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Antioxidant and Anti-inflammatory Activities of *Marantodes pumilum* (Blume) Kuntze and Their Relationship with the Phytochemical Content

Shihab Uddin Ahmad, 'Atiqah Azam, Ahmad Nazrun Shuid and Isa Naina Mohamed *

Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur, Malaysia

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Abstract: *Marantodes pumilum* is a herbaceous plant that has widely recognized for its medicinal use. The plant used widely has led to many studies on its phytochemical identification, pharmacological and toxicological activities. Phytoconstituents found in the *Marantodes pumilum* extracts showed high antioxidant and anti-inflammatory properties which are essential for many pharmacological effects. The aim of the systematic review is to provide the information of antioxidant and anti-inflammatory properties found in *Marantodes pumilum*. A critical literature search from three electronic databases such as SCOPUS, EBSCOhost and Ovid Medline was conducted for related studies published from the years 1946 to November 2017. The research studies published in English and related with the antioxidant and anti-inflammatory effects of *Marantodes pumilum* were the main inclusion criteria in this review. A total 512 relevant articles was identified, whereby 21 articles met the inclusion criteria. Twelve chemical assay studies, five animal studies, two *in vitro* cell culture study, one combined *in vivo* animal and chemical study and one combined chemical assay and *in vitro* cell culture study included in this review. All of the studies reported moderate to noticeable positive effects of *Marantodes pumilum* against oxidation and inflammation. This systematic review highlights the antioxidant and anti-inflammatory effects and their relation with phytoconstituents of *Marantodes pumilum* extracts.

Keywords: *Marantodes pumilum*; Primulaceae; antioxidant; anti-inflammatory; phytoconstituents. © 2018 ACG Publications. All rights reserved.

1. Introduction

Medicinal plants are used extensively as remedies for human health since ancient times due to its therapeutic efficacy associated with their purified constituents. At present, more than 2,000 species of medicinal plants have been discovered with therapeutic effects in Malaysia [1]. People have used them as healthcare medication for many centuries. Kacip Fatimah is one of the most popular and widely used herbal plants in Malaysia. Malaysian government has funded to be developed this plant for commercials purposes. The scientific name of Kacip Fatimah is *Marantodes pumilum* (Blume)

* Corresponding author: E-Mail: isanaina@ppukm.ukm.edu.my ; Phone: +60391459545, Fax: +60391459547

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Kuntze (*M. pumilum*). *M. pumilum* also known as other scientific names previously like *Labisia pumila* (Blume) Fern-Vill and *Ardisia pumila*. It belongs to Primulaceae family that mostly found in the South East Asian countries [2]. This plant is also known to local people as *Rumput Siti Fatimah, Selusuh Fatimah, Akar Fatimah, Kachit Fatimah, Mata Pelandok Rimba, Pokok Pinggang, Bunga Belangkas Hutan, Tadah Matahari* and *Rumput Palis* [3]. *M. pumilum* has found eight species in Malaysia [4]. Three species of them like *M. pumilum* var. *pumila*, var. *alata* and var. *lanceolata* have studied mostly [5]. These species look different from each other based on their petiole and leaf structure. *M. pumilum* var. *pumila* contains petiole that likes as marginated and var. *alata* one looks winged petiole. However, *M. pumilum* var. *lanceolata* contains non-winged petiole [6].

In Malaysia, *M. pumilum* is a popular medicinal plant that has long been recognized and much demanded its value as female tonics and health products [7]. Traditionally Malay women have been taken raw extracts, obtained by boiling the plants during child delivery. People are commonly believed that the plant extracts can make ease child delivery and help to reduce delivery pain. It can also help to maintain menstrual cycle regularly and relieve the menopausal symptoms [8]. The plant extracts can also drink to boostthe body strength. It also uses to treat common diseases such as dysentery, rheumatism, and gonorrhea [9]. It is also used to inhibit the formation of gas and enhance the abdominal muscles tonicity [10]. It has further been reported to reduce the risk of osteoporosis [11,12], metabolic disorders [13] and cardiovascular diseases [14].

Numerous studies of *M. pumilum* have been determined the bioactive phytochemicals contributing to its numerous pharmacological activities including phytoestrogenic, anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-fungal and anti-microbial effects [15-17]. *M. pumilum* contains many phytochemicals such as flavonoid and phenolic compounds, methyl gallate, carotenoids, ascorbic acids, fatty acids, saponins, alkenyl compounds and benzoquinone derivatives [18-21]. Phenolic compounds are the secondary metabolites showed the most antioxidant effects. It is believed that the digestive system can easily absorb phenolic acids and they offer numerous anti-aging benefits. The antioxidant activity might indirectly contribute to the reported anti-inflammatory, anti-carcinogenic, anti-bacterial and anti-viral properties. Flavonoids are most common sub-group of polyphenols which also known as secondary plant metabolites. Flavonoids have potential benefits for health promotion. Numerous studies showed that flavonoids have many biological effects such as antiviral, anti-allergic, antiplatelet, anti-inflammatory, anti-diarrheal and anti-tumor properties [22]. Flavonoids mainly apigenin, rutin, kaempferol, and myricetin were identified from *M. pumilum* var. *alata*. It has also identified phenolic compounds such as pyrogallol, gallic acid and caffeic acid [16, 18]. Methyl gallate could induce many biological effects such as anti-oxidant, anti-asthmatic, anti-microbial, protein tyrosine kinases inhibitor and collagenase inhibitor [23]. *β*-carotene has found in the *M. pumilum* extracts [24]. The *β*-carotene content was higher in *M. pumilum* var. *alata* than *M. pumilum* var. *pumila*. Study reorted that *β*-carotene has protective effect. *β*–carotene supplementation can protect the skin damage from sunlight [25]. Ascorbic acid (vitamin C), another powerful antioxidative compound identified from the extract of *M. pumilum* var. *pumila* and *M. pumilum* var. *alata* [24]. It is a common perception that this vitamin C could reduce the risk of strokes by decreasing systolic blood pressure. It can also protect many chronic diseases [26]. It can inhibit oxidation by free radicals accumulated in the human body. Usually, people consume the vitamin C to boost their immune system.

Many phytochemicals such as tannins, alkaloids, glycosides, sterols, anthocyanins, phenols and triterpenoids are responsible for anti-inflammatory activities. These phytoconstituents which are present in the bark exerted the desired pharmacological effects on the body and thus act as a natural anti-inflammatory agent. Inflammation may cause for many diseases such as polymyalgia rheumatica, chronic arthritis, gouty arthritis, tendonitis, inflammatory bowel disease, heart disease, cancer, and asthma [27,28]. During inflammatory responses, the membrane lipid can release more arachidonec acid by inducing phospholipase A2 [29]. The arachidonic acid produces prostaglandins with the presence of two enzymes including cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [27, 29]. Prostaglandins are associated many cytokines which cause of many pain-related diseases [30]. Phenolic compounds such as flavonoids, tannins, and curcumins can inhibit such type of ailments by the inhibition of pro-inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenases (LOX) in the inflammatory cascades or their free radical scavenging activities [31,32]. Flavonoids are polyphenol group compounds that inhibit prostaglandins synthesis [33]. Medicinal plants may,

therefore, be potential sources of COX-2/LOX inhibitors that may have fewer side effects than NSAIDs [34].

The purpose of the study is to evalute the antioxidative and anti-inflammatory activities of MP. This review is to provide information for further research on antioxidative and anti-inflammatory profiles of MP. This study may also give advantage to discover the new drug shortly.

2. Methodology

2.1. Search Strategy

The study was conducted to search the relevant studies on the antioxidant and anti-inflammatory properties of *M. pumilum*. The three online databases such as Scopus, EBSCOhost and Ovid Medline were retrieved to identify the studies. The articles included were published between 1946 and November 2017. The following two sets of keywords, (1) Kacip Fatimah OR *Labisia pumila** OR *Marantodes pumilum** OR *Ardisia pumila** AND (2) *inflammat* OR *oxida* were used as the search strategy. Furthermore, the references to all retrieved articles were reviewed for relevant citations.

2.2. Selection Criteria

Only the original articles published in English language were included in this review. Articles on antioxidant and/ or anti-inflammatory activities of *M. pumilum* were also included. Review articles, books, book chapters, news, conference proceedings, editorial letters, or case studies were excluded from this study.

2.3. Articles Screening

Articles screening process was in three steps. Firstly, articles published as a review, book, book chapter, editorial letter, conference proceeding, case study or any other supplement were sorted out based solely on the title. Secondly, articles without relevant with the antioxidant and anti-inflammatory properties of *M. pumilum* were excluded by reading the abstracts. Finally, the remaining articles did not match all inclusion criteria were excluded by reading thoroughly. After final screening, duplicate articles among the databases were removed. Then, articles were assessed for eligibility by checking all inclusion criteria and selected for final qualitative synthesis. This screening process has been done by two reviewers. Both reviewers were agreed that the included articles for the qualitative analysis in the review were fulfill the all inclusion criteria. Disagreements between the reviewers were resolved through a discussion. Data extraction was drawn in the data collection sheet for standardizing the data collection.

2.4. Data Extraction Process

The data was extracted based on characteristics of the studies including (1) study no (2) study design, (3) results, (4) outcomes and (5) ref. (Table 1). The data were also recorded based on phytochemistry of the studies such as (1) study no, (2) plant sources, (3) plant species, (4) plant parts, (5) type of extracts, (6) phytoconstituents, (7) ethnobotany and (8) ref. of each study (Table 2).

3. Results

3.1. Search Results

A total 512 potentially relevant articles was found by searching of three electronic databases. All articles were assessed independently by two reviewers for the screening process based on the inclusion and exclusion criteria. Seventy nine articles were related with reviews, books, book chapters,

and conference papers. Another 406 articles did not measure parameters related to antioxidant and/ or anti-inflammatory activities of *M. pumilum*. So, total 485 articles were sorted out as primary screening. After the primary screening of abstracts, 27 articles remained. A total of 6 articles was removed due to duplicate between the databases. A total of 21 articles were selected for the final qualitative analysis. The remaining 21 articles fulfill all inclusion and exclusion criteria. Finally, these 21 articles were included in this review. A flowchart was drawn on the articles selection process is shown in Figure1, where including reasons for sorted out of articles.

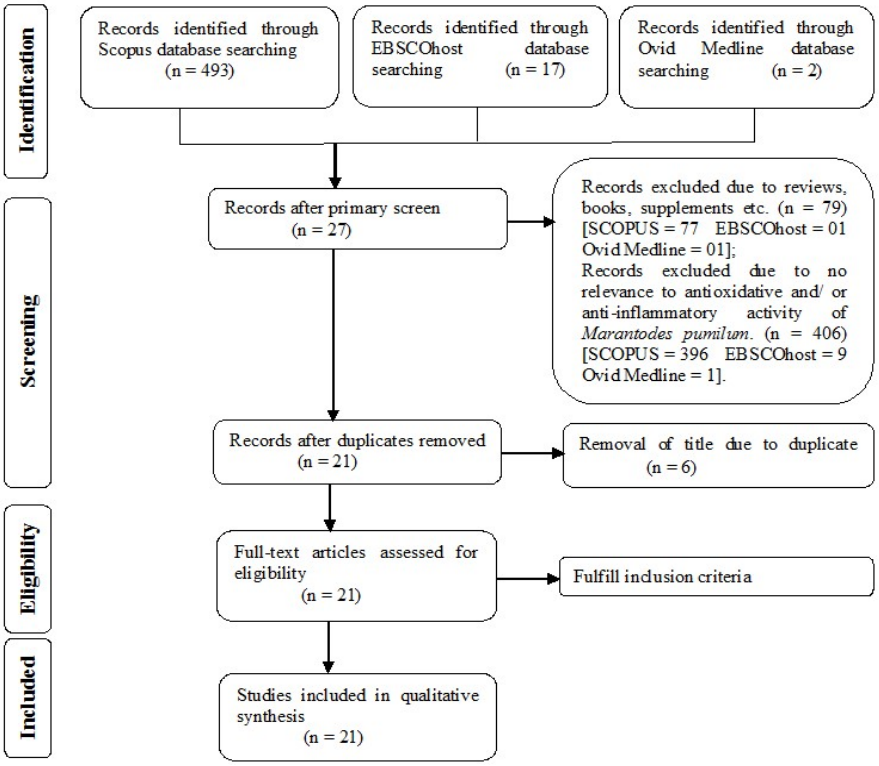

Figure 1. The Flowchart made according to PRISMA guideline shows the selection process of the articles in the review.

3.2. Study Design Characteristics

All studies were characterized in Table 1. All studies were published between the years 2009 to 2017 and consisted of twelve chemical assay studies, five animal studies, two *in vitro* cell culture study, one combined *in vivo* animal and chemical study and one combined chemical assay and *in vitro* cell culture study. Based on the types of activity, 16 studies focused on antioxidative activities, three studies focused on anti-inflammatory activities and two studies investigated both antioxidative and anti-inflammatory activities of *M. pumilum*. Animal studies used Sprague Dawley rats [35-37], Wistar rats [38-40] and ICR mice [36] as the experimental model. In the two *in vitro* cell culture studies were described in this review, where murine monocytic macrophage cell line RAW 264.7 was used in one study [41] and human peripheral blood mononuclear cells and plasma were used in another study [55]. Several chemical assays such as 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant potential (FRAP), oxygen radical absorbance capacity (ORAC), oxygen (O_2) radical scavenging, hydrogen peroxide (H_2O_2) radical scavenging, hydroxyl ($OH\cdot$) radical scavenging, β-carotene bleaching, nitric oxide (NO) radical scavenging and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical scavenging were used in the chemical studies [42-53]. Biochemical tests such as superoxide dismutase (SOD), glutathione peroxidise (GPx), and malondialdehyde (MDA) were also used to detect antioxidative activity [37-40]. Formalin-induced inflammation test, carrageenan-induced paw edema test and arachidonic acid-induced ear edema test were used to investigate anti-inflammatory activity in different studies [35,36]. Moreover, some inflammatory

mediators and gene expressions including type-1 pro-collagen, tumor necrotic factor (TNF-α), cyclooxygenase-2 (COX-2), matrix metalloproteinase-1 (MMP-1) and 9 (MMP-9) expression were analyzed to assess anti-inflammatory activities [54]. Most studies on antioxidative activity were carried out under different levels of environmental conditions such as different light source, CO_2 concentration, organic and inorganic fertilizers [42-49].

Table 1. Characteristics of studies included in the review

Study No	Study design	Results	Outcomes	Ref.
1	nine weeks in vivo animal study MPva extracts used. 96 female Sprague Dawley rats (aged 3–5 months and weight 200 - 250g) were randomly divided into six groups. Oxidative measurements include SOD, GPx and MDA levels of femora bone were assessed.	↑ Significantly of SOD and GPx levels and ↓ significantly MDA levels in treated groups than control groups.	MPva may prevent bone loss via its anti-oxidative property.	[37]
2	28 days in vivo animal study MPva extracts used. 54 male Wistar rats (weight 150 – 200g) were randomly divided into nine groups. Oxidative measurements include GPx, CAT and SOD levels in serum and myocardium homogenate were assessed.	↑ Significantly of GPx, CAT and SOD levels in treated groups than control groups.	MPva may have cardioprotective effects due to its anti-oxidative property.	[38]
3	28 days in vivo animal study MPva extracts used. 54 male Wistar rats (weight 150 – 200g) were randomly divided into nine groups. Oxidative measurements include GSH, GR, and SOD levels in serum were assessed.	↑ Significantly of GSH, GR and SOD levels in treated groups than control groups.	MPva may reduce the risk of dyslipidemia by modulating serum antioxidants.	[39]
4	Eight weeks in vivo animal study MP extract used. 25 female Wistar rats (aged 3–4 months and body weight of 150–200g) were randomly divided into five groups. Oxidative measurements include MDA and SOD levels in serum were assessed.	↓ Significantly of MDA and ↑ significantly of SOD levels in treated groups than control groups.	MP may normalize oxidative stress.	[40]
5	Chemical assay study. MPva and MPvp extracts used Antioxidative activity assay: DPPH free radical scavenging activity, FRAP, and β-Carotene bleaching assay Phytochemical content measurement: ascorbic acid, β-carotene, anthocyanin, TF, TP	Found antioxidative activity in both MPva and MPvp extracts. MPva contained higher antioxidative activities in all three methods applied including DPPH, FRAP, and β-carotene bleaching methods compared to MPvp. Higher content of ascorbic acid, β-carotene, and anthocyanin in MPva compared to MPvp. Higher content of total flavonoid in MPvp than MPva. No significant difference of total phenolic content in between two extracts	Antioxidative properties identified in both MP species.	[53]
6	Chemical assay study MPva extracts used Antioxidative activity assay: ORAC assay against ROO radical, O_2 radical, H_2O_2 radical and OH radical Phytochemical content measurement: TP, TF, GSH, GSSG, and SC The experiment was done at different	Found antioxidative activity in both MPva. ↑ Antioxidative activities of ROO, O_2, H_2O_2, and OH of MPva at elevated CO_2. Found phytochemical compounds like TP, TF, GSH, GSHH, and SC in MPva extract which might be enhanced antioxidative properties.	MPva has antioxidative properties.	[42]

	levels of CO_2.			
7	Chemical assay study MPva extracts used Antioxidative activity assay: APX, CAT, SOD and PAL activities determined Phytochemical content measurement: TP, TF, AA and Protein content The experiment was done under different potassium fertilization.	The APX, CAT, SOD and PAL activities were found in MPva extract. ↑ Significantly antioxidant enzymes activity including APX, CAT, SOD, and PAL of MPva at elevated potassium fertilization. ▲ TP, TF, AA, Protein and PAL content in the leaves of MPva followed by stems and roots and these secondary metabolites have a significant negative relationship with antioxidant enzymes activity under high potassium fertilization.	Antioxidant enzymes activities were found in MPva.	[43]
8	Chemical assay study MPva extracts used Antioxidative activity assay: DPPH Radical Scavenging and PAL activities determined Phytochemical content measurement: TP, TF and AC content The experiment was done at different levels of irradiances.	DPPH and PAL antioxidant activities were found in MPva ▲ Antioxidant activity in leaves of MPva followed by the stems and the roots in all levels of irradiances. ▲ Secondary metabolites like TP, TF and AC content in leaves followed by the stems and the roots of MPva. PAL activity had significant positive relationships with secondary metabolites	Antioxidative activity was found in MPva	[44]
9	Chemical assay study MPva extracts used Antioxidative activity assay: DPPH Radical Scavenging and FRAP assay Phytochemical content measurement: TF, GSH, GSSG, AC and AA content The experiment was done under different nitrogen fertilization treatments.	▲ DPPH and FRAP antioxidant activities in the leaves followed by stems and roots of MPva in all nitrogen application treatments. Antioxidant activities (DPPH and FRAP) have significant positive correlation and secondary metabolites (TF, GSH, GSSG, AC, and AA) suggesting that an increase in the antioxidative activities in MPva at low nitrogen fertilization could be induced to higher contents of these compounds.	MPva can be used as a primary antioxidant	[47]
10	Chemical assay study MPva extracts used Antioxidative activity assay: DPPH Radical Scavenging and FRAP assay Phytochemical content measurement: TP, TF, TS, AA, SS, nitrate and GSH content The experiment was done under different treatments organic and inorganic fertilizers.	▲ DPPH and FRAP antioxidant activities in the leaves followed by stems and roots of MPva under organic fertilization and ▼ inorganic fertilization. ↑ TP, TF, TS, AA, SS & GSH content and ↓ nitrate content in MPva under organic fertilizers compared to the use of inorganic fertilizers.	Antioxidant activity was highest under organic fertilizer.	[45]
11	Chemical assay study MPva extracts used Antioxidative activity assay: DPPH Radical Scavenging and PAL activities determined Phytochemical content measurement: TP, TF, AC, AA, SS and MDA content The experiment was done at different levels of CO_2 and light intensity.	DPPH and PAL activities were influenced by the interaction between elevated CO_2 and irradiance levels ↑ Antioxidant activities of DPPH and PAL in MPva with increasing CO_2 and decreasing of irradiance. ↑ TP, TF, AC, AA & SS content and ↓ MDA levels in MPva under high CO_2 and low irradiance. The production of secondary metabolites (TP, TF, AC, AA & SS) displayed a significant positive relationship with enhanced the antioxidant activity (DPPH) of MPva.	MPva had excellent free radical scavenging activity.	[46]
12	Chemical assay study Three extracts of MPva, MPvp, and MPvl were used in the study. Antioxidative activity assay: DPPH Radical Scavenging, FRAP assay, and PAL activity measured.	↑ Antioxidant activities of DPPH, FRAP, and PAL in all three varieties of LP with increasing CO_2 ▲ Phenolic compounds found in MPva followed by MPvp and MPvl and ▲ flavonoid compounds and PAL activity	All three varieties of MP can be used as a primary antioxidant	[48]

	Phytochemical content measurement: TP and TF content The experiment was done at different levels of CO_2.	found in MPvp followed by MPva and MPvl. Gallic acid and quercetin were the most abundant phenolics and flavonoids respectively present in all the varieties. The production of secondary metabolites, PAL displayed a significant positive relationship with enhancing the antioxidant activity (DPPH & FRAP) of LP under high CO_2.		
13	Chemical assay study Extracts of three varieties MP including MPva, MPvp, and MPvl with three different parts including leaf, stem, and root were used in the study Antioxidative activity assay: DPPH Radical Scavenging and FRAP assay Phytochemical content measurement: TP and TF content	DPPH and FRAP antioxidative activities were found in different parts of all three varieties of LP ▲ Antioxidative activity of MPva contained than MPvp and MPvl. ▲ TP and TF values in leaf compared to roots and stems. ▲ TF in MPvp than MPva and MPvl ▲ TP in MPva than MPvp and MPvl	MP species have the potential to be a natural source of antioxidants	[50]
14	Chemical assay study Extracts of three varieties MP including MPva, MPvp, and MPvl with three different parts including leaf, stem, and root were used in the study. Antioxidative activity assay: DPPH Radical Scavenging and FRAP assay Phytochemical content measurement: TP and TF content The experiment was done under different levels of light intensity.	DPPH and FRAP antioxidative activities were found in different parts of all three varieties of MP ↑ Antioxidant activities of MP with increasing light intensity ▲ Antioxidative activity in leaf compared to roots and stems in all varieties of MP. TF accumulation was highest in the leaves of MPvp and TP was highest in MPva under higher light intensity	MP contained antioxidants	[49]
15	Chemical assay study Extracts of three varieties MP including MPva, MPvp, and MPvl with three different parts including leaf, stem, and root were used in the study Antioxidative activity assay: ABTS and NO scavenging assay Phytochemical content measurement: TP, TF, and TFA	The antioxidant activities of aqueous extracts obtained from MPva, MPvp, and MPvl in the reactions with ABTS radical and nitric oxide respectively. The obtained results revealed that the MPva contained higher antioxidative activities compared to MPvp and MPvl. TP and TF contents of leaves in all three varieties of LP were significantly different with each other. Fatty acids including palmitic, palmitoleic, linoleic, stearic, oleic, and α-linolenic acid are the main components in three varieties of MP leaves.	MP has anti-oxidants activities.	[52]
16	Chemical assay study MPva leaves extract was used in the study Antioxidative activity assay: DPPH Radical Scavenging, FRAP assay, and NO scavenging activity Phytochemical content measurement: TP, TF, and TFA The experiment was done at different levels of CO_2.	DPPH, FRAP, and NO antioxidative activities were found in MP leaves extract. ↑ Antioxidant activities of DPPH, FRAP and NO in LP leaves extract with increasing CO_2. ↑ significantly TP, TF, & TFA content in MPva under high CO_2 which are related to antioxidative effects	MP has anti-oxidants activities.	[51]
17	*In vitro* cell culture study The leaves and roots of the three species of MP extracts were used in the study Anti-inflammatory activity assay: Performed using NO production by macrophage RAW 264.7 cell lines induced by LPS/ IFN-g	↓ Significantly NO production in the leaf and root extracts of all three varieties of MP including MPva, MPvp, and MPvl. ▲ Anti-inflammatory activity showed in root extracts compared to the leaf extracts.	MP has anti-inflammatory activity.	[41]
18	*In vivo* animal study MPvp leaf extract used in the study	↓ Significantly formalin-induced paw licking time in 50 mg/kg extract treated	MPvp could have potent anti-	[35]

	Anti-inflammatory activity assay: Formalin-induced inflammation test and carrageenan-induced paw edema test. 60 (30 x 2) male Sprague-Dawley Rats (weight 120-290g) were taken and divided equally into two different five groups for formalin-induced inflammation test and carrageenan-induced paw edema test respectively.	group than other treated and control groups. All treatments were able to suppress the edema formation induced by carrageenan as compared with the control. 50 mg/kg of MP extract was found to be the best treatment. This treatment could reduce inflammation with highest inhibition of 64.59% followed by 25 mg/kg with 56.99% and 10 mg/kg with 5.55%.	inflammatory activity	
19	*In vivo* animal and chemical assay study Leave extract of MP (DELP) used in the study Anti-inflammatory activities test: Arachidonic acid-induced ear edema was assessed by using mice model (20 ICR mice, 30-40g weight) to determined inhibitory activity and 35 male Sprague Dawley rats (6-8 month of age, weighing 150-200g) were divided equally into seven groups for mast cell stabilization test. Antioxidative activities assay: DPPH radical scavenging, O_2 radical scavenging, NO scavenging assay and TP content determined.	DELP was able to prevent arachidonic acid-induced ear edema in the mice. DELP was able to stabilize the mast cells and ↓ degranulated mast cells in the experimental rats. DPPH, O_2 and NO radicals scavenging antioxidative activities were found in DELP. Phenolic compounds were also found as gallic acid in DELP	DELP may enhance anti-inflammatory and antioxidant activity.	[36]
20	Chemical assay and *in vitro* cell culture study MP extract used in the study Antioxidative activities assay: DPPH radical scavenging assessed Anti-inflammatory activities assay: Cell culture assessed Type-1 pro-collagen, TNF-*α*, COX-2, MMP-1, MMP-9 expression.	DPPH radical scavenging antioxidative activities found in MP extract and ▲ than ascorbic acid ↑ of TNF-α secretion, COX-2 expression, MMP-1 and MMP-9 expression by inducing UVB (Ultraviolet B) irradiation and ↓ of TNF-α secretion, COX-2 expression, MMP-1 and MMP-9 expression by treating of MP extract. Restored of collagen and fibroblast synthesis by treating MP extract.	MP may have antioxidant activity and anti-inflammatory effects.	[54]
21	*In vitro* cell culture study The leaves and roots of the three species of MP extracts were used in the study Anti-inflammatory activity assay: Cytokine (IL-1*α*, IL-1*β*, IL-6, IL-8, and TNF-*α*) by using ELISA kits and prostaglandin E_2 (PGE_2) assay by using radioimmunoassay.	Maximum inhibition of IL-1*α*, IL-1*β*, IL-6, IL-8, and TNF-*α* release by treating MPvl roots extract than other groups. Maximum inhibition of PGE_2 release by treating MPvp roots extract compared to other groups.	MPvp and MPvl are potential for anti-inflammatory agents.	[55]

↑ = Increased, ↓ = Decreased, ▲ = Higher, ▼ = Lower, SOD = Superoxide Dismutase, GPx = Glutathione Peroxidise, MDA = Malondialdehyde, NO = Nitric Oxide, DPPH = 1-diphenyl-2-picrylhydrazyl, FRAP = Ferric reducing antioxidant potential, ORAC = Oxygen Radical Absorbance Capacity, ROO = Peroxyl radicals, O_2 = Superoxide Radicals, H_2O_2 = Hydrogen Peroxide, OH = Hydroxyl Radicals, TP = Total Phenolics, TF = Total Flavonoids, TS = Total Saponins, GSH = Gluthatione, GSSG = Oxidized Gluthatione, SC = Soluble Carbohydrate, SS = Soluble Sugar, PAL = Phenylalanine Ammonia Lyase, AA = Ascorbic Acid, AC = Anthocyanin, TFA = Total Fatty Acids, MP = *Marantodes pumilum*, MPva = *Marantodes pumilum* var. *alata,* MPvp = *Marantodes pumilum* var. *pumila*, MPvl = *Marantodes pumilum* var. *lanceolata*, TNF-α = Tumor Necrotic Factor-alpha, COX-2 = Cyclooxygenase-2, MMP-1 = Matrix Metalloproteinase-1, MMP-9 = Matrix Metalloproteinase-9, IL-1*α* = Interleukin-1 alpha, IL-1*β* = Interleukin-1 beta, IL-6 = Interleukin-6, IL-8 = Interleukin-8, PGE_2 = Prostaglandin E_2

3.3. Phytochemical Characteristics of M. pumilum

Phytochemical properties of all studies in this review were showed in Table 2. All the studies had used the three primary species of *M. pumilum* var. *alata,* var. *pumila*, andvar. *lanceolata*, which are commonly found in Malaysia. Most of the studies were conducted on *M. pumilum* var. *alata* [37-

39, 42-47,51]. Some studies have been conducted all of these three species of *M. pumilum* [41,48-50, 52,55]. There were only two studies on the other *M. pumilum* species, one on *M. pumilum* var. *pumila* [35] and the other study using both *M. pumilum* var. *pumila* and var. *alata* [53]. Three studies did not mention the *M. pumilum* species used [36,40,54].

Table 2. Phytochemistry and ethnobotany of MP among the studies included in the review

Study No.	Plant Sources	Plant Species	Plant parts	Type of extracts	Phytoconstituents	Ethnobotany	Ref.
1	Delima Jelita Herbs, Kedah, Malaysia	MPva	Whole plant	Aqueous	-	Antioxidative	[37]
2	Hill tracks, Perak, Malaysia	MPva	Whole plant	Aqueous, 80% ethanol	Flavonoids (rutin & myricetin), phenolic (gallic acid), 5-(*Z*-nonadec-14-enyl)resorcinol and demethylbelamcandaquinone B	Antioxidative	[38]
3	Hill tracks, Perak, Malaysia	MPva	Whole plant	Aqueous, 80% ethanol	Flavonoids (rutin & myricetin), phenolic (gallic acid), 5-(*Z*-nonadec-14-enyl)resorcinol and demethylbelamcandaquinone B	Antioxidative	[39]
4	-	MP		Ethanol	-	Antioxidative	[40]
5	-	MPva and MPvp	Leaf	Aqueous, 80% Methanol	Flavonoids (kaempferol), phenolic compounds (gallic acid), anthocyanin (petunidin), ascorbic acid, *β*-carotene	Antioxidative	[53]
6	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (rutin), phenolic (gallic acid) and Glutathione	Antioxidative	[42]
7	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (rutin), phenolic compounds (gallic acid), ascorbic acid, soluble sugar, Starch, non-structural carbohydrate	Antioxidative	[43]
8	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (quercetin), phenolic compounds (gallic acid), anthocyanin	Antioxidative	[44]
9	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (quercetin), anthocyanin, ascorbic acid, glutathione	Antioxidative	[47]
10	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (rutin), phenolics (gallic acid), saponins (diosgenin), ascorbic acid, soluble sugar (sucrose), nitrate, glutathione	Antioxidative	[45]
11	Glasshouse complex of University Putra Malaysia	MPva	Leaf, Stem and Root	Methanol, 80% ethanol	Flavonoids (rutin), phenolics (gallic acid), anthocyanin (petunidin), ascorbic acid, soluble sugar (sucrose), malondialdehyde	Antioxidative	[46]
12	Glasshouse complex of University Putra Malaysia	MPva, MPvp, and MPvl	Leaf	Methanol	Flavonoids (kaempferol, quercetin, myricetin, rutin & naringenin) and phenolics (gallic acid, pyrogallol & caffeic acid)	Antioxidative	[48]
13	Kota Tinggi,	MPva,	Leaf,	Methanol	Flavonoids (rutin) and phenolics	Antioxidative	[50]

	Johor; Hulu Langat, Selangor; and Sungkai, Perak.	MPvp, and MPvl	Stem and Root		(gallic acid)		
14	Glasshouse complex of University Putra Malaysia	MPva, MPvp, and MPvl	Leaf, Stem and Root	Methanol	Flavonoids (kaempferol, myricetin, naringin, quercetin & rutin) and phenolics (gallic acid, pyrogallol & caffeic acid)	Antioxidative	[49]
15	Kota Tinggi, Johor; Hulu Langat, Selangor; and Sungkai, Perak.	MPva, MPvp, and MPvl	Leaf	Microwave aqueous	Flavonoids (rutin), phenolics (gallic acid) and fatty acids (palmitic acid, palmitoleic acid, stearic acid, vaccenic acid, linoleic acid & α-linolenic acid)	Antioxidative	[52]
16	-	MPva	Leaf	Aqueous, 80% Methanol	Flavonoids (rutin, myricetin, quercetin, naringin, epicatechin, catechin & daidzein), phenolics (gallic acid & pyrogallol), saponin (diosgenin) and fatty acids (palmitic acid, palmitoleic acid, stearic acid, vaccenic acid, linoleic acid & α-linolenic acid)	Antioxidative	[51]
17	Kota Tinggi, Johor; Hulu Langat, Selangor; and Sungkai, Perak.	MPva, MPvp, and MPvl	Leaf and root	Microwave aqueous	-	Anti-inflammatory	[41]
18	Universiti Putra Malaysia	MPvp	Leaf	Aqueous	-	Anti-inflammatory	[35]
19	Universiti Putra Malaysia	MP	Leaf	Dichloro-methane	Phenolics (gallic acid)	Antioxidative & Anti-inflammatory	[36]
20	-	MP	Whole plant	Aqueous	-	Antioxidative & Anti-inflammatory	[54]
21	Hutan Gunung Bujang Melaka, Kampar, Perak, Malaysia.	MPva, MPvp, and MPvl	Leaf and root	Dichloro-methane, Methanol, aqueous	Quercetin and apigenin	Anti-inflammatory	[55]

*MP = *Marantodes pumilum*, MPva = *Marantodes pumilum* var. *alata,* MPvp = *Marantodes pumilum* var. *pumila*, MPvl = *Marantodes pumilum* var. *lanceolata*

The type of *M. pumilum* extracts used in the studies varies from each other. Readily dried powdered of *M. pumilum* has been used for the extraction in most of studies. Methanol and ethanol were used as a medium for extraction process in six studies [42-47]. Methanol and aqueous solutions were used individually for extraction in three [48-50] and five [35,37,41,52,54] of the studies, respectively. In the four studies, two of them were extracted by aqueous and ethanol process [38,39] and another two were by aqueous and methanol process [51,53]. Each of two studies was used two different solvents including dichloromethane extract [36] and ethanol [40]. Only one study has been extracted in three different medium such as dichloromethane, methanol and aqueous [55]. In most studies [42-47,49,50], extracts from all parts of *M. pumilum* (leaf, stem, and root) were used. In two studies [41,55], two types of extract (leaf and root) have been used. In six studies [35,36,48,51-53], leaf extracts were used, and in the other four studies [37-39,54], whole plant extract was used. In most of the studies, plants were collected from Universiti Putra Malaysia, Serdang, while others were

collected from Selangor; Perak and Johor. Phytoconstituents were identified in sixteen of the studies [36,38,39,42-53,55] which include flavonoids, phenolic compounds, saponins, fatty acids, ascorbic acids, anthocyanin, glutathione, nitrate, and sugars. Examples of flavonoids identified in all three varieties of *M. pumilum* were kaempferol, myricetin, naringin, quercetin, and rutinare. Examples of phenolic compounds identified were gallic acid, pyrogallol, caffeic acid, demethylbelamcandaquinone B and 5-(*Z*-nonadec-14-enyl) resorcinol. Examples of fatty acids identified were linoleic acid, α-linolenic acid, vaccenic acid, stearic acid, palmitic acid, and palmitoleic acid.

3.3. Antioxidant and Anti-inflammatory Properties of M. pumilum

In total twenty one studies, sixteen studies have shown antioxidative effects of *M. pumilum* which included four animal study and twelve chemical assays studies. Three studies have exhibited anti-inflammatory effects of *M. pumilum*, including one animal study and two in vitro cell culture study. The other two studies, an animal study and a combined cell culture and assay study, have shown both antioxidative and anti-inflammatory effects (Table 1). All types of studies (*in vivo* animal study, in vitro cell culture study and/or assay study) have demonstrated positive effects of *M. pumilum* extracts (parts or whole plant) on oxidation and inflammation conditions.

4. Discussion

4.1. Antioxidative Activities of M. pumilum

Nineteen studies observed the positive antioxidative activity of *M. pumilum*, including four animal study and fifteen chemical assay studies. In the animal studies, oxidative measurements were analyzed by various biochemical test including SOD, GPx, CAT, GSH, GR and MDA levels in rat model supplemented with *M. pumilum* extract [37-40]. One of chemical assay study by Ibrahim and Jaafar (2012a) also analyzed antioxidant enzymatic activities like APX, CAT and SOD levels. In these studies, the SOD, GPx, CAT, GSH, GR and APX levels exhibited a positive response to *M. pumilum* supplementation [44]. In the Effendy and Shuid (2014) study, SOD and GPx levels were significantly higher in *M. pumilum* treated groups than control groups [37]. In contrast, a significant change of MDA level in the treated groups at week 6 and 9. MDA in treated groups was significantly lower level compared to ovariectomized control group in the treatment period of week 6 and 9. Thus, *M. pumilum* supplementations may potential to reduce oxidative stress due to its antioxidant properties and subsequently prevent the bone loss. Similar trends have been shown in the other animal studies in case of antioxidant activity [38-40]. Antioxidant enzymes have played an important role by suppressing free radicals release and preventing the oxidation degredation of lipids [56]. Due to anti-oxidative activities, the anti-oxidative enzyme levels would be reduced as demonstrated by the low of antioxidant enzymes like SOD and GPx levels of ovariectomized rat model [57]. In the fifteen chemical assay studies, many chemical assays were conducted to assess antioxidative activities particularly DPPH, NO, ABTS radical scavenging, FRAP, ORAC, PAL and β-carotene bleaching. In most of the studies [36, 44-51, 53, 54], DPPH radical scavenging assay was conducted to determine antioxidant activity. In this method, an antioxidant can donate hydrogen atom and quench into the stable free radical. In all of the studies, DPPH radical scavenging of *M. pumilum* species was higher in leaves extract, followed by other two extracts, stems and roots extracts in different environmental conditions.

When the *M. pumilum* varieties were compared by DPPH radical scavenging assay, var. *alata* has more antioxidative properties followed by var *pumila* and var. *lanceolata*. The study indicated that DPPH scavenging of var. *alata* extracts may have high contents ofphenolic compounds, flavonoids and anthocyanins [58]. Besides, total antioxidant activity can also measure by FRAP assay. This method is very fast and accurate [59]. This assay measures the total antioxidant activity by the calculation of reducing power of ferric (Fe^{3+}) to ferrous (Fe^{2+}) [60]. In some studies [45,47-51,53], similar expressions in FRAP assay were shown as that in DPPH antioxidant activity. The FRAP activity in leaves extract was also higher compared to the stems, and roots extracts of *M. pumilum*. The antioxidant activity of dietary polyphenols can also measure by FRAP assay [61]. The antioxidant activity and the phytochemicals like total phenolics and flavonoids contents have a strong relationship

[2,63]. Current study has shown that FRAP activity is directly proportionated with total flavonoids and total phenolics. Moreover, PAL activity was measured to assess antioxidant activity in four of the studies [43,44,46,48]. This activity was influenced by environmental conditions and secondary plant metabolites because PAL is a precursor to total phenolics and flavonoids biosynthesis [64]. Other antioxidative assays used which include ORAC [42], *β*-carotene [53], ABTS [52] and NO radical scavenging [36,51,52] followed a similar trend of earlier activities.

Also, many secondary metabolites have been identified from *M. pumilum* including ascorbic acid, *β*-carotene, anthocyanin, flavonoid, phenolic, saponin, fatty acids and glutathione [36,42-53]. A previous study demonstrated that antioxidative effects has strong relationship with the contents of vitamins C and E, total carotenes, total xanthophylls, tannins and total phenolic compaounds[65]. Correlation analyses revealed significant positive coefficients of antioxidant activities with secondary metabolites [24]. Some secondary metabolites such as saponin, phenolic, ascorbic acid, *β*-carotene, and anthocyanin were found to be higher in var. *alata* compared to var. *pumila* and var. *lanceolata*. However, var. *pumila* had higher total flavonoid content than var. *alata* and var. *lanceolata* [53]. In most of the studies [42-47, 49, 50], bioactive compounds (total phenolics and flavonoid) of *M. pumilum* were highly accumulated in the leaf than other plant parts. The similar trend of antioxidant effects could also be found in secondary metabolites of all the studies.

4.2. Anti-inflammatory Activities of M. pumilum

Four studies, which consisted of two animal studies and two *in vitro* cell culture studies, had measured anti-inflammatory activities. In the animal studies [35,36], the anti-inflammatory activity was determined by formalin-induced inflammation, arachidonic acid-induced ear edema, carrageenan-induced paw edema, and mast cell stabilization test. In the *in vitro* cell culture studies [41,54,55], the anti-inflammatory activity was analyzed by determination of NO production, Type-1 pro-collagen levels, TNF-*α*, COX-2, MMP-1, MMP-9, IL-1*α*, IL-1*β*, IL-6, IL-8 and PGE_2 expression. Sanusi *et al.* (2013) evaluated the anti-inflammatory effects of three concentrations of *M. pumilum* var. *lanceolata* aqueous leaf extract in a rat model by using two inflammatory models like paw licking by formalin induction and paw edema test by carrageenan induction. Paw licking in *M. pumilum* var. *lanceolata* treated groups has reduced significantly than control groups. A similar trend was shown in carrageenan-induced edema test. The edema formation was better reduction in the treatment of *M. pumilum* var. *lanceolata* group compared to the control groups. The results suggested that *M. pumilum* extracts can efficiently reduce acute inflammation. The leaf extract has the highest level of anti-inflammatory contents compared to extracts from other parts of *M. pumilum* plant [62]. Chemical constituents may have impact of anti-inflammatory activity. Moreover, several studies have also shown that flavonoids such as rutin, hesperidin and bioflavonoids could produce significant anti-inflammatory activities [66,67]**.** Therefore, it is suggested that *M. pumilum* extract possesses a similar effect like *Crocus sativus* extract which contains a large amount of flavonoids which enhanced the anti-inflammatory effect. Besides, Ekeuku and Okechukwu (2013) investigated on the inhibition of arachidonic acid-induced ear edema by using *M. pumilum* extracts in mice model and determined its effect on mast cell stabilization using male rat model [36]. *M. pumilum* extract has potential against ear edema in mice and stabilize mast cells in experimental rats. Moreover, Karimi *et al.* (2013) demonstrated that the anti-inflammatory activity of leaves extract of three *M. pumilum* species was evaluated through *in vitro* cell culture [41]. This study demonstrated that NO release has significantly went down in all *M. pumilum* species. However, the activity of root extracts was better than the leaves extracts of all *M. pumilum* species. Kim *et al.* (2005) reported that iNOS has been extended levels in various types of cancer and chronic inflammatory diseases [68]. Thus, NO can induce inflammation and subsequently develop the cancer. Furthermore, Choi *et al.*, (2010) analyzed TNF-*α*, COX-2, collagen type-1, MMP-1 and MMP-9 expressions during inflammatory process induced by UV irradiation [54]. Treatment with *M. pumilum* extracts markedly inhibited TNF-*α* production, COX-2, and MMP-1 expressions and enhanced collagen production and MMP-9 expression. UVB irradiation can stimulate of skin cells to release of pro-inflammatory cytokines like TNF-*α*, IL-1*α*, IL-6 and inflammatory mediator like PGE_2 in keratinocytes [69,70]. Thus, inflammation can prevent by controlling the pro-inflammatory mediators. Also, elevated expression of MMP-9 cause apoptosis,

photoaging of skin epidermis [71]. The study results showed that *M. pumilum* extract has better effects against the photo aging in epidermis layer induced by UV compared to the ascorbic acid.

5. Limitations and Recommendations

This systematic review analyzed sixteen studies investigating the antioxidant and anti-inflammatory activities of *M. pumilum*. Most of the studies were based on chemical assays. There was no human study carried out about these two activities of *M. pumilum*. All the studies on the antioxidative and anti-inflammatory activities of *M. pumilum* were carried out using chemical assays and highlighted phytochemical profiling in various environmental aspects except for five studies [35,37,40,41,54]. All the studies did confirm the antioxidative effects of *M. pumilum* except for three studies [35,41,55].

Based on the potential shown by *M. pumilum*, it is recommended that further studies on the antioxidative and anti-inflammatory properties of *M. pumilum* extracts should be carried out in many more animal and human studies. Apart from this, studies are also needed to determine the phytochemical compounds responsible for these MP activities. These will support future studies on the specific active compounds of *M. pumilum* in the quest to discover new antioxidative and anti-inflammatory agents.

6. Conclusions

The above literatures concluded that *M. pumilum* extracts have antioxidative and anti-inflammatory activities. These activities are exhibited because of its phytoconstituents such as flavonoids, phenolics, ascorbic acid, beta-carotene, anthocyanin and fatty acids. MP has potential to be developed as alternative treatments for diseases related to oxidative and inflammatory conditions.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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ORCID
Shihab Uddin Ahmad : 0000-0002-7441-4471
Atiqa Azam : 0000-0002-3793-9025
Ahmad Nazrun Shuid : 0000-0003-3526-990X
Isa Naina Mohamed : 0000-0001-8891-2423

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