Malaysian Medicinal Plant and Their Potential as Novel Anti-Arthritic Substances

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Abstract. Rheumatoid Arthritis is an autoimmune disease that leads to bone and joint destruction. Statistic showed that rheumatoid arthritis can be suffered by at least 1% of adult population globally. It possesses to significant disability and consequent reduction in quality of life that contribute to substantial socio-economic impact. Current treatment is involving the prescriptions of many steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anti-cytokines and anti-rheumatic drugs. However, the major challenges of these drugs are poor bioavailability with potential to possess several adverse reactions such as gastrointestinal, cardiovascular disorders, stroke, kidney failures and costly. Therefore, scientific committees suggest medicinal plants extract need to be taken into consideration which most research studies reported for their anti-inflammatory, analgesic and anti-oxidant activities with minimum side effects, which has high potential to be used in arthritis treatment. In Malaysia, almost 2000 medicinal plant species are reported to promote several health benefits. Based on research studies, some medicinal plants possess potential bioactive compounds with the activity related to the various inflammation diseases, including arthritis. Therefore, this review focuses on Malaysian plant extracts with high therapeutic potential for the future development of novel anti-arthritic drugs. There are 5 Malaysian medicinal plants have been reviewed and all plants showed interesting anti-arthritic activities by reduced pro-inflammatory cytokines and enzymes that resulted into inhibitory arthritis manifestation that comparable to positive control group. All reviews concluded that natural active constituents contained inside the extracts as the main cause of successful anti-arthritic potential of each Malaysian medicinal plant.

1. Introduction

Inflammatory, chronic and systemic autoimmune diseases are the conditions definition of rheumatoid arthritis (RA). The primary symptoms of this illness include swelling, pain, bone and cartilage destruction which resulted with permanent disability and inability to work [1-4]. These symptoms occurred by the activation of several inflammatory/nociceptive mediators. The pathophysiology of RA is reported to be due to release of certain free radicals such as superoxide and nitrous oxide that generated as cellular metabolism by-products. These free radicals released can trigger the production of tumor necrosis factor (TNF-α) and interleukins (IL) from T-cells which altered the production of cytokines,
growth factors and adhesive molecules on immune cells, resulting with tissue destruction and inflammation [5].

The main goal of rheumatoid arthritis treatment is to eliminate symptoms, lowering progression of the disease and enhance life quality. Therefore, most medicines associate with anti-arthritis properties must enable to relief of analgesia, protection of articular structure, inflammation reduction, and maintenance of function and control of systemic involvement. Clinically, there are five strategies involved for the treatment of RA [6]. The main approach by the RA physicians is the oral prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and followed by mild glucocorticoids dosage for minimizing the inflammation signs as well as progression of disease. Drug substances such as sulfasalazine, methotrexate, and gold salts that categorized under disease modifying antirheumatic drugs (DMARDs) are specifically recommended for chronic RA patients [1]. Besides, another antirheumatic drugs for chronic condition are among cytotoxic and immunosuppressive groups such as azathioprine, cyclosporine and cyclophosphamide. These RA therapeutic agents are reported efficiently reduced the joint destruction and inflammation, however their long-term usage can lead to some health hazards [1].

As example, NSAIDs and steroids can lead to gastrointestinal, haematologic and renal complications and long-term consumption of these drugs may cause to severe adverse reactions such as gastrointestinal ulceration and bleeding [7-10]. Therefore recently, patients are seeking for complementary and alternative medicine for the safer management approach in the treatment of arthritis.

In worldwide, traditional medicines reported to possess wide range of remedies for the symptomatologies of arthritis management. The medicinal plant extracts as alternative treatment of arthritic have been explored by scientific committees. Malaysia is among the world’s countries cultivated by medicinal plants, about 2000 plants species that possess some pharmacological activities related to the various inflammation disorders including arthritis [11]. Therefore, this current review aims to discuss regarding several Malaysian medicinal plant with potential as anti-arthritic substances, focusing on phytochemicals constituent content and mechanism of action against arthritis via in vivo studies.

2. Methods
Some bibliographic research databases were used: Google Scholar, Science Direct, Scopus and Web of Science, where these databases were searched for related previous research studies which included at least one keyword from each of the following: (i) arthritis, (ii) Malaysia, (iii) medicinal plants, (iv) in vivo and about 5 medicinal plants have been reviewed.
Table 1. Lists of Malaysian Medicinal Plants and Their Anti-Arthritic Activities

| Scientific Name         | Family              | Active Constituents                                      | Local Name       | Types of Assays                                      | Anti-Arthritic Potential                                                                 | References |
|-------------------------|---------------------|----------------------------------------------------------|------------------|------------------------------------------------------|----------------------------------------------------------------------------------------|------------|
| Zingiber officinale     | Zingiberaceae       | Gingerols (essential oil)                                | Halia            | In vivo streptococcal cell wall (SCW)-induced arthritis | - Inhibited chronic phase of arthritis (days 13-28) after 28 mg/kg of ginger essential oil dosing  
- Decreased joint swelling 38%                                                                 | [12]        |
| Vernonia amygdalina     | Asteraceae          | Caffeoyl-quinic acid, flavanone-O-rutinoside, luteolin 7-O glucoside, dicaffeoyl-quinic acids, luteolin, apigenin derivative, and vernonioside | Pokok Bismillah  | In vivo Monosodium iodoacetate induced for osteoarthritis (OA) development on rats | - OA rats treated with Vernonia amygdalina 300 mg/kg reduced cartilage erosions and osteophytes unlike the control OA rat  
- Vernonia amygdalina extract significantly reduced the inflammatory prostaglandin E2, nuclear factor κB, IL-1β, ADAMTS-5, collagen type 10α1, and caspase3 in the OA rats | [13]        |
| Morinda citrifolia      | Rubiaceae           | Scopoletin (coumarin) and epicatechin (flavonoid)         | Mengkudu         | In vivo Monosodium iodoacetate induced for osteoarthritis (OA) development on rats | - After 28 days, the extract treatment reduced the in vivo joint tissues mRNA degradation and serum levels for joint cartilage degradation, aggrecanase, and collagenase biomarkers. | [14]        |
| Marantodes pumilum      | Primulaceae         | Quercetin, myricetin and kaempferol                      | Kacip fatimah    | In vivo anti-hyperuricemic effect on rats            | - Marantodes pumilum leaves extract promoted highest inhibitory activity on Xanthine Oxidase (IC50 130.5 μg/mL) compared to other extracts tested.  
- Oral administration of Marantodes pumilum leaves extract (200 mg/kg) significantly reduced serum uric acid level in hyperuricemic rats and comparable to positive control, allopurinol (5 mg/kg). | [15]        |
| *Achyranthes Aspera* | *Amaranthaceae* | Alkaloids, Carbohydrates, glycosides phenolic compound, flavonoids, tannin and proteins | *Pokok Jarong* | *In vivo arthritis induced by formaldehyde* |
|---------------------|-----------------|--------------------------------------------------------------------------------------|----------------|------------------------------------------|
|                     |                  | • Oral administration of the extract showed dose-dependent protection against formaldehyde induced arthritis.  
• At 21st day of treatment extract showed an inhibition of paw volume in the different doses of 250 mg/kg and 500 mg/kg at 30% and, 38.33% respectively.  
• At 14th day of treatment the joint swelling was found to be 27.2% (250 mg/kg) and 36.36 (500 mg/kg) |                  | [16] |
3. Discussions

In arthritis, the pro-inflammatory cytokines that cause joint-damaging are synthesized by macrophages and synoviocytes cells that inhibit the proteoglycans and collagen production in joints and increase their degradation [20]. These cells also potent to activate proteolytic enzymes such as matrix metalloproteinases (MMPs) and collagenases possessing cartilage destruction. Interleukin-1β (IL-1β), IL-6 and tumour necrosis factor-α (TNF-α) are the pro-inflammatory cytokines generate arthritis disease through increasing inflammatory cells (T cells, B cells and macrophages) and bone erosion [21]. The T-cell activation in human body lead to production of autoantibody and IL-6 and tumour necrosis factor-α (TNF-α) released, resulted into articular and extra-articular manifestation of arthritis occurs. Cyclooxygenase (COX)-2, the pro-inflammatory enzyme converts arachidonic acid into prostaglandin-E2 (PG E2) and promoted pannus and hyperplasia formation in synovial joints. This condition possesses to apoptosis in synovial fibrolasts and proliferation induction [20].

Therefore, the main aim of medicinal plants treatment is their capability to against pro-inflammatory cytokines and enzymes that manifest arthritis formation without toxic pharmacological consequences. According to the review of Malaysian medicinal plant, all plants have been proved to demonstrate interesting anti-arthritic pharmacological activity via in vivo assays.

Madzuki et al (2018) demonstrated successful anti-arthritic of Vernonia amygdalina extract that significantly reduced several pro-inflammatory cytokines and enzymes: prostaglandin E2, nuclear factor κB, IL-1β, ADAMTS-5, collagen type 10α1, and caspase3 in the osteoarthritis induced rats by 300 mg/kg oral administration. The anti-arthritic performance of the extract was revealed to be better than positive control group, rats orally administered with diclofenac (NSAIDs) [13]. The Vernonia amygdalina extract contained active constituents: Caffeoyl-quinic acid, flavanone-O-rutinoside, luteolin 7-O glucoside, dicafeoyl-quinic acids, luteolin, apigenin derivative, and vernonioside D suppressed the formation of osteoarthritis via inflammation reduction and cartilage-degrading proteases, besides reducing pain [13].

Another medicinal plant, Marantodes pumilum or locally known as ‘kacip fatimah’ was revealed to potent reduced serum level of uric acid in gout-induction rats at 200 mg/kg of dosage which comparable to control group (allopurinol, 5 mg/kg). This was attributable to inhibitory activity of uricosuric effects that possessed by flavonoids contained inside the extract such as rutin, quercetin and kaempferol [15-18].

Other medicinal plants reviewed also demonstrated interesting anti-arthritic activities, where Zingiber officinale inhibited chronic arthritis phase by decreased joint swelling at 38% [12]. Morinda citrifolia extract treatment reduced the in vivo joint tissues mRNA degradation and serum levels for joint cartilage degradation, aggrecanase, and collagenase biomarkers [14]. Besides, dose-dependent of Achyranthes Aspera extract 250 mg/kg and 500 mg/kg of oral administration inhibited rats paw volume at 30% and, 38.33% respectively [19].

4. Conclusion

According to the all Malaysian medicinal plants, the review showed successful anti-arthritic potential of each plant by their potential against pro-inflammatory cytokines and enzymes that resulted into inhibitory of arthritis manifestation. Active constituents presented in each extract were reported to be the main cause of anti-arthritic potential of each extract.
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