Review Article

A Review of Malaysian Medicinal Plants with Potential Anti-Inflammatory Activity

Fazleen Izzany Abu Bakar,1,2 Mohd Fadzelly Abu Bakar,1,2 Norazlin Abdullah,1,2 Susi Endrini,3 and Asmah Rahmat1

1Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia (UTHM), Hab Pendidikan Tinggi Pagoh, KM 1, Jalan Panchor, 84600 Muar, Johor, Malaysia
2Centre of Research for Sustainable Uses of Natural Resources (CoR-SUNR), Universiti Tun Hussein Onn Malaysia (UTHM), Parit Raja, 86400 Batu Pahat, Johor, Malaysia
3Faculty of Medicine, YARSI University, 10510 Jakarta, Indonesia

Correspondence should be addressed to Mohd Fadzelly Abu Bakar; fadzelly@uthm.edu.my

Received 30 January 2018; Revised 25 April 2018; Accepted 20 May 2018; Published 9 July 2018

Academic Editor: Mohammad A. Rashid

Copyright © 2018 Fazleen Izzany Abu Bakar et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This article aims to provide detailed information on Malaysian plants used for treating inflammation. An extensive search on electronic databases including PubMed, Google Scholar, Scopus, and ScienceDirect and conference papers was done to find relevant articles on anti-inflammatory activity of Malaysian medicinal plants. The keyword search terms used were “inflammation,” “Malaysia,” “medicinal plants,” “mechanisms,” “in vitro,” and “in vivo.” As a result, 96 articles on anti-inflammatory activity of Malaysian medicinal plants were found and further reviewed. Forty-six (46) plants (in vitro) and 30 plants (in vivo) have been identified to possess anti-inflammatory activity where two plants, Melicope ptelefolia (Tenggek burung) and Portulaca oleracea (Gelang pasir), were reported to have the strongest anti-inflammatory activity of more than 90% at a concentration of 250 µg/ml. It was showed that the activity was mainly due to the occurrence of diverse naturally occurring phytochemicals from diverse groups such as flavonoids, coumarins, alkaloids, steroids, benzophenone, triterpenoids, curcuminoids, and cinnamic acid. Hence, this current review is a detailed discussion on the potential of Malaysian medicinal plants as an anti-inflammatory agent from the previous studies. However, further investigation on the possible underlying mechanisms and isolation of active compounds still remains to be investigated.

1. Introduction

A primary physiologic defence mechanism known as inflammation helps to protect the body from noxious stimuli, resulting in the swelling or edema of tissues, pain, or even cell damage. The main purpose of this mechanism is to repair and return the damaged tissue to the healthy state [1]. The increase in size of the vessels only occurs around the inflammatory loci (i.e., neutrophils, macrophages, and lymphocytes) during the early stages of inflammation, but after 24 hours, many kinds of cells reach neutrophils, followed by macrophages within 48 hours and lymphocytes after several days [1]. It is well known that the disruption of cells occurs during inflammation processes, leading to the release of arachidonic acid, and further undergoes two metabolic pathways known as the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. COX pathways consist of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), while 5-lipoxygenase (5-LOX), 12-lipoxygenase (12-LOX), and 15-lipoxygenase (15-LOX) are the examples of the LOX pathway. The products of the COX pathway are prostaglandins (mediators of acute inflammation) and thromboxanes, while those of the LOX pathway are leukotrienes and hydroperoxy fatty acids [2, 3].

Clinically, the common signs of inflammation include pain, heat, redness, loss of function, and swelling on the affected tissue [4]. Other signs include fever, leukocytosis, and sepsis. There are many causes of inflammation such as pathogens (e.g., bacteria, viruses, and fungi), external injuries, and effects of chemicals or radiation. Inflammation can be classified into two categories: acute and chronic inflammation. Acute
inflammation is considered as the first line of defence against injury. It occurs in a short period of time and is manifested by the excretion of fluid and plasma proteins along with the emigration of leukocytes such as neutrophils. Meanwhile, chronic inflammation takes prolonged duration and is manifested by the action of lymphocytes and macrophages, resulting in fibrosis and tissue necrosis. Inflammation is considered as one of the most common concerns of diseases, ranging from the minor to a serious condition like cancer. Based on the recent advancement in imaging technologies, the chronic vascular inflammation is not involved in atherosclerosis but also in arterial hypertension and metabolic syndrome [5].

Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin, diclofenac, and celecoxib are extensively used for the treatment of inflammation. These drugs exhibit their anti-inflammatory properties by inhibiting the COX-1 activity and thus preventing the synthesis of prostaglandins [4]. However, the major concern is that NSAIDs may cause various side effects such as gastrointestinal complications [6]. Considering this, the quests for the new drug with anti-inflammatory properties from the medicinal plants with fewer or no side effects are greatly needed for the pharmaceutical industry [7, 8].

Plant-based or herbal medicine has been used traditionally to treat pain, inflammation, and inflammatory-mediated pain [9]. Malaysia is among the world’s 12 megadiverse countries where endemism is highest. At least a quarter of our tree flora is not found elsewhere in the world, and many of our herbaceous flora and other groups of species are unique [10]. In Malaysia, about 2000 medicinal plant species are reported to possess health benefit properties [11]. Based on nutritional studies, these medicinal plants contain diverse nutritive values and possess potential bioactive compounds with the activity related to the various inflammation disorders including gout [12] or age-related diseases [13]. Hence, this current review aims to disseminate detailed information on the anti-inflammatory potential of Malaysian medicinal plants, focusing on the bioactive phytochemicals, and mechanisms of action against inflammation in both in vitro and in vivo studies.

2. Methods

The bibliographic research was performed in the following databases: PubMed, Google Scholar, Scopus, and ScienceDirect, where these databases were searched for relevant studies which included at least one keyword from each of the following: (i) inflammation, (ii) Malaysia, (iii) medicinal plants, (iv) mechanisms, (v) in vitro, and (vi) in vivo. No limit was placed on the search time frame in order to retrieve all relevant papers, and the last search was performed on April 20, 2018. About 96 papers have been reviewed including journal articles and proceedings as well as the reference lists of articles for additional relevant studies.

3. Discussion

The World Health Organization (WHO) defines medicinal plants as plants which possess compounds that can be used for the therapeutic purposes as well as producing useful drugs from the metabolites. According to the WHO, medicinal plants are still being used by the people in developing countries to treat various diseases, and these products’ market continue to grow [14] which gives a good sign of economic importance of medicinal plants. Based on the previous report, 15% out of 300,000 plant species in the world have been studied for the pharmacological activity. Interestingly, about 25% of modern medicines have been developed from the natural resources such as medicinal plants [15]. Recently, the research on the medicinal plants for the health benefit purposes has increased worldwide and gained attention from all researchers all over the world including Malaysia. Malaysia is known as a country that is rich in the medicinal plant species. For instance, 1300 medicinal plant species and 7411 plant species have been recorded in Peninsular Malaysia and Sabah, respectively [16, 17].

Inflammation is a response of tissue to cell injury due to pathogens, damaged tissues, or irritants which initiates the chemical signals to heal the afflicted tissue [18]. The leukocytes such as neutrophils, monocytes, and eosinophils are activated and migrated to the sites of damage. During the inflammatory processes, the excessive nitric oxide (NO) and prostaglandin E2 (PGE2) as well as proinflammatory cytokines (i.e., tumour necrosis factor-alpha (TNF-α) and interleukins) are secreted by the activated macrophages. The nitric oxide and prostaglandin productions from the inducible nitric oxide synthase (iNOS) and COX-2, respectively, are the proinflammatory mediators responsible for many inflammatory diseases [19, 20]. Inflammation can be classified into two types known as acute and chronic inflammation. The vascular response to inflammation in the early stage (acute inflammation) can be clearly seen at the affected tissue as it becomes reddened due to the increase of blood flow and swollen due to edema fluid. Three main processes that involve during the vascular response to acute inflammation are (1) changes in vessel caliber and blood flow, (2) the increase in vascular permeability, and (3) fluid exudate formation. It is important to understand that an uncontrolled inflammation may contribute to many chronic illnesses [21]. For instance, chronic inflammation may lead to infectious diseases and cancer [22], while the prolonged inflammation may cause abnormal gene expression, genomic instability, and neoplasia [23, 24]. Currently, NSAIDs exhibit great effects in inhibiting the activity of COX-1 and COX-2, but COX-1 inhibitors are reported to exert side effects such as gastrointestinal erosions and renal and hepatic insufficiency [25]. COX-2 (Vioxx) also has been reported to cause serious cardiovascular events [2]. To overcome this, many studies on anti-inflammatory drugs from natural resources have been conducted. Enzyme inhibitory assays (i.e., COX and LOX) have been extensively used to study the effectiveness of medicinal plants in treating the inflammation due to the presence of many phytochemicals, and they are being consumed as a food or food supplement for many years. The Malaysian medicinal plants that possess an anti-inflammatory activity are shown in Tables 1 and 2 for in vitro and in vivo studies, respectively.

Based on the results obtained, many studies used the NO inhibition assay as a method to show the anti-inflammatory
| Scientific name | Family | Local name | Part/solvent used | Types of assays | Anti-inflammatory activity (%) | IC_{50} | Active compounds | References |
|-----------------|--------|------------|-------------------|-----------------|-------------------------------|---------|-----------------|------------|
| *Agelae borneensis* | Connaraceae | Akar rusa-rusa | Bark/methanol | LOX inhibition | 71%–100% at 100 μg/ml | NA | NA | [26] |
| *Anacardium occidentale* | Anacardiaceae | Pokok gajus | Leaves/methanol | NO inhibition | 16.10% at 250 μg/ml | NA | NA | [13] |
| *Averrhoa bilimbi* | Oxalidaceae | Belimbing buluh | Fruits/water, Leaves/chloroform | NO inhibition | 57.7% at 100 μg/ml | NA | NA | [13] |
| *Barringtonia racemosa* | Lecythidaceae | Putat kampung | Leaves/ethanol | Griess assay (NO inhibition) | 29.80% at 100 μg/ml | NA | NA | [27] |
| *Boesenbergia rotunda* | Zingiberaceae | Temu kunci | Rhizomes/hexane | Griess assay (nitrite determination) | NA | 36.68 μM | Boesenbergin A | [28] |
| *Boswellia serrata* | Burseraceae | Salai guggul and kemenyan | Leaves/methanol | Human red blood cell method | 80.00% at 2000 μg/ml | NA | NA | [29] |
| *Buchanania insignis* | Anacardiaceae | Tais/manga hutan | Bark/methanol | LOX inhibition | 41%–70% at 100 μg/ml | NA | NA | [26] |
| *Canarium patentinervium* | Burseraceae | Kedondong and kaju kedapak | Leaves and barks/hexane, chloroform, and ethanol | 5-LOX inhibition | NA | 1.76 μM | Scopoletin | [30] |
| *Carica papaya* | Caricaceae | Betik | Leaves/methanol | Griess assay (NO inhibition) | 72.63% at 100 μg/ml | 60.18 μg/ml | NA | [31] |
| *Chisocheton polyandrus* | Meliaceae | Lisi-lisi | Leaves/hexane, dichloromethane, and methanol | Soybean LOX inhibition assay | NA | 0.69 μM and 1.11 μM | Dammara-20,24-dien-3-one and 24-hydroxydammara-20,25-dien-3-one | [32] |
| *Citrus lanatus* | Cucurbitaceae | Tembikai | Fruit pulp/petroleum ether, chloroform, and 90% ethanol | COX-2 inhibitory activity | 60–70% at 100 μM | 69 μM | Cucurbitacin E | [33] |
| *Cosmos caudatus* | Asteraceae | Ulam raja | Leaves/methanol | Griess assay (NO inhibition) | 15.40% at 250 μg/ml | 17.6 μM | NA | [13] |
| *Crinum asiaticum* | Amaryllidaceae | Pokok bakung | Leaves/ethanol | NO inhibition | NA | 58.5 μg/ml | NA | [34] |
| *Curcuma longa* | Zingiberaceae | Kunyit | Rhizomes/hexane-ethyl acetate and methanol | COX-2 inhibitory activity | 82.50% and 58.90% at 125 μg/ml | NA | Monodemethoxycurcumin and bisdemethoxycurcumin | [35] |
| *Curcuma mangga* | Zingiberaceae | Temu mangga | Rhizomes/methanol | NO inhibition | 19.20% at 250 μg/ml | NA | NA | [13] |
| Scientific name          | Family            | Local name       | Part/solvent used                        | Types of assays                                                                 | Anti-inflammatory activity (%) | IC_{50}  | Active compounds                                      | References |
|-------------------------|-------------------|------------------|------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|----------|------------------------------------------------------|------------|
| Cythostema excelsia     | Annonaceae        | Lianas           | Leaves and stems/methanol                | LOX inhibition                                                                 | 41%–70% at 100 μg/ml          | NA       | NA                                                   | [26]       |
| Desmos chinensis        | Annonaceae        | Kenanga hutan    | Bark/methanol                            | LOX inhibition                                                                 | 41%–70% at 100 μg/ml          | NA       | NA                                                   | [26]       |
| Eurycoma longifolia     | Simaroubaceae     | Tongkat ali      | Root/hydroalcoholics                     | Human red blood cell membrane stabilization method                           | 70.97% at 1000 μg/ml          | NA       | NA                                                   | [36]       |
| Ficus deltoidea         | Moraceae          | Mas cotek        | Leaves/methanol                          | LOX inhibition                                                                 | 10.35% at 100 μg/ml           | NA       | NA                                                   | [37]       |
| Garcinia cuspidata      | Clusiaceae        | Asam kandis      | Bark/methanol                            | LOX inhibition                                                                 | 71%–100% at 100 μg/ml         | 28.3 μg/ml | NA                                                   | [26]       |
| Garcinia subelliptica   | Guttiferae        | Pokok penanti    | Seeds/chloroform                         | Chemical mediator released from mast cell and neutrophil inhibition          | NA                             | NA       | Garsubellin A and garcinelliptin oxide               | [38]       |
| Gynura pseudochina      | Asteraceae        | Pokok daun dewa  | Leaves/ethyl acetate                     | IL-6/luciferase assay                                                        | NA                             | 11.63 μg/ml | NA                                                   | [39]       |
| Jatropha curcas         | Euphorbiaceae     | Jarak pagar      | Latex and leaves/aqueous methanol        | NO inhibition                                                                 | NA                             | 29.7 and 93.5 μg/ml | NA                                                   | [40]       |
| Kaempferia galanga      | Zingiberaceae     | Cekur            | Rhizomes/petroleum ether, chloroform, methanol, and water | COX-2 inhibitory screening assay                                           | 57.82% at 200 μg/ml          | 0.83 μM  | Ethyl-β-methoxycinnamate                             | [41]       |
| Labisia pumila var. alata | Myrsinaceae    | Kacip fatimah    | Roots/methanol                           | Colorimetric nitric oxide assay (macrophage cell line)                     | 75.68% at 100 μg/ml           | NA       | NA                                                   | [42]       |
| Leucas linifolia        | Lamiaceae         | Ketumbak         | Whole plant/methanol                     | LOX inhibition                                                                 | 34% at 100 μg/ml              | NA       | NA                                                   | [43]       |
| Litsea garciae          | Lauraceae         | Engkala/pengalaban | Fruits/methanol                        | LOX assay                                                                     | NA                             | NA       | p-O-geranylcoumaric acid, kokusaginine, and scoparone | [13, 45]   |
| Melicope ptelefolia     | Rutaceae          | Tenggek burung   | Leaves/methanol                          | NO inhibition Soybean 15-LOX inhibition assay                                 | NA                             | 0.136 μg/ml | (1) 4-((2-0-Acetyl-α-L-rhamnosyl)benzyl] isothesiocyanate | [46]       |
|                         |                   |                  |                                          |                                                                            | 1.67 μM                        | 0.136 μg/ml | (2) 4-((3-0-Acetyl-α-L-rhamnosyl)benzyl] isothesiocyanate |            |
|                         |                   |                  |                                          |                                                                            |                                | 2.66 μM  | (3) 4-((4-0-Acetyl-α-L-rhamnosyl)benzyl] isothesiocyanate |            |
| Moringa oleifera        | Moringaceae       | Kelur            | Fruits/ethyl acetate                     | NO inhibition                                                                 | NA                             | 2.71 μM  | Soybean 15-LOX inhibition assay                      | [46]       |
| Scientific name          | Family             | Local name          | Part/solvent used                          | Types of assays              | Anti-inflammatory activity (%) | IC_{50}  | Active compounds                                  | References |
|-------------------------|--------------------|---------------------|-------------------------------------------|-------------------------------|-------------------------------|----------|--------------------------------------------------|------------|
| *Musa acuminata*        | Musaceae           | Pisang abu nipah   | Flowering stalk/methanol                  | Griess assay (NO inhibition) | 71.06% at 100 μg/ml          | 42.24 μg/ml | NA                                               | [31]       |
| *Ocimum basilicum*      | Lamiaceae          | Daun selasih       | Leaves/methanol                           | NO inhibition                 | 30.00% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Ocimum canum*          | Lamiaceae          | Kemangi putih      | Whole plant/methanol                      | LOX inhibition                | 75.64% at 100 μg/ml          | 54.12 μg/ml | NA                                               | [31]       |
| *Oenanthe javanica*     | Apiaceae           | Selom               | Whole plant/methanol                      | Griess assay (NO inhibition) | 75.64% at 100 μg/ml          | 54.12 μg/ml | 5.2 μM (eupatorin) 9.2 μM (sinensetin) | [47]       |
| *Orthosiphon stamineus* | Lamiaceae          | Misai kucing        | Leaves/petroleum ether, chloroform, and methanol | NO inhibition               | NA                            | NA       | Eupatorin and sinensetin                          | [47]       |
| *Pandanus amaryllifolius* | Pandanaceae         | Pandan              | Leaves/methanol                           | NO inhibition                 | 34.10% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Persicaria tenella*    | Polygonaceae       | Daun kesum          | Leaves/methanol                           | NO inhibition                 | 87.80% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Phaleria macrocarpa*   | Thymelaeaceae      | Mahkota dewa       | Pericarp/methanol                         | NO inhibition                 | 69.50% at 200 μg/ml          | NA       | NA                                               | [48]       |
| *Piper sarmentosum*     | Piperaceae         | Kaduk               | Leaves/methanol                           | Griess assay (NO inhibition) | 62.82% at 100 μg/ml          | 60.24 μg/ml | NA                                               | [31]       |
| *Pithecellobium conforturn* | Fabaceae          | Medang              | Seeds/methanol                            | NO inhibition                 | 23.50% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Portulaca oleracea*    | Portulacaceae      | Gelang pasir        | Leaves/methanol                           | NO inhibition                 | 94.80% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Psophocarpus tetragonolobus* | Fabaceae           | Kacang botol       | Pod/methanol                              | Griess assay (NO inhibition) | 39.28% at 100 μg/ml          | >100 μg/ml | NA                                               | [31]       |
| *Sauropus androgymus*   | Phyllanthaceae     | Cekur manis         | Leaves/methanol                           | Griess assay (NO inhibition) | 68.28% at 100 μg/ml          | 58.34 μg/ml | NA                                               | [31]       |
| *Solanum nigrum*        | Solanaceae         | Terung meranti      | Leaves/methanol                           | NO inhibition                 | 27.60% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Solanum torvum*        | Solanaceae         | Terung belanda      | Leaves and fruits/methanol                | NO inhibition                 | 25.20% at 250 μg/ml          | NA       | NA                                               | [13]       |
| *Thymus vulgaris*       | Lamiaceae          | Taim                | Whole plant/methanol                      | LOX inhibition                | 62% at 100 μg/ml             | NA       | NA                                               | [43]       |
| *Timonius flavescens*   | Rubiaceae          | Batut               | Leaves/methanol                           | LOX inhibition                | 71%–100% at 100 μg/ml        | 8.9 μg/ml | NA                                               | [26]       |
Table 2: The medicinal plants which are considered to possess anti-inflammatory activity based on in vivo studies.

| Scientific name               | Family              | Local name       | Part/solvent used         | Dose of the extract       | Experimental animals | Results                                                                                                                                                                                                 | References |
|------------------------------|---------------------|------------------|---------------------------|---------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| *Achyranthes aspera*         | Amaranthaceae       | Ara songsang     | Root/ethyl alcohol        | 50, 100, and 200 mg/kg   | Wistar rats          | All the doses caused significant reduction in paw edema compared to control                                                                                                                                  | [49]       |
| *Annona muricata*            | Annonaceae          | Durian belanda   | Leaves/aqueous ethanol    | 10–300 mg/kg             | Sprague-Dawley rats | A significant decrease of the proinflammatory cytokines TNF-α and IL-1β was observed. A significant inhibition (93.34%) was observed in carrageenan-induced edema in rats at a dose of 300 mg/kg. | [50]       |
| *Ardisia crispa*             | Myrsinaceae         | Mata pelandok    | Root/ethanol              | 3, 10, 30, 100, and 300 mg/kg of body weight | Sprague-Dawley rats | The extract displayed significant inhibition of inflammation.                                                                                                                                                | [51]       |
| *Atylosia scarabaeoides*     | Fabaceae            | Kara-kara/kacang kerara | Leaves/ethanol           | 150, 300, and 450 mg/kg | Swiss albino mice   | Highest inhibition of paw edema (38.38%) at a dose of 450 mg/kg after 4h of administration.                                                                                                               | [52]       |
| *Citrullus lanatus*          | Cucurbitaceae       | Tembikai         | Fruit pulp/petroleum ether, chloroform, and 90% ethanol | 30 and 60 mg/kg of body weight | BALB/c mice         | Cucurbitacin E inhibits inflammation significantly from the fourth hour and is able to revert paw edema through the COX-2 inhibition.                                                               | [33]       |
| *Corchorus capsularis*       | Malvaceae           | Kancing baju     | Leaves/chloroform         | 20, 100, and 200 mg/kg   | BALB/c mice and Sprague-Dawley rats | The extract caused significant reduction in the thickness of edematous paw for the first 6 h                                                                                                               | [53]       |
| *Crinum asiaticum*           | Amaryllidaceae      | Pokok bakung     | Leaves/methanol           | 50 mg/kg of the extract  | Mice                | Inhibition of paw edema (94.8%). No significant suppression was observed after oral administration of all doses on carrageenan-induced paw edema.                                                      | [54]       |
| *Curcuma aeruginosa*         | Zingiberaceae       | Temu hitam       | Rhizomes/chloroform, methanol, and water | 100, 200, 400, and 800 mg/kg | Swiss mice and Wistar rats | No suppression of anti-inflammatory/proinflammatory cytokines was observed with all doses.                                                                                                                   | [55]       |
| *Curcuma longa*              | Zingiberaceae       | Kunyit            | Rhizomes/water            | 200 mg/kg of body weight | Wistar albino rats  | The production of anti-inflammatory/proinflammatory cytokines is decreasing. All extracts displayed a significant dose-dependent inhibition in the carrageenan-, arachidonic acid-, and xylene-induced tests. | [56]       |
| *Cyathula prostrata*         | Amaranthaceae       | Ketumbar         | Leaves/methanol           | 50, 100, and 200 mg/kg   | Wistar rats and Swiss albino mice | The extract produced significant anti-inflammatory activity that did not depend on the doses of the extract.                                                                                             | [57]       |
| *Dicranopteris linearis*     | Gleicheniaceae      | Resam            | Leaves/chloroform         | 10, 100, and 200 mg/kg   | BALB/c mice and Sprague-Dawley rats | The extract produced significant anti-inflammatory activity that did not depend on the doses of the extract.                                                                                             | [58]       |
| Scientific name         | Family          | Local name  | Part/solvent used       | Dose of the extract          | Experimental animals | Results                                                                 | References |
|------------------------|----------------|-------------|-------------------------|----------------------------|----------------------|--------------------------------------------------------------------------|------------|
| *Ficus deltoidea*      | Moraceae       | Mas cotek   | Whole plant/water       | 30, 100, and 300 mg/kg     | Sprague-Dawley rats   | The rats’ paw edema volume reduced significantly in a dose-dependent manner | [59]       |
| *Garcinia subelliptica*| Guttiferae     | Pokok penanti | Seeds/chloroform       | 3, 10, 30, 50, and 100 μM | Sprague-Dawley rats   | A potent inhibitory effect on fMLP/CB-induced superoxide anion generation was observed in the isolated compound garcinelliptin oxide | [38]       |
| *Justicia gendarussa*  | Acanthaceae    | Daun rusa   | Root/methanol           | 50 mg/kg of the extract    | Wistar rats           | 80% and 93% edema inhibition at the third and fifth hours                | [60]       |
| *Kaempferia galanga*   | Zingiberaceae  | Cekur       | Rhizomes/chloroform     | 2 g/kg of the extract      | Male Sprague-Dawley rats | Highest edema inhibition (42.9%)                                          | [41]       |
| *Manilkara zapota*     | Sapotaceae     | Ciku        | Leaves/ethyl acetate    | 300 mg/kg of body weight  | Albino Wistar rats     | Inhibition of paw edema (92.4%)                                          | [61]       |
| *Mitragyna speciosa*   | Rubiaceae      | Biak-biak and ketom | Leaves/methanol      | 50, 100, and 200 mg/kg    | Sprague-Dawley rats   | Both doses of 100 and 200 mg/kg showed a significant inhibition of the paw edema (63%) | [62]       |
| *Moringa oleifera*     | Moringaceae    | Kelur       | Leaves/water            | 10, 30, and 100 mg/kg     | BALB/c mice and Sprague-Dawley rats | Highest edema inhibition (66.7%) at the second hour at 100 mg/kg of dose | [63]       |
| *Muntingia calabura*   | Muntingiaceae  | Kerukup siam | Leaves/water            | 27 mg/kg, 135 mg/kg, and 270 mg/kg | Sprague-Dawley rats | The extract was found to exhibit a concentration-independent anti-inflammatory activity | [64]       |
| *Orthosiphon stamineus*| Lamiaceae     | Misai kucing | Leaves/methanol:water   | 125, 250, 500, and 1000 mg/kg | Charles River mice and Sprague-Dawley rats | Increase in edema inhibition (26.7%)                                       | [65]       |
| *Peperomia pellucida*  | Piperaceae     | Ketumpangan air | Whole plant/petroleum ether | 1000 mg/kg      | Sprague-Dawley rats | The extract showed significant inhibition in magnitude of swelling after 4h of administration | [66]       |
| *Phyllanthus acidus*   | Phyllanthaceae | Cermai      | Leaves/methanol, ethyl acetate, and petroleum ether | 250 and 500 mg/kg | Wistar rats and albino mice | All the extracts showed reduction in carrageenan-induced paw edema with highest inhibition (90.91%) in the methanol extract | [67]       |
| *Physalis minima*      | Solanaceae     | Pokok letup-letup | Whole plant/methanol and chloroform fraction | 200 and 400 mg/kg | NMRI mice and Wistar rats | Crude extract and chloroform fraction showed highest inhibition of paw edema at 66% and 68% at 400 mg/kg, respectively | [68]       |
| *Piper sarmentosum*    | Piperaceae     | Kaduk       | Leaves/water            | 30–300 mg/kg of the extract | Sprague-Dawley rats and male BALB/c mice | All doses exerted anti-inflammatory activity in a dose-dependent manner | [69]       |
### Table 2: Continued.

| Scientific name                  | Family         | Local name  | Part/solvent used    | Dose of the extract          | Experimental animals | Results                                                                                                                                                                                                 | References |
|----------------------------------|----------------|-------------|----------------------|------------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| *Polygonum minus*                | Polygonaceae   | Kesum       | Aerial parts/water   | 100 mg/kg and 300 mg/kg      | Wistar albino rats    | The extracts significantly reduced the paw edema volume in the rats after 4 h. A significant inhibition (94%) in TPA-induced edema was observed in the isolated compound 3-oxo-12-olean-29-oic acid. | [70]       |
| *Sandoricum koetjape*            | Meliaceae      | Sentul      | Stems/methanol       | 5 mg/ear                     | BALB/c mice          | Extracts produce apparently two-phase anti-inflammatory activity: the first phase between 1 and 2 h and the second phase between 5 and 7 h after carrageenan administration. | [71]       |
| *Solanum nigrum*                 | Solanaceae     | Terung meranti | Leaves/water        | 10, 50, and 100% of concentration | BALB/c mice and Sprague-Dawley rats | Extracts produce apparently two-phase anti-inflammatory activity: the first phase between 1 and 2 h and the second phase between 5 and 7 h after carrageenan administration. | [72]       |
| *Stachytarpheta jamaicensis*     | Verbenaceae    | Selasih dandi | Leaves/ethanol      | 50, 100, and 150 mg/kg       | BALB/c albino strain mice and Sprague-Dawley rats | A significant dose-dependent anti-inflammatory activity was observed 30 min after the administration of the extract at all doses. | [73]       |
| *Vitex negundo*                  | Lamiaceae      | Legundi     | Leaves/ethanol       | 2 mg/ear                     | Mice                 | The extract showed an inhibitory activity of 54.1%. A significant antiedema activity was observed at all doses in a dose-dependent manner (i.e., 50 and 100 mg/kg doses of the extract exhibited activity at 90 min after administration, while 25 mg/kg exhibited at 150 min). | [74]       |
| *Zingiber zerumbet*              | Zingiberaceae  | Lempoyang   | Rhizomes/methanol    | 5, 10, 50, and 100 mg/kg     | ICR mice             | The isolated compound (zerumbone) significantly showed dose-dependent inhibition of paw edema induced by carrageenan at all doses (5, 10, 50, and 100 mg/kg) in mice with percentage of inhibition of 33.3, 66.7, 83.3, and 83.3%, respectively. | [75]       |
activity of the plants. Many diseases such as rheumatoid arthritis, diabetes, and hypertension have been reported to be occurred due to the excessive production of NO [77]. NO is synthesized by inducible NO synthase which has three isomers: (i) neuronal nitric oxide synthase (nNOS), (ii) endothelial nitric oxide synthase (eNOS), and (iii) iNOS [78]. For instance, signaling molecules such as mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-kB), activator protein-1 (AP-1), and signal transducer and activator of transcription (STAT) regulate the inducible enzyme (i.e., iNOS), which then make this enzyme to be expressed in some tissues [79]. Apart from the nitric oxide inhibition assay, some studies used the LOX assay in order to evaluate the anti-inflammatory activity of the plants. In this mechanism, arachidonic acid is metabolized by 5-LOX to various forms of inflammatory leukotrienes such as leukotriene (LT) A₄, LTB₄, LTC₄, LTD₄, and LTE₄ [80], where LTB₄ (one of the mediators of inflammation) is reported to be the most crucial in the inflammatory response [81]. To support this, it is reported that patients with rheumatoid arthritis and inflammatory bowel disease possess high levels of LTB₄ [82, 83]. In addition, LTs are reported to be linked with few diseases such as bronchial asthma and skin inflammatory disorders [84]. In 2011, Kwon et al. [85] demonstrated that esculetin, one of the examples of coumarins, exhibited anti-inflammatory activity in vivo against animal models of skin inflammation. In the LOX assay, any LOX inhibitors will reduce Fe³⁺ to Fe²⁺, providing a rapid colorimetric assay [26]. Another common assay in determining the anti-inflammatory activity is COX. Two isoforms of COX, COX-1 (mainly involved in physiological functions and constitutively expressed) and COX-2 (involved in inflammation and induced in the inflamed tissue), are the enzymes responsible for the synthesis of prosta-glandins [86]. Besides, the COX-2 gene is also a gene for iNOS induced during inflammation and cell growth [87]. The Griess assay is another assay commonly used in the murine macrophage cell line (RAW 264.7) as a culture medium in the cell-based study in order to determine the concentration of nitrite (NO₂⁻), the stable metabolite of NO.

Based on Table 1 (in vitro study), 46 plants have been identified and studied for the anti-inflammatory activity from the previous studies. As a result, only two plants have been reported to exhibit more than 90% of anti-inflammatory activity using the nitric oxide inhibition assay, which were Melicope ptelefolia (Tenggek burung) and Portulaca oleracea (Gelang pasir) with the values of 95.00% and 94.80% at 250 µg/ml, respectively [13]. Besides that, 30 plants have been reported to have anti-inflammatory activity between 70% and 80% at 100 µg/ml from the previous studies due to the different types of assays used by previous studies. For example, plants from the Zingiberaceae, Lamiaceae, Annonaceae, and Fabaceae families have been studied extensively for the anti-inflammatory activity. Among these families, the active compound of Curcuma longa from the Zingiberaceae family, monodemethoxycurcumin, had the highest activity with 82.50% at 125 µg/ml [35]. Of the other study, Kaempferia galanga from the Zingiberaceae family exhibited moderate activity with 57.82% at 200 µg/ml where the isolated compound, ethyl-p-methoxycinnamate, was found to have anti-inflammatory activity via inhibiting the actions of COX-1 and COX-2 [41]. In the Lamiaceae family, Thymus vulgaris showed the highest percentage of anti-inflammatory activity compared to other plants with 62% at 100 µg/ml [43], with the total phenolic content of 350 µg GAE/ml.

In this study, it was found that the results of anti-inflammatory activity of the methanolic extract of the leaves of Melicope ptelefolia (Tenggek burung) varied between two previous studies due to the different types of assays used by both studies: nitric oxide inhibition and soybean 15-lipoxygenase inhibition assays with the values of 95% and 72.3%, respectively [13, 45]. Another study also reported that the anti-inflammatory activity of the methanolic extract of Litsea garciae fruits showed 9.42% (lipoxygenase assay) and 27.70% (hyaluronidase assay) [44]. Based on these results, it can be concluded that different assays used might produce different results. For the COX inhibition assay, all the curcuminoids isolated from Curcuma longa rhizomes (i.e., curcumin I, curcumin II (monodemethoxycurcumin), and curcumin III (bisdemethoxycurcumin)) displayed greater inhibition of COX-2 compared to COX-1 at the same test concentration [35]. For the Griess assay, all the species tested such as the leaves of Carica papaya, Sauropus androgynus, and Piper sarmentosum, the flowering stalk of Musa acuminate, and the whole plant of Oenanthe javanica displayed significant NO inhibitory activity in a concentration-dependent manner against IFN-γ/LPS-treated macrophages [31].

For the in vivo study (Table 2), 30 plants have been identified in this study for the anti-inflammatory activity. Many of the studies from the previous years used the carrageenan-induced rat paw edema method (a reliable inflammation model) as this carrageenan has been found to be more trenchant in producing the edema compared to formalin [88]. It is also one of the conventional methods used to evaluate the anti-inflammatory effect of drugs or medicinal plants at the acute stage [89] and involves a bi- phasic event. Normally, the release of histamine and serotonin happens in the early phase (1-2 h), while the second phase (3-5 h) involves the release of prostaglandins and kinins [90, 91]. For the edema formation, the rat paw is injected with carrageenan. This method is also a COX-dependent reaction with the control of arachidonate COX [92]. The ability of the plant extracts to lessen the thickness of the rats’ paw edema indicates the ability of these plant extracts to exert the anti-inflammatory properties. Based on
Table 2, the highest dose of the extract used was 1000 mg/kg of body weight, while the lowest one was 3 mg/kg of body weight. Most of the previous studies reported that the extract was able to inhibit paw edema induced by carrageenan. For instance, a significant highest paw edema inhibition (93.34%) was observed in rats at a dose of 300 mg/kg of the *Ardisia crispa* (Mata pelandok) root extract [51]. Another study also showed that a significant highest inhibition was observed in two isolated compounds from *Sandoricum koelreuteria* stems, 3-oxo-12-oleanen-29-oic acid and katonic acid with 94% and 81%, respectively, where 3-oxo-olean-12-en-29-oic acid had the percentage inhibition almost similar to the reference drug, indomethacin (97%) [71].

Based on the results obtained, few studies isolated the bioactive compounds to be further analyzed for the anti-inflammatory activity such as flavonoids (boesenbergin A, eupatorin, and sinensetin), coumarins (scopoletin and scoparone), triterpenoids (dammara-20,24-dien-3-one and 24-hydroxydammara-20,25-dien-3-one), steroids (cucurbitacin E), curcuminoïds (monodemethoxycurcumin and bisdemethoxycurcumin), benzophenones (garsubellin A and garci- nielliptin oxide), cinnamic acid (ethyl-p-methoxycinnamate), alkaloids (kokusagine), benzene (p-O-geranylcoumaric acid), 4-[(20-O-acetyl-a-L-rhamnosoxy)benzyl]isothiocyanate, 4-[(30-O-acetyl-a-L-rhamnosoxy)benzyl]isothiocyanate, and 4-[(40-O-acetyl-a-L-rhamnosoxy)benzyl]isothiocyanate [28, 30, 32, 33, 35, 38, 41, 45–47]. Interestingly, some of them exerted significant inhibition on inflammation. In 2000, Abad et al. [93] evaluated the common anti-inflammatory drug naproxene isolated from *Musa acuminate* (pisang abu nipah) which exhibited good inhibition in COX-1 and COX-2 activities. Besides, in *Carica papaya* leaves, coumarin was isolated and exerted anti-inflammatory activity by suppressing the cytokine TNF-a production [94, 95]. A compound known as dammara-20,24-dien-3-one was isolated from *Chicoscheton polyandrus* and displayed good inhibition of both human 5-LOX and COX-2 [32]. Flavonoids have been confirmed by *in vitro* studies to be able to suppress iNOS expression and to prevent nitric oxide production, depending on their structure or subclass of flavonoids for the strength level [96].

4. Conclusion

In overall, this review clearly demonstrates the potential of Malaysian medicinal plants as anti-inflammatory agents in which *Melicope ptelefolia* (Tenggek burung) and *Portulaca oleracea* (Gelang pasir) were found to exhibit potent anti-inflammatory activity *in vitro*. Pharmacological studies revealed that chemical diverse groups of naturally occurring substances derived from the plants show promising anti-inflammatory activity. Therefore, this review suggests further research needs to be carried out on the bioactive compounds present in the particular plants which have a potential to treat an inflammation and the possible under-lying mechanisms of inflammation.

Conflicts of Interest

The authors do not have any conflicts of interest regarding the content of the present work.

Acknowledgments

This research was financially supported by Universiti Tun Hussein Onn Malaysia (UTHM) (Vot No. U758, U673, and U908).

References

[1] C. H. Lee and E. Y. Choi, "Macrophages and inflammation," *Journal of Rheumatic Diseases*, vol. 25, no. 1, pp. 11–18, 2018.
[2] K. D. Rainsford, "Anti-inflammatory drugs in the 21st century," in *Inflammation in the Pathogenesis of Chronic Diseases*, Springer, Dordrecht, Netherlands, pp. 3–27, 2007.
[3] S. Yedgar, M. Krimsky, Y. Cohen, and R. J. Flower, "Treatment of inflammatory diseases by selective eicosanoid inhibition: a double-edged sword?", *Trends in Pharmacological Sciences*, vol. 28, no. 9, pp. 459–464, 2007.
[4] Y. Monnier, J. Zaric, and C. Ruegg, "Inhibition of angiogenesis by non-steroidal anti-inflammatory drugs: from the bench to the bedside and back," *Current Drug Targets-Inflammation and Allergy*, vol. 4, no. 1, pp. 31–38, 2005.
[5] V. Fuster and J. Sanz, "Vascular inflammation," *Journal of the American Society of Hypertension*, vol. 1, no. 1, pp. 68–81, 2007.
[6] G. McKellar, R. Madhok, and G. Singh, "The problem with NSAIDs: what data to believe?", *Current Pain and Headache Reports*, vol. 11, no. 6, pp. 423–427, 2007.
[7] E. K. Akkol, "New strategies for anti-inflammatory drug development," *Journal of Pharmacogenomics and Pharmacoproteomics*, vol. 3, p. e118, 2012.
[8] D. Russo, P. Valentão, P. B. Andrade, E. C. Fernandez, and L. Millela, "Evaluation of antioxidant, antidiabetic and anti-cholinesterase activities of *Smallanthus sonchifolius* landraces and correlation with their phytochemical profiles," *International Journal of Molecular Sciences*, vol. 16, no. 8, pp. 17696–17718, 2015.
[9] J. H. Wirth, J. C. Hudgins, and J. A. Paice, "Use of herbal therapies to relieve pain: a review of efficacy and adverse effects," *Pain Management Nursing*, vol. 6, no. 4, pp. 145–167, 2005.
[10] M. N. Salleh, A. A. Kadir, K. Shaari, and Z. Ibrahim, "Medicinal products from the tropical rain forests of the Far East 95-105," in *Prospects in Biodiversity Prospecting*, A. H. Zakri, Ed., Genetics Society, Universiti Kebangsaan, Bangi, Malaysia, 1995.
[11] A. Latif, "Medicinal and aromatic plants of Asia: approaches to exploitation and conservation," in *Proceedings of the Symposium State-of-the-Art Strategies and Technologies for Conservation of Medicinal and Aromatic Plants*, pp. 20–31, Kuala Lumpur, Malaysia, September 1997.
[12] F. I. Abu Bakar, M. F. Abu Bakar, A. Rahmat, N. Abdullah, S. F. Sabran, and S. Endrini, "Anti-gout potential of Malaysian medicinal plants," *Frontiers in Pharmacology*, vol. 9, p. 261, 2018.
[13] F. Abas, N. H. Lajis, D. A. Israfl, S. Khozirah, and Y. U. Kalsom, "Antioxidant and nitric oxide inhibition activities of selected Malay traditional vegetables," *Food Chemistry*, vol. 95, no. 4, pp. 566–573, 2006.
[14] WHO (World Health Organization), "The world traditional medicines situation," in *Traditional Medicines: Global Situation, Issues and Challenges*, no. 3, pp. 1–14, WHO, Geneva, Switzerland, 2011.
[15] V. De Luca, V. Salim, S. M. Atsumi, and F. Yu, "Mining the biodiversity of plants: a revolution in the making," *Science*, vol. 336, no. 6089, pp. 1658–1661, 2012.
leaves inhibit inflammatory gene expression and STAT1 activation,” *Planta Medica*, vol. 78, no. 8, pp. 779–786, 2012.

R. Hendra, S. Ahmad, E. Oskoueian, A. Sukari, and M. Y. Shukor, “Antioxidant, anti-inflammatory and cytotoxicity of Phaleria macrocarpa (Boerl.) Scheff Fruit,” *BMC Complementary and Alternative Medicine*, vol. 11, p. 110, 2011.

S. V. Kumar, P. Sankar, and R. Varatharajan, “Anti-inflammatory activity of roots of Achyranthes aspera,” *Pharmaceutical Biology*, vol. 47, no. 10, pp. 973–975, 2009.

C. P. Foong and R. A. Hamid, “Evaluation of anti-inflammatory activities of ethanolic extract of Annona muricata leaves,” *Revista Brasileira de Farmacognosia*, vol. 22, no. 6, pp. 1301–1307, 2012.

A. Roslida and K. Kim, “Anti-inflammatory and anti-hyperalgesic effects of Ardisia crispa Thunb. D.C,” *Pharmacognosy Magazine*, vol. 4, no. 16, pp. 262–268, 2008.

S. Sarwar, M. A. Sufian, M. R. Islam et al., “Investigation of Z. A. Zakaria, M. R. Sulaiman, and H. K. Gopalan et al., “Anti-inflammatory and anti-pyretic activities of Crotalaria spectabilis leaves,” *Journal of Pharmacognosy and Toxicology*, vol. 12, no. 3, pp. 120–128, 2017.

Z. A. Zakaria, M. R. Sulaiman, H. K. Gopalan et al., “Anti-inflammatory and anti-inflammatory properties of Corchorus capsularis leaves chloroform extract in experimental animal models,” *Yakugaku Zasshi*, vol. 127, no. 2, pp. 359–365, 2007.

A. M. Samud, M. Z. Asmawi, J. N. Sharma, and A. P. M. Yusof, “Anti-inflammatory activity of Crinum asiaticum plant and its effect on bradykinin-induced contractions on isolated uterus,” *Immunopharmacology*, vol. 43, no. 2-3, pp. 311–316, 1999.

W. Reanmongkol, S. Subhadhirasakul, N. Khaisombat, and A. Sowemimo, “Investigation the antiinociceptive, antipyretyc and anti-inflammatory activities of Curcuma aeruginosa Roxb. extracts in experimental animals,” *Journal of Science Technology*, vol. 28, pp. 999–1008, 2006.

G. Ramadan, M. A. Al-Kahtani, and W. M. El-Sayed, “Anti-inflammatory and anti-oxidant properties of Curcuma longa (turmeric) versus Zingiber officinale (ginger) rhizomes in rat adjuvant-induced arthritis,” *Inflammation*, vol. 34, no. 4, pp. 291–301, 2011.

B. Ibrahim, A. Sovemimo, A. van Rooyen, and M. Van de Venter, “Antiinflammation, analgesic and antioxidiant activities of Cyathula prostrata (Linn.) Blume (Amaranthaceae),” *Journal of Ethnopharmacology*, vol. 141, no. 1, pp. 282–289, 2012.

Z. A. Zakaria, Z. D. F. A. Ghani, R. N. S. R. M. Nor, H. K. Gopalan, M. R. Sulaiman, and F. C. Abdullah, “Anti-inociceptive and anti-inflammatory activities of Dicranopteris linearis leaves chloroform extract in experimental animals,” *Yakugaku Zasshi*, vol. 126, no. 11, pp. 1197–1203, 2006.

Z. A. Zakaria, M. K. Hussain, A. S. Mohamad, F. C. Abdullah, and M. R. Sulaiman, “Anti-inflammatory activity of the aqueous extract of Ficus deltoidea,” *Biological Research for Nursing*, vol. 14, no. 1, pp. 90–97, 2012.

K. S. Kumar, V. Vijayan, S. Bhaskar, K. Krishnan, V. Shalini, and A. Helen, “Anti-inflammatory potential of an ethyl acetate fraction isolated from Justicia gendarussa roots through inhibition of iNOS and COX-2 expression via NF-kB pathway,” *Cellular Immunology*, vol. 272, no. 2, pp. 283–289, 2012.

A. Ganguly, Z. Al Mahmud, M. M. N. Uddin, and S. A. Rahman, “In-vivo anti-inflammatory and anti-pyretic activities of Manilkara zapota leaves in albino Wistar rats,” *Asian Pacific Journal of Tropical Disease*, vol. 3, no. 4, pp. 301–307, 2013.

W. S. Mossadeq, M. R. Sulaiman, T. T. Mohamad et al., “Anti-inflammatory and antinociceptive effects of Mitragyna speciosa Korth methanolic extract,” *Medical Principles and Practice*, vol. 18, no. 5, pp. 378–384, 2009.

M. R. Sulaiman, Z. A. Zakaria, A. S. Bujarimin, M. N. Somchit, D. A. Israf, and S. Moin, “Evaluation of Moringa oleifera aqueous extract for antinociceptive and anti-inflammatory activities in animal models,” *Pharmacological Biology*, vol. 46, no. 12, pp. 838–845, 2008.

Z. A. Zakaria, N. M. N. Hazalin, S. M. Zaid et al., “Anti-inociceptive, anti-inflammatory and antipyretic effects of Muntingia calabura aqueous extract in animal models,” *Journal of Natural Medicines*, vol. 61, no. 4, pp. 443–448, 2007.

M. F. Yam, M. Z. Asmawi, and R. Basri, “An investigation of the anti-inflammatory and analgesic effects of Orthosiphon stamineus leaf extract,” *Journal of Medicinal Food*, vol. 11, no. 2, pp. 362–368, 2008.

A. F. Muttee, S. M. Salihmi, M. F. Yam et al., “In vivo anti-inflammatory and in vitro antioxidant activities of Peperomia pellucida,” *International Journal of Pharmacology*, vol. 6, no. 5, pp. 686–690, 2010.

R. Chakraborty, D. Biplab, N. Devanna, and S. Sen, “Anti-inflammatory, antinociceptive and antioxidant activities of Phyllanthus acidus L. extracts,” *Asian Pacific Journal of Tropical Biomedicine*, vol. 2, no. 2, pp. S953–S961, 2012.

M. A. Khan, H. Khan, S. Khan, T. Mahmood, P. M. Khan, and A. Jabar, “Anti-inflammatory, analgesic and antipyretic activities of Physalis minima L,” *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 24, no. 3, pp. 632–637, 2009.

Z. A. Zakaria, A. S. Mohamad, C. T. Chear, Y. Y. Wong, D. A. Israf, and M. R. Sulaiman, “Antiinflammatory and antinociceptive effects of Zingiber zerumbet methanol extract in experimental model systems,” *Medical Principles and Practice*, vol. 19, no. 4, pp. 287–294, 2010.

A. George, S. Chinnappan, M. Chintamani et al., “Anti-inflammatory effects of Polygonum minus (Huds) extract (Lineminus)” in *in-vitro* enzyme assays and carrageenan induced paw edema,” *BMC Complementary and Alternative Medicine*, vol. 14, p. 355, 2014.

M. A. Rasadah, S. Khozirah, A. A. Aznie, and M. M. Nik, “Anti-inflammatory agents from Spondorium koetjape Merr,” *Phytochemistry*, vol. 11, no. 2-3, pp. 261–263, 2004.

Z. A. Zakaria, M. R. Sulaiman, N. A. Morsidi et al., “Anti-nociceptive, anti-inflammatory and antipyretic effects of Solanum nigrum aqueous extract in animal models,” *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 31, no. 2, p. 81, 2009.

M. R. Sulaiman, Z. A. Zakaria, H. S. Chiong, S. K. Lai, D. A. Israf, and T. A. Shah, “Antiinociceptive and anti-inflammatory effects of Stachytarapheta jamaicensis (L) Vahl (Verbenaceae) in experimental animal models,” *Medical Principles and Practice*, vol. 18, no. 4, pp. 272–279, 2009.

N. M. Yunos, R. Mat Ali, O. B. Kean, and R. Abas, “Cytotoxicity evaluations on Vitex negundo anti-inflammatory extracts,” *Malaysian Journal of Science*, vol. 24, no. 1, pp. 213–217, 2005.

Z. A. Zakaria, H. Patahuddin, A. S. Mohamad, D. A. Israf, and M. R. Sulaiman, “In vivo anti-nociceptive and anti-inflammatory activities of the aqueous extract of the leaves of Piper sarmentosum,” *Journal of Ethnopharmacology*, vol. 128, no. 1, pp. 42–48, 2010.

M. R. Sulaiman, E. K. Perimal, M. N. Akhtar et al., “Anti-inflammatory effect of zerumbone on acute and chronic inflammation models in mice,” *Fitoterapia*, vol. 81, no. 7, pp. 855–858, 2010.

P. Pacher, J. S. Beckman, and L. Liaudet, “Nitric oxide and peroxynitrite in health and disease,” *Physiological Reviews*, vol. 87, no. 1, pp. 315–424, 2007.
[78] D. Fukumura, T. Gohongi, A. Kadambi et al., "Predominant role of endothelial nitric oxide synthase in vascular endothelial growth factor-induced angiogenesis and vascular permeability," *Proceedings of the National Academy of Sciences*, vol. 98, no. 5, pp. 2604–2609, 2001.

[79] H. Kleinert, A. Pautz, K. Linker, and P. M. Schwarz, "Regulation of the expression of inducible nitric oxide synthase," *European Journal of Pharmacology*, vol. 500, no. 1–3, pp. 255–266, 2004.

[80] R. De Caterina and A. Zampolli, "From asthma to atherosclerosis—5-lipoxygenase, leukotrienes, and inflammation," *New England Journal of Medicine*, vol. 350, no. 1, pp. 4–7, 2004.

[81] Y. Y. Zhang, J. L. Walker, A. Huang et al., "Expression of 5-lipoxygenase in pulmonary artery endothelial cells," *Biochemical Journal*, vol. 361, no. 2, pp. 267–276, 2002.

[82] C. Schmidt, E. Kosche, B. Baumeister, and H. Vetter, "Arachidonic acid metabolism and intracellular calcium concentration in inflammatory bowel disease," *European Journal of Gastroenterology and Hepatology*, vol. 7, no. 9, pp. 865–869, 1995.

[83] M. Chen, B. K. Lam, Y. Kanaoka et al., "Neutrophil-derived leukotriene B4 is required for inflammatory arthritis," *Journal of Experimental Medicine*, vol. 203, no. 4, pp. 837–842, 2006.

[84] P. Rubin and K. W. Mollison, "Pharmacotherapy of diseases mediated by 5-lipoxygenase pathway eicosanoids," *Prostaglandins and Other Lipid Mediators*, vol. 83, no. 3, pp. 188–197, 2007.

[85] O. S. Kwon, J. S. Choi, M. N. Islam, Y. S. Kim, and H. P. Kim, "Inhibition of 5-lipoxygenase and skin inflammation by the aerial parts of *Artemisia capillaris* and its constituents," *Arzneimittelforschung*, vol. 54, no. 9, pp. 1561–1569, 2011.

[86] J. R. Vane and R. M. Botting, "Mechanism of action of anti-inflammatory drugs," *Scandinavian Journal of Rheumatology*, vol. 25, no. 102, pp. 9–21, 1996.

[87] R. P. Ryseck, C. Raynoschek, H. Macdonald-Bravo, K. Dorfman, M. G. Mattei, and R. Bravo, "Identification of an immediate early gene, pghs-B, whose protein product has prostaglandin synthase/cyclooxygenase activity," *Cell Growth and Differentiation*, vol. 3, no. 7, pp. 443–450, 1992.

[88] M. Mohan, V. S. Gulecha, V. M. Aurangabadkar, R. Balaraman, A. Austin, and S. Thirunghananampathan, "Analgesic and anti-inflammatory activity of a polyherbal formulation (PHF-AROGH)," *Oriental Pharmacy and Experimental Medicine*, vol. 9, no. 3, pp. 232–237, 2009.

[89] A. Panthong, P. Norkaew, D. Kanjanapothi, T. Taesotikul, N. Anantachoke, and V. Reutrakul, "Anti-inflammatory, analgesic and antipyretic activities of the extract of gamboge from *Garcinia hanburyi* Hook F.," *Journal of Ethnopharmacology*, vol. 111, no. 2, pp. 335–340, 2007.

[90] P. Crunkhorn and S. C. R. Meacock, "Mediators of the inflammation induced in the rat paw by carrageenin," *British Journal of Pharmacology*, vol. 42, no. 3, pp. 392–402, 1971.

[91] C. G. Van Arman, A. J. Begany, L. M. Miller, and H. H. Pless, "Some details of the inflammations caused by yeast and carrageenin (with appendix on kinetics of the reaction)," *Journal of Pharmacology and Experimental Therapeutics*, vol. 150, no. 2, pp. 328–334, 1965.

[92] P. M. Brooks and R. O. Day, "Nonsteroidal antiinflammatory drugs—differences and similarities," *New England Journal of Medicine*, vol. 324, no. 24, pp. 1716–1725, 1991.

[93] T. Abad, G. McNaughton-Smith, W. Q. Fletcher et al., "Isolation of (S)-(+)-naproxene from *Musa acuminata*. Inhibitory effect of naproxene and its 7-methoxy isomer on constitutive COX-1 and inducible COX-2," *Planta Medica*, vol. 66, no. 5, pp. 471–473, 2000.

[94] E. Y. Bissonnette, G. M. Tremblay, V. Turmel, B. Pirotte, and M. Reboud-Ravaux, "Coumarinic derivatives show anti-inflammatory effects on alveolar macrophages, but their anti-elastase activity is essential to reduce lung inflammation in vivo," *International Immunopharmacology*, vol. 9, no. 1, pp. 49–54, 2009.

[95] A. M. Pendzhiev, "Proteolytic enzymes of papaya: medicinal applications," *Pharmaceutical Chemistry Journal*, vol. 36, no. 6, pp. 315–317, 2002.
