacological evaluation. These outcomes of recent studies indicate that mentioned herbs and actives may effective to modulate the pathophysiology of arthritis and may provide better alternative for conventional therapies.

ABBREVIATIONS

MMP-matrix metalloproteinase, NF-κB-nuclear factor-κB, RA-Rheumatoid arthritis, RANKL-receptor activator of nuclear factor kappa-B ligand, MHCII-major histocompatibility complex class II, CD4-cluster of differentiation 4, ALP -alkaline phosphatase, ALT-alanine transaminase, AST-aspartate aminotransferase, WBC-White Blood Cell, RBC- Red Blood Cell, CRP-C-reactive protein, Hb-hemoglobin, ATF4, activating transcription factor 4, NF-κB p65 -Nuclear factor kappa B p65, IκBα-inhibitor of nuclear factor kappa B, ERK1/2-extracellular signal-regulated protein kinase ½, JNK-c-Jun N-terminal kinases, TNF-α- Tumor necrosis factor-α, IL-12- interleukin-12, IFN-γ -Interferon-γ, MHC-II- Major histocompatibility complex II, TGF-β- Transforming growth factor beta, IL-1β- interleukin-1 beta, IL-6- interleukin-6, IL-8- interleukin-8, IL-10- interleukin-10, IL-17A- interleukin-17A, CFA- complete Freund's adjuvant.

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