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Review Article

Medicinal Plants Used for Treatment of Rheumatoid Arthritis: A Review

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ABSTRACT

The objective of this present review is to evaluate the therapeutic potential of *Zingiber officinale* in rheumatoid arthritis. We have also aimed to present a summary of mechanism of action of specific phytochemicals of *Zingiber officinale* to reduce the pain claimed by RA-affected patients. Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, which affects synovial tissue in multiple joints. Although conventional treatments of RA commonly alleviate the symptoms, high incidence of adverse reactions leads to research tendency towards complementary and alternative medicine. As various medicinal plants are traditionally used for the management of symptomatologies associated with RA in Persian medicine, we reviewed medicinal literature to confirm their efficacy in the management of RA. Key findings Scientific evidence revealed that traditional medicaments exert beneficial effects on RA through several cellular mechanisms including downregulation of pro-inflammatory cytokines such as TNF-a, IL-6 and NF-jB, suppression of oxidative stress, inhibition of cartilage degradation with destructive metalloproteinases and enhancement of antioxidant performance. Various active constituents from different chemical categories including flavonols, lignans, coumarins, terpenes, glycosylflavons, dihydroflavonols, phytoestrogens, sesquiterpene lactones, anthraquinones, alkaloids and thymoquinones have been isolated from the medicinal plants.

Keyword: A review, Medicinal plants, rheumatoid, Genetic factors, Infectious agents.

INTRODUCTION

Rheumatoid Arthritis (RA) is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs[1]. According to Data Monitor, RA affects approximately 1.8 million people in the U.S. and has no known cause. RA is not associated with factors such as aging. RA occurs when the body's immune system malfunctions, attacking healthy tissue and causing inflammation, which leads to pain and swelling in the joints, and may eventually cause permanent joint damage and painful disability. The primary symptoms of RA include progressive immobility and pain, especially in the morning, with long-term sufferers experiencing continual joint destruction for the remainder of their lives. There is no known cure for RA. Once the disease is diagnosed, treatment is prescribed to alleviate symptoms and/or to slow or stop disease progression. RA is associated with a heavy burden on society in terms of disability and health and economic costs. Because RA tends to be progressive in nature, involving a worsening of symptoms over time, and often begins for many people during the early or middle years of life, the disease often has a long-term impact on functioning (over 30 years for many individuals), which translates to a considerable social and economic cost[2]. For many patients, the chronic fatigue and pain associated with RA interferes significantly with the ability to function normally. Consequently, RA may take away a person's ability to work. One study estimated that as many as one-third of people with RA are forced to stop working within 10 years of being diagnosed. This makes loss of productivity an important part of the overall burden of the disease. Additionally, the many health complications associated with RA make the disease expensive from a cost standpoint and can have a pronounced negative impact on quality of life[3]. Fortunately, improvements in diagnosis and treatment of RA have meant that the impact of the disease on functioning and quality of life can be lessened. It is important to keep in mind that many of the studies that measure the impact of RA were conducted before some of the important recent treatment advances and don't reflect the potential for the latest treatments to improve functioning. Many RA patients, who only decades ago would have lost the ability to work and care for themselves, with newer treatments are able to continue to work and lead full lives.

Healthcare costs associated with RA are quite high. Based on American College of Rheumatology estimates, there are a quarter of a million hospital admissions and 9 million doctor visits annually in the US due to RA[3]. The annual cost of care for a patient with RA in the US averages

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almost $6,000 in direct costs related to RA (not including pharmaceutical costs) and another $2500 in costs not related to RA. One half of all health costs for RA are related to hospital admissions[4]. The higher the disability associated with RA, the higher the health cost. For example, in one study that rated disability using the Health Assessment Questionnaire, patients who had a score of 3 on the questionnaire (this indicates a high level of disability) also had about 3 times the cost in terms of health services compared with patients who had a score of 1, which indicates a lower level of disability[5]. This statistic emphasizes the importance of aggressive treatment to prevent or delay the disability that can be caused by RA. RA can cause economic burden, where it can severely restrict a person's ability to carry out tasks related to work and may even force an individual to reduce the amount they work or make changes in employment to accommodate their disability. In some cases, where the disease is severe, a person may be forced to leave the workforce altogether. All of these scenarios translate to lost income over the course of a lifetime[3].One study found that restrictions in work often affect individuals with RA early in the course of the disease, with the use of disability benefits increasing sharply within 2 years of diagnosis[6]. Another study that looked at the economic burden imposed by RA and osteoarthritis found that patients with RA had significantly higher expenses in terms of home care, child care, use of medical equipment and devices, and home remodeling than people without the disease. Patients with RA also had a significantly higher economic burden than patients with osteoarthritis and were 3 times more likely to have had a reduction in household income. Compared with osteoarthritis patients, individuals with RA had a greater reduction in work hours and a greater likelihood of having lost a job or taken early retirement. Additionally, a significantly higher percentage of RA patients in the study were unable to find work because of their condition compared with both osteoarthritis patients and people without either disease[7].

Genetic factors

Genetic factors account for 50% of the risk for developing RA[8]. About 60% of RA patients in the United States carry a shared epitope of the human leukocyte antigen (HLA)-DR4 cluster, which constitutes one of the peptide-binding sites of certain HLA-DR molecules associated with RA (eg, HLA-DR beta *0401, 0404, or 0405); HLA-DR1 (HLA-DR beta *0101) also carries this shared epitope and confers risk, particularly in certain southern European areas. Other HLA-DR4 molecules (eg, HLA-DR beta *0402) lack this epitope and do not confer this risk. Genes other than those of the major histocompatibility complex (MHC) are also involved, and results from sequencing genes of families with RA suggest the presence of several resistance and susceptibility genes, including *PTPN22* and *TRAF5*[9,10]. Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA), is a heterogeneous group of diseases that differs markedly from adult RA. JIA is known to have genetically complex traits in which multiple genes are important for disease onset and manifestations, and it is characterized by arthritis that begins before the age of 16 years, persists for more than 6 weeks, and is of unknown origin[11]. The *IL2RA/CD25* gene has been implicated as a JIA susceptibility locus, as has the *VTCN1* gene[12]. Some investigators suggest that the future of treatment and understanding of RA may be based on imprinting and epigenetics. RA is significantly more prevalent in women than in men[13,14], which suggests that genomic imprinting from parents participates in its expression[15,16]. Imprinting is characterized by differential methylation of chromosomes by the parent of origin, resulting in differential expression of maternal over paternal genes. Epigenetics is the change in DNA expression that is due to environmentally induced methylation and not to a change in DNA structure. Clearly, the research focus will be on environmental factors in combination with immune genetics.

Infectious agents

For many decades, numerous infectious agents have been suggested as potential causes of RA, including *Mycoplasma* organisms[17], Epstein-Barr virus (EBV), and rubella virus[18]. This suggestion is indirectly supported by the following evidence:

Occasional reports of flulike disorders preceding the start of arthritis

The inducibility of arthritis in experimental animals with different bacteria or bacterial products (eg, streptococcal cell walls)

The presence of bacterial products, including bacterial RNA, in patients' joints

The activity of several agents that have antimicrobial effects as disease-modifying drugs (eg, gold salts, antimalarial agents, and minocycline)

Emerging evidence also points to an association between RA and periodontopathic bacteria. For example, the synovial fluid of RA patients has been found to contain high levels of oral anaerobic bacterial antibodies common in periodontal infection, including *Porphyromonas gingivalis*[19,20].

Pathogenesis

RA is characterized not only by local inflammation damaging small and medium-sized joints but also by systemic inflammation. Different autoimmune and inflammatory processes are variably active in RA, making the entire disease entity clinically and pathobiologically heterogeneous. The e common denominators of differing RA subsets, such as autoimmunity and inflammation, are of key interest[21].

Synovial Immunologic Processes and Inflammation

Synovitis occurs when leukocytes infiltrate the synovial compartment. Leukocyte accumulation primarily reflects migration rather than local proliferation. Cell migration is enabled by endothelial activation in synovial microvessels, which increases the expression of adhesion molecules (including integrins, selectins, and members of the immunoglobulin superfamily) and chemokines. Accordingly, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which limits cellular egress, are characteristic features of early and established synovitis[22,23]. These microenvironmental changes,

combined with profound synovial architectural reorganization and local fibroblast activation, permit the buildup of synovial inflammatory tissue in rheumatoid arthritis.

Adaptive Immune Pathways

The genetics of rheumatoid arthritis and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis. However, even though T cells are abundant in the synovial milieu, the functional role of T cells remains insufficiently understood. Direct targeting of T cells by cyclosporine or T-cell–depleting therapeutics has shown limited or no efficacy[24]. This finding may reflect "broad spectrum" deletion of regulatory as well as effector T cells and suggests the need to target T-cell subsets. The synovium in rheumatoid arthritis contains abundant myeloid cells and plasmacytoid dendritic cells that express cytokines (interleukin-12, 15, 18, and 23), HLA class II molecules, and costimulatory molecules that are necessary for T-cell activation and antigen presentation[25,26]. Moreover, the use of abatacept (a fusion protein containing cytotoxic T-lymphocyte–associated antigen 4 and the FC fragment of IgG1) to disrupt antigen presentation by blocking T-cell costimulation (through the interaction of CD28 with CD80 or CD86) is efficacious in rheumatoid arthritis. Autoreactive T cells against citrullinated self-proteins have been identified. Synovial T-cell oligoclonality, germinal-center reactions, and B-cell hypermutation suggest ongoing local antigen-specific, T-cell–mediated B-cell help[27,28]. Although rheumatoid arthritis is conventionally considered to be a disease that is mediated by type 1 helper T cells, attention has increasingly focused on the role of type 17 helper T cells (Th17), a subset that produces interleukin-17A, 17F, 21, and 22 and tumor necrosis factor α (TNF-α)[29,30]. Macrophage-derived and dendritic-cell–derived transforming growth factor β and interleukin-1β, 6, 21, and 23 provide a milieu that supports Th17 differentiation and suppresses differentiation of regulatory T cells, thus shifting T-cell homeostasis toward inflammation. Interleukin-17A, which synergizes with TNF-α to promote activation of fibroblasts and chondrocytes, is currently being targeted in clinical trials. Regulatory (forkhead box P3 [Foxp3+]) T cells that are detected in tissues from patients with rheumatoid arthritis appear to have limited functional capability[31]. This imbalance between Th17 and regulatory T cells may also reflect local TNF-α, which blocks the activity of regulatory T cells[32]. An additional pathogenic pathway comprises antigen-nonspecific, T-cell contact–mediated activation of macrophages and fibroblasts, operating through interactions between CD40 and CD40 ligand, CD200 and CD200 ligand, and intracellular adhesion molecule 1 and leukocyte-function–associated antigen 1[18]. Humoral adaptive immunity is integral to rheumatoid arthritis. Synovial B cells are mainly localized in T-cell–B-cell aggregates — indeed, some tissues have ectopic lymphoid follicles [33] that are supported by the expression of factors that include a proliferation-inducing ligand (APRIL), B-lymphocyte stimulator (BLyS), and CC and CXC chemokines (e.g., CXC chemokine ligand 14 and CC chemokine ligand 21). Plasmablasts and plasma cells are more widely distributed in the synovium and also in juxta-articular bone marrow. A pathogenic role for CD20+ B cells is confirmed by the efficacy of rituximab in rheumatoid arthritis[34]. Because plasma cells are not targeted by anti-CD20 antibodies, and autoantibody levels are variably altered after treatment, these clinical observations suggest that the role of B cells and their progeny in the pathogenesis of rheumatoid arthritis goes beyond autoantibody production to include autoantigen presentation and cytokine production (e.g., interleukin-6, TNF-α, and lymphotoxin-β).

Blood tests

Routine viral screening by serologic testing does not significantly facilitate the diagnosis of RA in patients with early RA, nor is it helpful as a potential identifier of disease progression[35]. Potentially useful laboratory studies in suspected RA fall into 3 categories—markers of inflammation, hematologic parameters, and immunologic parameters—and include the following:

Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP) level
Complete blood count (CBC)
Rheumatoid factor (RF) assay
Antinuclear antibody (ANA) assay
Anti−cyclic citrullinated peptide (anti-CCP) and anti−mutated citrullinated vimentin (anti-MCV) assays (currently used in the 2010 American College of Rheumatology [ACR]/European League against Rheumatism [EULAR] classification criteria).
Anti filaggrin antibodies (AFA)
Micro RNA (miRNA)

Hematologic parameters

Complete blood count (CBC)

A CBC will test various levels of cells and chemicals present in your blood, including red and white blood cells, platelets, markers of liver and kidney function, and uric acid. Patients with RA often have an abnormal CBC, with anemia (decreased red blood cells or hemoglobin) and thrombocytopenia (decreased platelets)[36].

Immunologic parameters

Immunologic parameters include autoantibodies (eg, RF, Anti-citrullinated protein antibodies (ACPA) (including anti-cyclic citrullinated peptide [anti-CCP] and anti-mutated citrullinated vimentin [MCV] antibody tests) and ANAs, Anti filaggrin antibodies (AFA) and Micro RNA (miRNA).

Rheumatoid Factor (RF)

Rheumatoid factor is an immunoglobulin (Ig) M antibody directed against the Fc (crystallisable fraction) fragment of IgG, that is present in approximately 60-80% of patients with RA over the course of their disease but in less than 40% of patients with early RA)(Steiner, 2007). 3% to 5% of healthy adults have serum RF; this increases to 10%–30% in the elderly[37]. RF is more established as a biomarker for RA than anti-CCP, having been adopted as one of the American College of Rheumatology (ACR) classification criteria for RA in 1987[38]. The European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) notes that it is one of several prognostic markers used to identify patients with persistent

and/or erosive disease but does not recommend RF as a diagnostic marker for RA[39] most likely at least in part due to its limited specificity. RF is also common in other autoimmune diseases, infectious diseases, and malignancies, making it a relatively nonspecific marker of RA[40]. Although ANAs are present in approximately 40% of patients with RA, test results for antibodies to most nuclear antigen subsets are negative.

Treatment

After RA has been diagnosed and an initial evaluation performed, treatment should begin. Recent guidelines have addressed the management of RA[41,42], but patient preference also plays an important role. There are special considerations for women of childbearing age because many medications have deleterious effects on pregnancy. Goals of therapy include minimizing joint pain and swelling, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), maintaining quality of life (personal and work), and controlling extra-articular manifestations[43].

Mortality

Mortality rates are higher among RA patients than in the general population. The life expectancy decrease is about 3 to 10 years[44]. The excess mortality associated with RA has remained unchanged over the last two to three decades. In addition, recent studies show that RA patients have not experienced the survival gains seen in the general population, so that the gap between the two has widened[45]. The main causes of death in RA patients are cardiovascular, infectious, haematological, gastrointestinal, and pulmonary complications. Positive responses to treatment may indicate a better prognosis. A 2005 study by the Mayo Clinic noted that RA sufferers suffer a doubled risk of heart disease, independent of other risk factors such as diabetes, alcohol abuse, and elevated cholesterol, blood pressure and body mass index. The mechanism by which RA causes this increased risk remains unknown; the presence of chronic inflammation has been proposed as a contributing factor. It is possible that the use of new biologic drug therapies extend the lifespan of people with RA and reduce the risk and progression of atherosclerosis[46]. This is based on cohort and registry studies, and still remains hypothetical. It is still uncertain whether biologics improve vascular function in RA or not. There was an increase in total cholesterol and HDLc levels and no improvement of the atherogenic index.

Natural products from plants against Rheumatoid Arthritis

Natural products from plants have played a remarkable role to cure and avert different diseases from ancient times[47-49]. A study conducted by World Health Organization (WHO) has reported that about 80% of world's population relies on traditional medicine[50]. In USA, nearly 121 drugs are prescribed today, where 90 of themcome from the natural sources particularly from plants in a direct or indirect manner[51]. Herbal remedies can forman alternative source to relieve symptoms in patients having RA as well as to address the drawbacks associated with present treatment methods with allopathic drugs. It is scientifically palpable that *Zingiber officinale* Roscoe (Zingiberaceae) has a pivotal role to lessen the unbearable pain and inflammation associated with RA[52,53]. Ginger is obtained from rhizomes of *Zingiber officinale*.The plant belongs to Zingiberaceae family. Since ancient times, it has been widely used as a medicinal herb and spice[39]. Because of containing phytochemical ingredients and as a beneficial therapeutic agent, *Zingiber officinale* has been contributing pivotal roles against a broad range of diseases like asthma, diabetes, stroke, constipation, and others[54]. It is reported that 100,000 tons of gingers are annually produced, and 80% of this is produced in China[55]. Beneficial Effects of *Zingiber officinale* on Arthritis Associated Symptoms. Ginger has been cultivated since ancient period as a source of medicinal plant in China as well as other countries all over the world for use as a spice and for therapeutic benefits[56]. Evidences reported that consumption of ginger aids in relieving pain of joints associated with rheumatoid arthritis. Anti-inflammatory effect of ginger was scientifically proved first by Kiuchi et al. in 1982[57]. They isolated four new different compounds from ginger and all showed potential inhibitory effect to reduce prostaglandin synthesis, which is the key to inflammation. In another study carried out in 1992, they found that ginger showed anti-inflammatory activity by inhibiting not only prostaglandin but also leukotriene biosynthesis. A diarylheptanoid having catechol group showed activity against 5-lipoxygenase which further inhibited leukotriene biosynthesis which can produce an anti-inflammatory effect. Another constituent, namely, yakuchinone A, inhibited prostaglandin production, which can again result in an anti-inflammatory effect. The activity of *Zingiber officinale* as an anti-inflammatory agent was investigated by Thomson and his group in rats[58-90]. Experimental rats were treated with aqueous extract of *Zingiber officinale* either orally or intraperitoneally daily for 4 weeks. Though at low dose ginger did not reduce prostaglandin E2 concentrations, at high doses it significantly lowered PGE2 levels. Therefore, ginger could reduce inflammation associated with RA. *Aloe barbadensis* is cultivated in Europe and in many parts of India, including north-west Himalayan region. Aloe vera has been one of the most important plants used in folk medicine. Anthraquinone, anthracene, cinnamic acid and anthranilic acid are found in the Aloe vera plants that are responsible for its activity. Aloe vera is used in variety of skin ailments such as mild cuts, insect stings, bruises, poison ivy and eczema. It has also antibacterial and antifungal properties, used as blood purifier, anti-inflammatory, diuretic, uterine tonic, spermatogenic, laxative, purgative and fever reliever. The anti-arthritis property of aloe vera is due to the anthraquinone compound. Aloe vera stimulates the immune system and it is a powerful anti-inflammatory agent. Topical application of aloe vera extract result in the reduction of inflammation and arthritis in adjuvant induced arthritis in Sprague Dawley rats[91-93]. Ashwagandha also known as Indian ginseng, is an important ancient plant. The roots of Ashwagandha have been employed in Indian traditional systems of medicine, Ayurveda and Unani. It grows in dry parts in sub-tropical regions, Rajasthan, Punjab, Haryana,

Uttar Pradesh, Gujarat, Maharashtra and Madhya Pradesh. The pharmacological activity of the root is attributed to the alkaloids and steroidals lactones. Among the alkaloids, withanine, withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, somnine are mainly present. Two acyl glucosides viz sitoindoside-7 and sitoindoside-8 have been isolated from roots. The plant has been used as an aphrodisiac, liver tonic, anti-inflammatory agent, and more recently to treat asthma, ulcers, insomnia, and senile dementia. Clinical trials and animal research support the use of Ashwagandha for anxiety, neurological disorders, inflammation, and Parkinson's disease. Incorporation of Ashwagandha in the diet may prevent or decrease the growth of tumors in human. It helps in providing progressive, long lasting results for various health concerns like aging, anemia, arthritis, fatigue, sports fitness and stress-disorders. Oral administration of *Withenia somnifera* Linn., root powder showed the anti arthritic effect in adjuvant induced arthritic rats[94,95]. Black pepper is indigenous and cultivated in South India. It is also cultivated in Indonesia, Brazil, Malaysia and Shrilanka. India ranks first in the cultivation of this drug. Pipper contains an alkaloid piperine, volatile oil, pungent resins, piperidine and starch. It is used as a aromatic, stimulant, stomachic and carminative. It increases the secreation of gastric juices. It also increases the bio-availability of certain drugs. Piperine isolated from black pepper. Piperine administered orally at a dose of 20 and 100 mg/kg/day for eight days cause decrease in the arthritic symptoms in carrageenan-induced acute paw arthritis[96,97]. *Cissampelos pareira* Linn. is a species of flowering plant. It contains alkaloids, moderate quantity of flavonoids and saponins. It is used as antibacterial, anti-inflammatory, antihistamine, antioxidant, antispasmodic, diuretic, hypotensive, muscle relaxant, uterine relaxant, antiseptic, aphrodisiac, analgesic, anti-hemorrhagic, cardiotonic, diaphoretic, expectorant, febrifuge, hepatoprotective stimulant and tonic. The roots are administered against dyspepsia, diarrhoea, dropsy, cough, urinary difficulties like cystitis, dysentery, asthma and heart diseases. The leaves are used as an antiseptic against inflammation. The ethanolic extract of the roots are useful for relieving diarrhoea, pain and arthritis. The ethanolic extract of the roots of *Cissampelos pareira* Linn. significantly protective effect against complete Freund's adjuvant induced arthritis in dose dependent manner[98-100].

Arctium lappa L. (Asteraceae) Different species of Arctium have been used in traditional medicine for managing topical and systemic inflammatory conditions like rheumatoid disorders and chronic inflammatory bowel disease. Arctigenin is a lignan compound considered as one of the main constituents of *Arctium lappa* seeds. Upon inflammatory condition of RA pathogenesis, macrophages release pro-inflammatory cytokines and also nitric oxide (NO). Experimental investigations showed that arctigenin and its glycoside, arctiin, exhibit anti-inflammatory activity by suppressing a wide range of interleukins like IL-1b, IL-6, IL-4 and IL-5, as well as TNFa. This natural compound also alleviates the level of NO, which is mediated by suppressing the activity and expression of inducible NO synthase (iNOS). The cellular mechanism of anti-arthritic and anti-inflammatory activity of arctigenin is attributed to inhibiting nuclear signaling pathway (NF-jB) and mitogen-activated protein kinases (MAPKs) phosphorylation. MAPK is a major molecular target component that increases the expression of mediators of inflammation, which are central to the pathophysiology of RA. The a-isoform is important to the intracellular signalling pathway for the generation of TNFa or IL-1b. It also regulates the expression of COX-2, the enzyme that regulates PGE2 in inflammation[101] Inhibitors of MAPK such as arctigenin block the production of TNFa and IL-1b in monocytes and in synovial tissue of arthritic animals[102-104] Likewise, the leaf of A. minus (Hill) Bernh. exhibits anti-inflammatory potential in animal model of carrageenan-induced paw oedema[105].

Artemisia absinthium L. (Asteraceae) In traditional Persian medicine, the aerial part of A. absinthium is one of the ancient drugs that possess medicinal effects on neuralgia, rheumatoid disorder, as well as inflammatory diseases. Scoparone, one of the main active constituents of A. capillaris Thunb., suppresses inflammatory cascade produced by macrophages significantly in IFN-cand LPS-stimulated RAW 264.7 cell mediated by reducing the release of NO and PGE2 [106]. Any decrease in the level of NO is mediated by inhibition of iNOS expression. Likewise, inhibition of COX-2 expression by scoparone has a pivotal role in reduction in inflammatory reaction mediators[107].

Expression of COX-2 and synthesis of cytokines, such as TNF-a, IL-1b, IL-6 and IL-8, in RA condition is mediated by nuclear signalling pathway[108]. Aerial parts of A. sylvatica Maxim. and A. douglasiana Besser suppress nuclear signalling pathway (NF-jB), so they play an important role in the reduction in RA symptoms[37,39]. Phytochemical investigations have shown that numerous chemical constituents are considered as responsible agents for anti-arthritis and anti-inflammatory potentials of Artemisia spp including, artemisolide, 3-methoxytanapartholide, deacetyllaurenobiolide, moxartenolide, arteminolides, dehydroleucodine, scopoletin, scopolin and esculetin[109].

Cassia angustifolia M. Vahl (Fabaceae) *Cassia angustifolia* is one of the important traditional remedies used for clinical symptoms of RA. There is no scientific evidence on the efficacy of this species in managing rheumatoid disorders. However, the leaf of C. alata L. improves RA symptoms, including swelling, and cartilage degradation, and inhibits leucocyte infiltration into synovial fluid of rat knee joint[110,119]. *Citrus medica* L. (Rutaceae) *Citrus medica* commonly known as citron is cultivated worldwide, and the peel, leaves and root have been used in folk medicine of Asian nations particularly India and Iran. In traditional medicine, this natural drug is suggested to be useful for the treatment of rheumatism, hepatitis and arthritis. It has been confirmed that the fruits possess antioxidant and anti-inflammatory activity. The peels of *C. medica* and fruits of *C. unshiu* (Swingle) Marcow.

CONCLUSION

In conclusion, various phytochemical constituents of ginger have potential therapeutic roles in amelioration of RA symptoms and even possibly RA itself. It is expected that further elucidation of the molecular mechanisms behind the action of these phytochemicals not only can lead to discovery of new drugs for symptomatic relief of RA conditions like inflammation and pain, but also may make it possible to stop further progress or even reverse the damage caused by RA. Based on reviewed cellular and animal studies, various active phytochemical agents derived from mentioned medicinal plants are potentially efficacious on RA. These phytoconstituents are from different chemical categories including flavonols (quercetin), lignans (arctigenin), coumarins (scopoletin and scoparone), oxyanthraquinones, terpenes (limonene), triterpene saponin, steroidal saponin (seiboldogenin), glycosylflavons, phytoestrogens (ferutinin), sesquiterpenes (umbelliprenin), sesquiterpenoid (ilicic acid and inuviscolide), sesquiterpene lactones (ergolide and granilin), dihydroflavonols (sakuranetin and 7-Omethylaromadendrin), anthraquinones (emodin), alkaloids (brucine and brucine N-oxide), as well as thymoquinone. Further research is mandatory to focus on bioefficacy and safety aspects of these phytochemical agents for finding novel natural drugs.

REFERENCES

1. Firestein, G.S. Etiology and pathogenesis of rheumatoid arthritis. In: Ruddy S, Harris ED, Sledge CB, Kelley WN, eds. Kelley's Textbook of Rheumatology. 7th ed. Philadelphia: *W.B. Saunders*, 996–1042 (2005).
2. Kobelt, G. The social and economic impact of rheumatoid arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. Rheumatoid Arthritis. Philadelphia, Penn: *Mosby Elsevier*. 83-89 (2009).
3. Emery, P., McInnes, I.B., van Vollenhoven, R. and Kraan, M.C. Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis. *Rheumatology* (Oxford), 47(4): p. 392-8(2008).
4. Yelin, E. and Wanke, L.A. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum*. 42:1209-18(1999).
5. Fries, J.F. Safety, cost and effectiveness issues with disease modifying anti-rheumatic drugs in rheumatoid arthritis. *Ann Rheum Dis*. 58: I86-I9 (1999).
6. Geuskens, G.A., Burdorf, A. and Hazes, J.M. Consequences of rheumatoid arthritis for performance of social roles--a literature review. *J Rheumatol*. 34: 1248-60(2007).
7. Gabriel, S.E., Crowson, C.S., Kremers, H.M., Doran, M.F., Turesson, C., O'Fallon, W.M. and Matteson, E.L . Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. *Arthritis and Rheumatism*,48(1): p. 54-58(2003).
8. Barton, A. and Worthington, J. Genetic susceptibility to rheumatoid arthritis: an emerging picture. *Arthritis Rheum*. Oct 15. 61(10):1441-6(2009).
9. Begovich, A.B., Carlton, V.E., Honigberg, L.A. et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet*. 75(2):330-7(2004).
10. Potter, C., Eyre, S., Cope, A., Worthington, J. and Barton, A. Investigation of association between the TRAF family genes and RA susceptibility. *Ann Rheum Dis*. 66(10):1322-6(2007).
11. Prakken, B., Albani, S. and Martini, A. Juvenile idiopathic arthritis. *Lancet*. 377(9783):2138-49(2011).
12. Hinks, A., Ke, X., Barton, A., Eyre, S., Bowes, J. and Worthington, J. Association of the IL2RA/CD25 gene with juvenile idiopathic arthritis. *Arthritis Rheum*.. 60(1):251-7(2009).
13. Areskoug-Josefsson, K. and Oberg, U. A literature review of the sexual health of women with rheumatoid arthritis. *Musculoskeletal Care*. 7(4):219-26(2009).
14. Ahlmen, M., Svensson, B., Albertsson, K., Forslind, K. and Hafstrom, I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. *Ann Rheum Dis*. 69(1):230-3(2010).
15. Zhou, X.; Chen, W.; Swartz, M.D. et al. Joint linkage and imprinting analyses of GAW15 rheumatoid arthritis and gene expression data. *BMC Proc*. 1(1), S53(2007).
16. Martin-Trujillo, A., van Rietschoten, J.G., Timmer, T.C. et al. Loss of imprinting of IGF2 characterises high IGF2 mRNA-expressing type of fibroblast-like synoviocytes in rheumatoid arthritis. *Ann Rheum Dis*. 69(6):1239-42(2010).
17. Hoffman, I.E., Peene, I. and Cebecauer, L. Presence of rheumatoid factor and antibodies to citrullinated peptides in systemic lupus erythematosus. *Ann Rheum Dis.*64:330-332(2005).
18. McInnes, I.B. and Schett, G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol*.7:429-442(2007).
19. Hitchon, C.A., Chandad, F. and Ferucci, E.D. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. *J Rheumatol*. 37(6):1105-12(2010).
20. Routsias, J.G., Goules, A., Charalampakis, G. and Pikazis, D. Autopathogenic correlation of periodontitis and rheumatoid arthritis. *Rheumatology (Oxford)*. 50(7):1189-93(2011).
21. Kerola, A .Pathophysiology.Epidemiology of comor bidities in early rheumatoid arthritis with emphasis on cardiovascular disease, (1):3(2015).
22. Polzer, K., Baeten, D., Soleiman, A., Distler, J., Gerlag, D.M., Tak, P.P., Schett, G. and Zwerina, J. Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints. *Ann Rheum Dis*. 67:1610-1616(2008).

23. Szekanecz, Z., Soos, L., Szabo, Z. et al. Anti-citrullinated protein antibodies in rheumatoid arthritis: as good as it gets? *Clin Rev Allergy Immunol*. 34(1):26–31(2008).
24. Panayi, G.S. Even though T-cell-directed trials have been of limited success, is there reason for optimism? Nat Clin Pract Rheumato.2:58-59(2006).
25. Schroder, A.E., Greiner, A., Seyfert, C. and Berek, C. Differentiation of B cells in the nonlymphoid tissue of the synovial membrane of patients with rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 93:221-225(1996).
26. Lebre, M.C., Jongbloed, S.L., Tas, S.W., Smeets, T.J., McInnes, I.B. and Tak, P.P. Rheumatoid arthritis synovium contains two subsets of CD83-DC-LAMP-dendritic cells with distinct cytokine profiles. *Am J Pathol*. 172:940-950(2008).
27. Cantaert, T., Brouard, S., Thurlings, R.M., Pallier, A., Salinas, G.F., Braud, C., Klarenbeek, P.L. ,Vries, N. ,Zhang, Y., Soulillou, J.P., Tak ,P.P. and Baeten, D. Alterations of the synovial T cell repertoire in anti-citrullinated protein antibody-positive rheumatoid arthritis. *Arthritis Rheum*. 60:1944-1956(2009).
28. Humby, F., Bombardieri, M., Manzo, A. et al. Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. PLoS Med. 6:e1-e1(2009).
29. Chabaud, M., Fossiez, F., Taupin, J.L., Miossec, P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J Immunol*. 161:409-414(1998).
30. Miossec, P., Korn, T. and Kuchroo, V.K. Interleukin-17 and type 17 helper T cells. N Engl J Med. 361:888-898(2009).
31. Behrens, F., Himsel, A. and Rehart, S. Imbalance in distribution of functional autologous regulatory T cells in rheumatoid arthritis. Ann Rheum Dis. 66:1151-1156(2007).
32. Nadkarni, S., Mauri, C. and Ehrenstein, M.R. Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta. *J Exp Med*; 204:33-39(2007).
33. Seyler, T.M., Park, Y.W., Takemura, S. *et al*. BLyS and APRIL in rheumatoid arthritis. J Clin Invest. 115:3083-3092(2005).
34. Edwards, J.C., Szczepanski, L. and Szechinski, J. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 350:2572-2581(2004).
35. Varache, S., Narbonne, V. and Jousse-Joulin, S. Is routine viral screening useful in patients with recent-onset polyarthritis of a duration of at least 6 weeks? Results from a nationwide longitudinal prospective cohort study. Arthritis Care Res (Hoboken). 63(11):1565-70(2011).
36. Venables, P.J.W. and Maini, R.N. Clinical features of rheumatoid arthritis. In: O'Dell JR, Romain PR, eds. Up-to-date. *Wolters Kluwer Health*. Accessed at: 2013.
37. Nijenhuis, S., Zendman, A.J.W., Vossenaar, E.R., Pruijn, G.J.M. and Van venrooij, W.J. *Clin Chem*., 350, 17(2004).
38. Arnett, F.C., Edworthy, S.M. and Bloch, D.A. *Arthritis Rheumat*. 31, 315(1988).
39. Combe, B., Landewe, R. and Lukas, C. Eular recommendations for the management of early arthritis: Report of a task force of the european standing committee for international clinical studies including therapeutics (escisit). *Ann Rheum Dis* .66:34-45(2007).
40. Aletaha, D., Neogi, T., Silman, A.J., Funovits, J., Felson, D.T. and Bingham, C.O. 3rd. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum.62(9):2569-2581(2010).
41. Saag, K.G., Teng, G.G., Patkar, N.M. et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 59(6):762–784(2008).
42. Deighton, C., O'Mahony, R., Tosh, J., Turner, C. and Rudolf, M. Guideline Development Group. Management of rheumatoid arthritis: summary of NICE guidance. *BMJ*. 338: b702(2009).
43. Wasserman. Diagnosis and Management of Rheumatoid Arthritis. *Am Fam Physician.* 1; 84(11):1245-1252(2011).
44. Kitas, George. Why is life span shortened by Rheumatoid Arthritis? National Rheumatoid Arthritis Society. (2006).
45. Gonzalez, A., Maradit, Kremers, H., Crowson, C.S. and Nicola, P.J. Davis 3rd JM, Therneau, T.M. The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum*.56:3583–7(2007).
46. Atzeni, F., Turiel, M., Caporali, R., Cavagna, L., Tomasoni, L., Sitia, S., Sarzi-Puttini, P., Turiel, Caporali, Cavagna, Tomasoni, Sitia and Sarzi-Puttini. "The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases". *Autoimmun Rev*. 9 (12): 835–9(2010).
47. Phillipson, J. D. "Phytochemistry and medicinal plants," *Phytochemistry*, vol. 56, no. 3, pp. 237–243(2001).
48. Grindlay, D. and T. Reynolds, "The Aloe vera phenomenon: a review of the properties and modern uses of the leaf parenchyma gel," *Journal of Ethnopharmacology*, vol. 16, no. 2-3, pp. 117–151(1986).
49. Kong, J. M., Goh, N. K., Chia, L. S. and T. F. Chia, "Recent advances in traditional plant drugs and orchids," *Acta Pharmacologica Sinica*, vol. 24, no. 1, pp. 7–21(2003).
50. WHO, Traditional Medicine Strategy Launched, vol. 80 of 610, WHO News, Geneva, Switzerland, (2002).

51. Benowitz, S. "As war on cancer hits 25-year mark, scientists see progress, challenges," *Scientist*. 10:24(1996).
52. Mascolo, N., Jain, R., Jain, S. C. and F. Capasso, "Ethnopharmacologic investigation of ginger (Zingiber officinale)," *Journal of Ethnopharmacology*, 27: (1-2) :129–140(1989).
53. Mustafa T. and K. C. Srivastava, "Ginger (Zingiber officinale) in migraine headache," *Journal of Ethnopharmacology*, vol. 29(3): 267–273(1990).
54. White, B. "Ginger: an overview," *The American Family Physician*, 75(11): 1689–1691 (2007).
55. Kumar, S. and Saxena, K., U. N. Singh, and R. Saxena, "Antiinflammatory action of ginger: a critical review in anemia of inflammation and its future aspects," *International Journal of Herbal Medicine*, 1:416–20(2013).
56. Altman R. D. and Marcussen, K.. C. "Effects of a ginger extract on knee pain in patients with osteoarthritis," *Arthritisam and Rheumatism*. 44(11), 2531–2538 (2001).
57. Feng,T., Su, J. and Ding, Z.H. "Chemical constituents and their bioactivities of "tongling White Ginger" (Zingiber officinale)," *Journal of Agricultural and Food Chemistry*, vol. 59, no. 21, pp. 11690–11695(2011).
58. Thomson,M. , Al-Qattan, K. K. , Al-Sawan, S.M. , Alnaqeeb, M.A., I.Khan, M. Ali, "The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent, *Prostaglandins Leukotrienes and Essential Fatty Acids*.67(6)475–478(2002).
59. Kadhim, M.J., Sosa, A.A. and Hameed, I.H. Evaluation of anti-bacterial activity and bioactive chemical analysis of *Ocimum basilicum* using Fourier transform infrared (FT-IR) and gas chromatography-mass spectrometry (GC-MS) techniques. *International Journal of Pharmacognosy and Phytochemical Research*.8(6),127-146 (2016).
60. Mohammed, G.J., Kadhim, M.J. and Hussein, H.M. Characterization of bioactive chemical compounds from *Aspergillus terreus* and evaluation of antibacterial and antifungal activity. *International Journal of Pharmacognosy and Phytochemical Research*, 8(6): 889-905(2016).
61. Hameed, I.H., Altameme, H.J., Idan, S.A. Artemisia annua: Biochemical products analysis of methanolic aerial parts extract and anti-microbial capacity. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 7(2): 1843- 1868(2016).
62. Hussein, A.O., Mohammed, G.J., Hadi, M.Y. and Hameed, I.H. Phytochemical screening of methanolic dried galls extract of *Quercus infectoria* using gas chromatography-mass spectrometry (GC-MS) and Fourier transform-infrared (FT-IR). *Journal of Pharmacognosy and Phytotherapy*, 8(3): 49-59(2016).
63. Sosa, A.A., Bagi, S.H. and Hameed, I.H. Analysis of bioactive chemical compounds of Euphorbia lathyrus using gas chromatography-mass spectrometry and fourier-transform infrared spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research*, 8(5): 109-126(2016).
64. Altameme, H. J., Hadi, M.Y. and Hameed, I.H. Phytochemical analysis of *Urtica dioica* leaves by fourier-transform infrared spectroscopy and gas chromatography-mass spectrometry. *Journal of Pharmacognosy and Phytotherapy*,7(10): 238-252(2015a).
65. Mohammed, G.J., Omran, A.M., Hussein, H.M. Antibacterial and Phytochemical Analysis of *Piper nigrum* using Gas Chromatography-Mass Spectrum and Fourier-Transform Infrared Spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research*, 8(6): 977-996(2016).
66. Hamza, L.F., Kamal, S.A., and Hameed, I.H. Determination of metabolites products by *Penicillium expansum* and evaluating antimicobial activity. *Journal of Pharmacognosy and Phytotherapy*, 7(9): 194-220(2015).
67. Jasim, H., Hussein, A.O., Hameed, I.H. and Kareem, M.A. Characterization of alkaloid constitution and evaluation of antimicrobial activity of *Solanum nigrum* using gas chromatography mass spectrometry (GC-MS). *Journal of Pharmacognosy and Phytotherapy*, 7(4): 56-72(2015).
68. Hadi, M.Y., Mohammed, G.J. and Hameed, I.H. Analysis of bioactive chemical compounds of *Nigella sativa* using gas chromatography-mass spectrometry. *Journal of Pharmacognosy and Phytotherapy*, 8(2): 8-24(2016).
69. Hameed, I.H., Ibraheam, I.A. and Kadhim, H.J. Gas chromatography mass spectrum and fourier-transform infrared spectroscopy analysis of methanolic extract of *Rosmarinus oficinalis* leaves. *Journal of Pharmacognosy and Phytotherapy*. 7 (6): 90-106(2015).
70. Shareef, H.K., Muhammed, H.J., Hussein, H.M. and Hameed, I.H. Antibacterial effect of ginger (*Zingiber officinale*) roscoe and bioactive chemical analysis using gas chromatography mass spectrum. *Oriental Journal of Chemistry*,32(2): 20-40(2016).
71. Al-Jassaci, M.J., Mohammed, G.J. and Hameed, I.H**.** Secondary Metabolites Analysis of ***Saccharomyces cerievisiae*** and Evaluation of Antibacterial Activity**.** *International Journal of Pharmaceutical and Clinical Research*, 8(5): 304-315(2016).
72. Mohammed, G.J., Al-Jassani, M.J. and Hameed, I.H. Anti-bacterial, Antifungal Activity and Chemical analysis of *Punica grantanum* (Pomegranate peel) using GC-MS and FTIR spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research.* 2016; 8(3): 480-494.
73. Al-Marzoqi, A.H., Hadi, M.Y. and Hameed, I.H. Determination of metabolites products by *Cassia angustifolia* and evaluate antimicobial activity. *Journal of Pharmacognosy and Phytotherapy*. 2016; 8(2): 25-48.
74. Altameme, H.J., Hameed, I.H. and Abu-Serag, N.A. Analysis of bioactive phytochemical compounds of

two medicinal plants, *Equisetum arvense* and *Alchemila valgaris* seed using gas chromatography-mass spectrometry and fourier-transform infrared spectroscopy. *Malays. Appl. Biol*. 44(4): 47–58(2015b).
75. Hameed, I.H., Hamza, L.F., Kamal, S.A. Analysis of bioactive chemical compounds of *Aspergillus niger* by using gas chromatography-mass spectrometry and fourier-transform infrared spectroscopy. *Journal of Pharmacognosy and Phytotherapy*,7(8): 132-163(2015b).
76. Hameed, I.H., Hussein, H.J., Kareem, M.A. and Hamad, N.S. Identification of five newly described bioactive chemical compounds in methanolic extract of *Mentha viridis* by using gas chromatography-mass spectrometry (GC-MS). *Journal of Pharmacognosy and Phytotherapy*, 7 (7): 107-125(2015).
77. Hussein, H.M., Hameed, I.H. and Ibraheem, O.A. Antimicrobial Activity and spectral chemical analysis of methanolic leaves extract of *Adiantum Capillus-Veneris* using GC-MS and FT-IR spectroscopy. *International Journal of Pharmacognosy and Phytochemical Research*, 8(3): 369-385(2016).
78. Hussein, H.J., Hadi, M.Y. and Hameed, I.H. Study of chemical composition of *Foeniculum vulgare* using Fourier transform infrared spectrophotometer and gas chromatography - mass spectrometry. *Journal of Pharmacognosy and Phytotherapy*, 8(3): 60-89(2016).
79. Kadhim, M.J., Mohammed, G.J. and Hameed, I.H. In *vitro* antibacterial, antifungal and phytochemical analysis of methanolic fruit extract of *Cassia fistula*. *Oriental Journal of Chemistry*,32(2): 10-30(2016).
80. Altameme, H.J., Hameed, I.H., Idan, S.A. and Hadi, M.Y. Biochemical analysis of *Origanum vulgare* seeds by fourier-transform infrared (FT-IR) spectroscopy and gas chromatography-mass spectrometry (GC-MS). *Journal of Pharmacognosy and Phytotherapy*, 7(9): 221-237(2015c).
81. Hussein, H.M. Determination of phytochemical composition and ten elements content (CD, CA, CR, CO, FE, PB, MG, MN, NI AND ZN) of *CARDARIA DRABA* by GC-MS, FT-IR and AAS technique. *Int. J Pharm Bio Sci.* 7(3): (B) 1009 – 1017(2016).
82. Hussein, H.M. Analysis of trace heavy metals and volatile chemical compounds of *Lepidium sativum* using atomic absorption spectroscopy, gas chromatography-mass spectrometric and fourier-transform infrared spectroscopy. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 7(4): 2529 – 2555(2016).
83. Jaddoa, H.H., Hameed, I.H., and Mohammed, G.J. Analysis of volatile metabolites released by *Staphylococcus aureus* using gas chromatography-Mass spectrometry and determination of its antifungal activity. *Orient J Chem*.32(4) 2016.
84. Hameed, I.H., Salman, H.D. and Mohammed, G.J. Evaluation of antifungal and antibacterial activity and analysis of bioactive phytochemical compounds of *Cinnamomum zeylanicum* (Cinnamon bark) using gas chromatography-mass spectrometry. *Orient J Chem*.;32(4)(2016).
85. Kadhim, M.J., Mohammed, G.J. and Hussein, H.M. Analysis of bioactive metabolites from *Candida albicans* using (GC-MS) and evaluation of antibacterial activity. *International Journal of Pharmaceutical and Clinical Research*, 8(7): 655-670(2016).
86. Ubaid, J.M., Hussein, H.M. and Hameed, I.H. Analysis of bioactive compounds of *Tribolium castaneum* and evaluation of anti-bacterial activity. *International Journal of Pharmaceutical and Clinical Research*,8(7): 655-670(2016).
87. Hameed, I.H., Jebor, M.A., Ommer, A.J. and Abdulzahra, A.I. Haplotype data of mitochondrial DNA coding region encompassing nucleotide positions 11,719–12,184 and evaluate the importance of these positions for forensic genetic purposes in Iraq. *Mitochondrial DNA*, 27(2): 1324-1327(2016).
88. Hameed, I.H.. A new polymorphic positions discovered in mitochondrial DNA hypervariable region HVIII from central and north-central of Iraq. *Mitochondrial DNA*, 27(5): 3250-4(2016).
89. Mohammad, A. and Imad, H. Autosomal STR: From locus information to next generation sequencing technology. *Research Journal of Biotechnology*. (2013).
90. Hameed, I.H., Abdulzahra, A.I., Jebor, M.A., Kqueen, C.Y. and Ommer, A.J. Haplotypes and variable position detection in the mitochondrial DNA coding region encompassing nucleotide positions, *Mitochondrial DNA*, 10:716-11,184 (2015).
91. Altaee, N., Kadhim, M.J. and Hameed, I.H. Detection of volatile compounds produced by *Pseudomonas aeruginosa* isolated from UTI patients by gas chromatography-mass spectrometry. *International Journal of Current Pharmaceutical Review and Research*. 7(6) (2017).
92. Altaee, N., Kadhim, M.J. and Hameed, I.H. Characterization of metabolites produced by *E. coli* and analysis of its chemical compounds using GC-MS. *International Journal of Current Pharmaceutical Review and Research*. 7(6) (2017).
93. Hussein, J. H., Ubaid, J.M. and Hameed, I.H. Gas chromatography – mass spectrum analysis of volatile components of methanolic leaves extract of *Cordia myxa*. *International Journal of Current Pharmaceutical Review and Research*. 7(6) (2017).
94. Kadhim, M.J. *In Vitro* antifungal potential of *Acinetobacter baumannii* and determination of its chemical composition by gas chromatography-mass spectrometry. *Der Pharma Chemica*, 8(19): 657-665 (2016).
95. Al-Yaseri, A., Kadhim, W.A. and Hameed, I.H. Detection of volatile compounds emitted by *Proteus mirabilis* isolated from UTI patients and its anti-fungal potential. *Der Pharma Chemica*, 8(19): 671-678(2016).
96. Ubaid, J.M., Kadhim, M.J. and Hameed, I.H. Study of bioactive methanolic extract of *Camponotus fellah*

using Gas chromatography – mass spectrum. *International Journal of Current Pharmaceutical Review and Research*. 7(6) (2017).

97. Davis, R.H., Agnew PS and Shapiro E Antiarthritic Activity of Anthraquinones found in aloe vera for podiatric medicine. *Journal of the American Podiatric Medical Assoc*. 76(2): 1-8(1986).
98. Joshph, B. and Raj, S.J. Pharmacognostic and pharmacology properties of Aloe vera. *International journal of Pharmaceutical Sciences Review and Research*,4(2): 106-109(2010).
99. Devis, R.H. Agnew, P.S. and Shapiro, E. Anti arthritic activity of anthraquinones found in aloe for Podiatric Medicine. *Journal of the American Podiatric Medical Assoc*. 76(2), 61-66(1986).
100. Patwardhan, S.K., Bodas, K.S. and Gundewar, S.S. Coping with Arthritis sing safer herbal options. *International Journal of Pharmacy and Pharmaceutical Science*,2(1): 6-7(2010).
101. Mirjalili, M.H., Moyano, E., Bonfill, M., Cusido, R.M. and Palajon, J. Steroidal Lactones from *Withenia somnefera*, an ancient plant for noval medicines. *Molecules*, 14: 2373-2393(2009).
102. Bang, J.S., Oh, D.H., Choi, H.M., Sur, B.J., Lim, S.J., Kim, J.Y. *et al* Anti-inflammatory and anti-arthritic effect of piperine in human interleukin 1β-stimulated fibroblast like synoviocytes and in rat arthritis models. *Arthritis Research and Therapy* 11(20): 1-9 (2009).
103. Amresh, G., Singh, P.N. and Rao, Ch.V. Antinociceptive and antiarthritic activity of *Cissampelos pareira* roots. *J Ethnopharmacol* ,111(3): 531-6 (2007).
104. Singh, A., Duggal, S., Singh, J. and Katekhaye, S. An inside preview of Ethnopharmacology of *Cissampelos pareira* Linn. *International Journal of Biological Technology* 1(1): 114-120 (2010).
105. Arya, V., Gupta, V.K. and Kaur, R. A. review on plants having anti-arthritic potential. *International Journal of Pharmaceutical Sciences Review and Research*. 7(2), 131-136 (2011).
106. Tripathy, S., Pradhan, D. and Anjana, M. Anti-inflammatory and antiarthritic potential of *Ammania baccifera* Linn. *International Journal of Pharma and Bio Sciences* .1(3): 1-7(2010).
107. Kim, H.J. Scopoletin suppresses pro-inflammatory cytokines and PGE from LPS-stimulated cell line, RAW 2647 cells. *Fitoterapia*. 75, 261– 266 (2004).
108. Guan, Z. Induction of cyclooxygenase- 2 by the activated MEKK1 SEK1/MKK4 p38 mitogen-activated protein kinase pathway. *J Biol Chem*. 273: 12901–12908 (1998).
109. Zhao, F. et al. In vitro anti-inflammatory effects of arctigenin, a lignin from Arctium lappa L, through inhibition on iNOS pathway. *J Ethnopharmacol* .122: 457–462 (2009).
110. Hameed, I.H., Al-Rubaye A.F. and Kadhim, M.J. Antimicrobial Activity of Medicinal Plants and Urinary Tract Infections. *International Journal of Pharmaceutical and Clinical Research*. 8(11), (2017).
111. Kadhim WA, Kadhim, M.J., Hameed, I.H. Antibacterial Activity of Several Plant Extracts Against *Proteus Species*. *International Journal of Pharmaceutical and Clinical Research*. 8(11), (2017).
112. Sohn, E.H. Anti-allergic and anti-inflammatory effects of butanol extract from Arctium Lappa L. *Clin Mol Allergy*. 9, 4 (2011).
113. Hyam, S.R. Arctigenin ameliorates inflammation in vitro and in vivo by inhibiting the PI3K/AKT pathway and polarizing M1 macrophages to M2- like macrophages. *Eur J Pharmacol*. 708, 21–29 (2013).
114. Erdemoglu, N. et al. Estimation of anti-inflammatory, antinociceptive and antioxidant activities on *Arctium minus* (Hill) Bernh ssp Minus. *J Ethnopharmacol*. 121, 318–323 (2009).
115. Tak, P.P., Firestein, G.S. NF-jB: a key role in inflammatory diseases. *J Clin Invest*. 107, 7–11 (2001).
116. Guardia, T. et al. Anti-inflammatory activity and effect on gastric acid secretion of dehydroleucodine isolated from Artemisia douglasiana. *J Ethnopharmacol*. 88, 195–198 (2003).
117. Jin, H.Z. Inhibitors of the LPSinduced NF-jB activation from Artemisia sylvatica. *Phytochemistry*. 65, 2247–2253 (2004).
118. Kwon, O.S. et al. Inhibition of 5-lipoxygenase and skin inflammation by the aerial parts of Artemisia capillaris and its constituents. *Arch Pharm Res* 34, 1561–1569 (2011).
119. Lewis, A. and Levy, A. Anti-inflammatory activities of Cassia alata leaf extract in complete Freund's adjuvant arthritis in rats. *West Indian Med J*. 60, 615–621 (2011).