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REVIEW

Immunomodulatory Activities of Thai Herbs and the Druggability of Their Bioactive Constituents: A Comprehensive Review for Potential Phytopharmaceutical Product Development

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Background: Thai herbs have been studied and developed as alternative or complementary medicines for several diseases. Some Thai herbs show immunomodulatory activities and might be beneficial for the development of novel phytopharmaceutical products.

Purpose: This study aimed to review the immunomodulatory activities of Thai herbs to determine the druggability of the major bioactive components of these herbs.

Materials and Methods: A list of 129 monographs (88 herbs) in the Thai Herbal Pharmacopoeia 2021 and its supplement from 2022 was used to review the immunomodulatory activities from various records and bibliological evidence. The potential bioactive components of these herbs were analyzed, and we determined druggability in compliance with Lipinski's rule of five.

Results: Among the 74/88 (84%) herbs with immunomodulatory activity, 35 were studied in vitro and ex vivo and 39 were studied in vivo. The major immunomodulatory activity was decreased tumor necrosis factor-α (20%), interleukin-6 (15%), interleukin-1β (12%), interferon-γ (8%), and interleukin-10 (7%). Only 43/74 (58%) showed an association between their immunomodulatory activity and their major bioactive compounds. We excluded 18/43 (42%) of herbs because their bioactive compound concentration exceeded the cut-off of 10 μM, and Simplified Molecular Input Line Entry System format data were lacking. The remaining 25/43 (58%) contained 32 bioactive compounds, of which 17 were potential bioactive compounds that complied with all the criteria of Lipinski's rule of five. However, most of these potential bioactive compounds showed limitations in water solubility, and some compounds were reported to be extensively biotransformed in vivo.

Conclusion: Some phytoconstituents of Thai herbs showed potential druggability as immunomodulatory agents in compliance with Lipinski's rule of five, the criteria for drug discovery. However, limitations in water solubility and metabolic stability mean these potential bioactive compounds might need some modifications for drug development. Addition of solubilizers, bioenhancers, and other drug delivery systems to improve pharmacokinetic profiles might be appropriate strategies to develop these bioactive compounds for future clinical applications.

Keywords: Thai herbs, drug candidate, Lipinski's rule of five, immunomodulatory agent, phytopharmaceutical product

Introduction

Immune cells have an important role in human health, especially in secreting cytokines to communicate with different cells to coordinate an immune response. Cytokines are classified into various groups, such as interleukins, interferons, and chemokines, according to the structure of their receptors. The release of cytokines from immune cells can activate or suppress inflammatory responses or alter the production of other cytokines.[1] On the basis of their functions, cytokines can be classified

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into pro-inflammatory cytokines and anti-inflammatory cytokines. Pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), are primarily involved in initiating and amplifying immune responses.[2] These cytokines are produced in response to infection, tissue damage, or other inflammatory stimuli. Pro-inflammatory cytokines promote the recruitment and activation of immune cells to sites of inflammation, increase blood vessel permeability, and stimulate the production of acute-phase proteins.[3] Anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-β), play a crucial role in dampening and resolving immune responses.[2] These cytokines act to counter-balance the effects of pro-inflammatory cytokines and prevent excessive inflammation. Anti-inflammatory cytokines help regulate immune cell activity, promote tissue repair and regeneration, and maintain immune homeostasis.[3]

Cytokines regulate immune responses via signaling pathways that activate or suppress inflammation. Upon infection or injury, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α initiate immune activation via the nuclear factor-kappa B (NF-κB), Janus kinase-signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinase (MAPK) pathways. These cascades drive the expression of inflammatory mediators, recruit immune cells, and promote adaptive immune function.[2,3] IL-1β activates NF-κB and MAPK, leading to the transcription of inflammatory mediators and promoting inflammasome formation.[4] IL-6 signals via the JAK/STAT3 pathway to regulate leukocyte recruitment, B cell development and Th17 cell differentiation.[5,6] TNF-α also utilizes NF-κB and MAPK signaling to induce cytokine and adhesion molecule expression and to enhance endothelial permeability and leukocyte extravasation.[7,8] Additional cytokines, including interferon-gamma (IFN-γ), IL-2, IL-12, IL-17, and IL-21, enhance antigen presentation, T cell activity, and antibody production.[9–11] Conversely, anti-inflammatory cytokines attenuate immune responses once the pathogenic threat is eliminated and maintain immune homeostasis: IL-10 inhibits NF-κB and activates STAT3 to upregulate anti-inflammatory gene expression;[12] TGF-β suppresses T cell activation via the SMAD pathway and supports regulatory T cell differentiation;[13] IL-4 shifts immune responses toward a less inflammatory state by promoting the degradation of pro-inflammatory cytokine mRNA.[14] These regulatory mechanisms, ranging from transcriptional repression to RNA degradation and protein inhibition, ensure a balanced immune response, preventing excessive inflammation and tissue damage (Figure 1).[6,12]

In recent decades, plant extracts have been studied for their immunomodulatory activities and have been developed as alternative or complementary medicines.[15–17] Herbal medicines are often used as alternative treatments because they have fewer side effects than modern medicine and possible efficacy.[18] In fact, many studies have shown that herbal medicines provide adequate efficacy for the treatment of several diseases, such as infectious diseases and some cancers.[19,20] Interestingly, 80% of the population in Africa uses herbal medicines as the primary treatment for many illnesses, while in China, herbal medicine comprises approximately 30–50% of the country's total drug prescription.[21] In

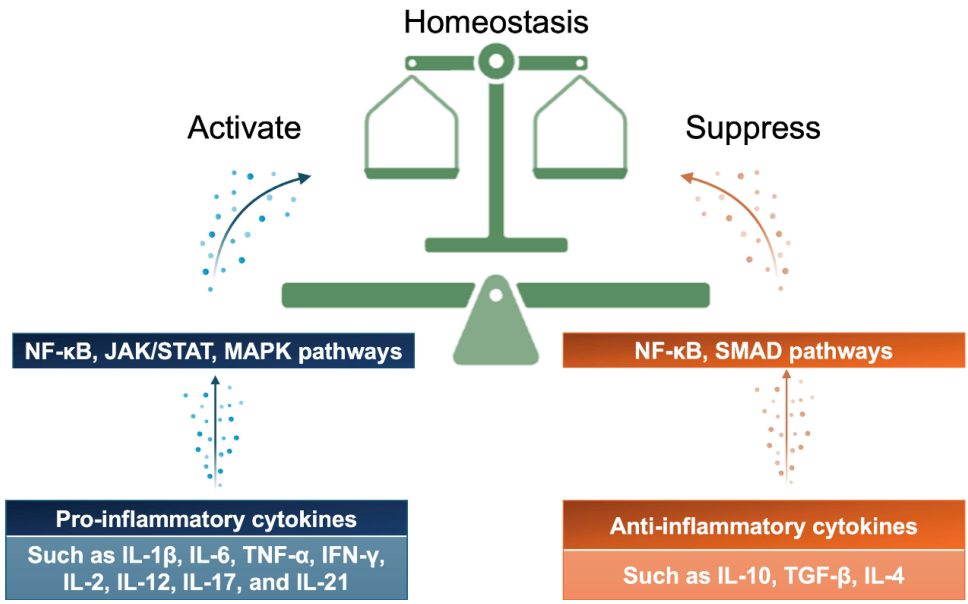

Figure 1 Schematic representation of immune homeostasis regulated by pro- and anti-inflammatory signaling pathways.

Thailand, herbal medicine has been and still is used for the treatment and prevention of many diseases. However, comprehensive information regarding the immunomodulatory activities of Thai herbs, as recorded in the Thai Herbal Pharmacopoeia, is limited.[22,23] The pharmacological activity of stimulation or suppression of cytokines by herbal bioactive compounds has been described in several studies. For example, baicalein and baicalin from *Scutellaria baicalensis* Georgi have been shown to inhibit infection and the replication of HIV through interferon activation.[24] Additionally, Radix Stephaniae Tetrandrine extracted from the dried root of *Stephania tetrandra* S. Moore has shown anticancer effects through the modulation of various pathways, such as the reduction of inflammatory processes, suppression of cellular proliferation, and initiation of apoptotic pathways.[25,26]

Lipinski et al introduced the following criteria for compounds that could be developed as oral drug candidates: (I) a molecular weight (MW) <500 Da because small molecules have better permeability across cell membranes and are more easily absorbed by the body; (II) a partition rule is related to moderate lipophilicity and ensures passive diffusion across biological membranes into body fluids and efficient absorption; (III) hydrogen bond donors (HBDs) are <5; and (IV) hydrogen bond acceptors (HBAs) are <10, indicating that the compound has a balanced ability to form a hydrogen bond with biological targets, which can influence its binding affinity and selectivity. Lipinski's rule of five serves as a fundamental guideline for assessing the drug-likeness and oral bioavailability of potential drug candidates on the basis of key physicochemical properties. The primary benefits of using the rule of five include efficient screening of drug-like compounds based on their properties, which enhances the likelihood of identifying orally bioavailable compounds. This rule of five facilitates reduction in the cost and time for drug development by eliminating compounds with poor absorption early in the research phase. In addition, the rule enhances the probability of discovering bioactive compounds by prioritizing compounds with favorable pharmacokinetic properties, which can be further optimized for therapeutic use.

This study aimed to review the immunomodulatory activities of tropical herbs listed in the Thai Herbal Pharmacopeia. We evaluated some potential bioactive constituents for their druggability in compliance with Lipinski's rule of five. The results of our evaluations are expected to be useful for further development of immunomodulatory agents in drug discovery and development from natural resources.

Materials and Methods

Inclusion of Data

A list of 88 herbs from the Thai Herbal Pharmacopeia 2021 and a supplement from 2022 were used for this study (Figure 2). The data included in the study came from in vitro, ex vivo, in vivo, and clinical studies that reported the immunomodulatory activities of these Thai herbs. The criteria categorizing the type of study were as follows: The in vitro studies involved the isolation and manipulation of cells, tissues, or biomolecules from a living organism, which were then subjected to controlled experimental conditions, such as specific culture media, temperature, and exposure to various stimuli or treatments outside of a living organism. The ex vivo studies involved experiments conducted using living tissues, organs, or biological samples that were removed from an organism and maintained in a controlled environment outside the organism's body. The in vivo studies involved investigations conducted within a living organism, typically an animal model or human subjects. The data were collected from related published articles found in PubMed, ScienceDirect, Scopus, Web of Science, MEDLINE, and Google Scholar. We searched these databases using the scientific name of each herb as well as the following keywords: immune response, immune function enhancement, immune system modulation, adaptive and innate immunity, cytokine production, cytokine modulators, cytokine response, cytokine interactions, herbal immunoregulation, plant-derived immunomodulators, immunomodulatory activity, immunomodulatory effect, bioactive compound, dosage of medicinal plants in immunotherapy, and therapeutic doses of phytochemicals. Information on the part of the herb used, its bioactive compounds, dosages tested, and the immunomodulatory effects of the herbs were extracted from the studies.

To ensure that current and recent research was presented in this study, only articles published from 2001 onward were included (with a few exceptions due to the relevance of the work), with preference given to articles published within 2011–2024 in order to improve contemporary relevance. Only articles available in English were considered. Non-peer-reviewed articles, including opinion pieces, commentaries, and anecdotal reports were excluded. The articles referenced

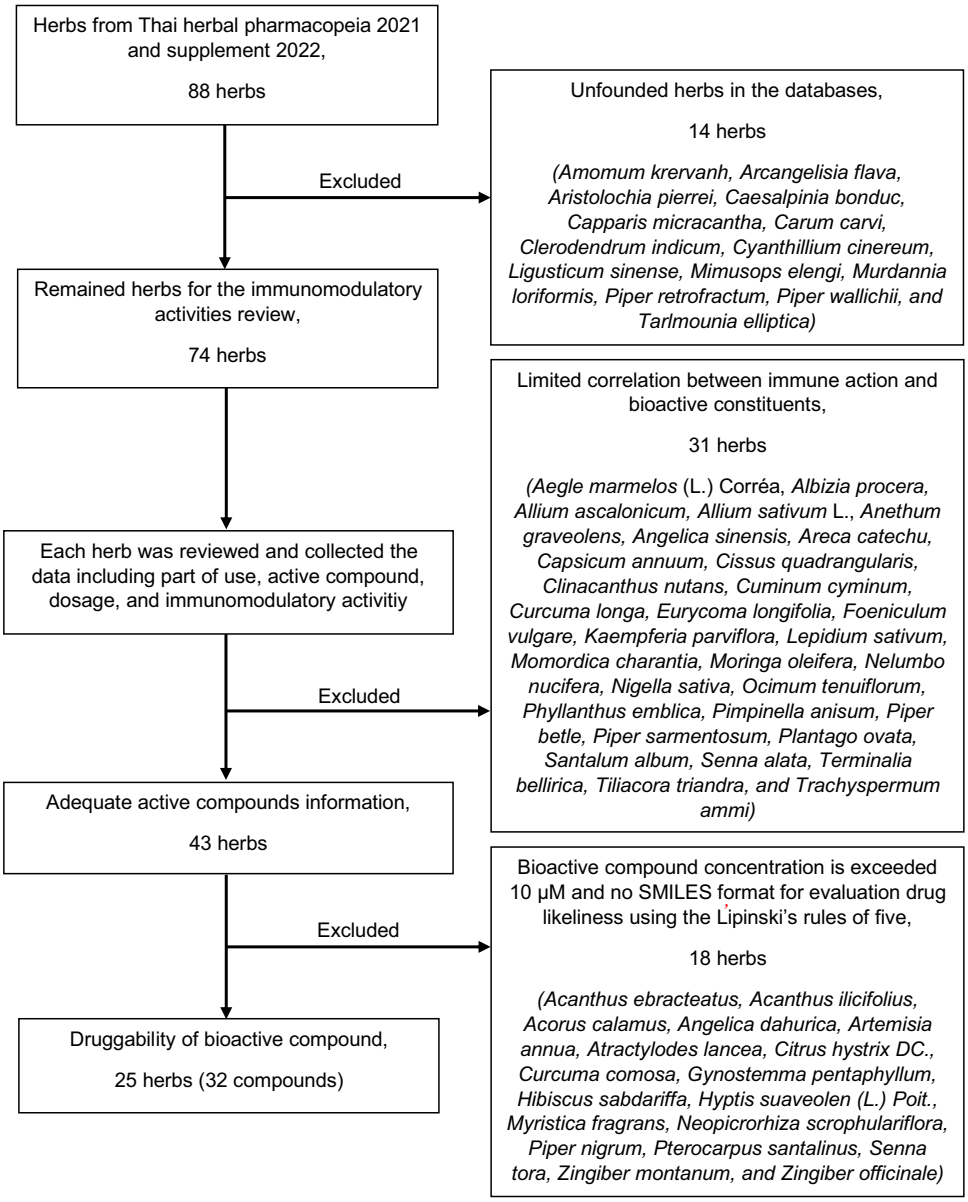

Figure 2 Flowchart of the literature review.

in this study were evaluated and categorized based on their methodological quality. The criteria for each rating level were defined as follows: Excellent—studies that included a negative control, positive control, and a standard compound of the bioactive ingredient, and reported results with highly significant differences compared to the control group; Good—studies that incorporated a negative control, a positive control, and a standard compound, but demonstrated only moderately significant differences relative to the control group; Fair—Studies that included both negative and positive control groups but did not specify or utilize a standard reference compound for the bioactive ingredient. This classification system was applied to ensure the inclusion of references with appropriate scientific rigor and to clearly indicate the reliability and strength of evidence presented in the literature.

Exclusion of Data

Information on immunomodulatory activity was not available for the following 14 herbs: *Amomum krervanh, Arcangelisia flava, Aristolochia pierrei, Caesalpinia bonduc, Capparis micracantha, Carum carvi, Clerodendrum indicum, Cyanthillium cinereum, Ligusticum sinense, Mimusops elengi, Murdannia loriformis, Piper retrofractum, Piper wallichii, and Tarlmounia elliptica.*

Included Herbs

Of the 74 herbal species in the review, only 43 were found to have a major bioactive compound associated with immunomodulatory activities, with only 25 herbs with 32 compounds showing druggability potential. Only bioactive compounds with a half maximal inhibitory concentration (IC50) <10 μM and with an available Simplified Molecular Input Line Entry System (SMILES) notation in the database were selected for evaluation of their druggability.[27] Ultimately, we evaluated 32 potential compounds for drug likeness based on Lipinski's rule of five: an MW <500 Da, partition coefficient (LogP) <5, HBDs <5, and HBAs <10 indicated a compound with a high likeliness of druggability.[28] All of the properties were calculated by RDKit using Python programming language (https://www.rdkit.org).

Results

Characteristics of Thai Herbs and Their Bioactive Compounds

All herbs in the Thai Herbal Pharmacopeia 2021 and a supplement from 2022 were categorized into plant family, the part of the herb used, and related inflammatory mediators (Figure 3). Most of the herbs in the Thai Herbal Pharmacopoeia are in Apiaceae (12%) followed by Zingiberaceae (10%), Fabaceae (9%), Acanthaceae (6%), Asteraceae (6%), and Piperaceae (6%). After excluding some herbs using the criteria stated above, 25 herbs were considered to have 32

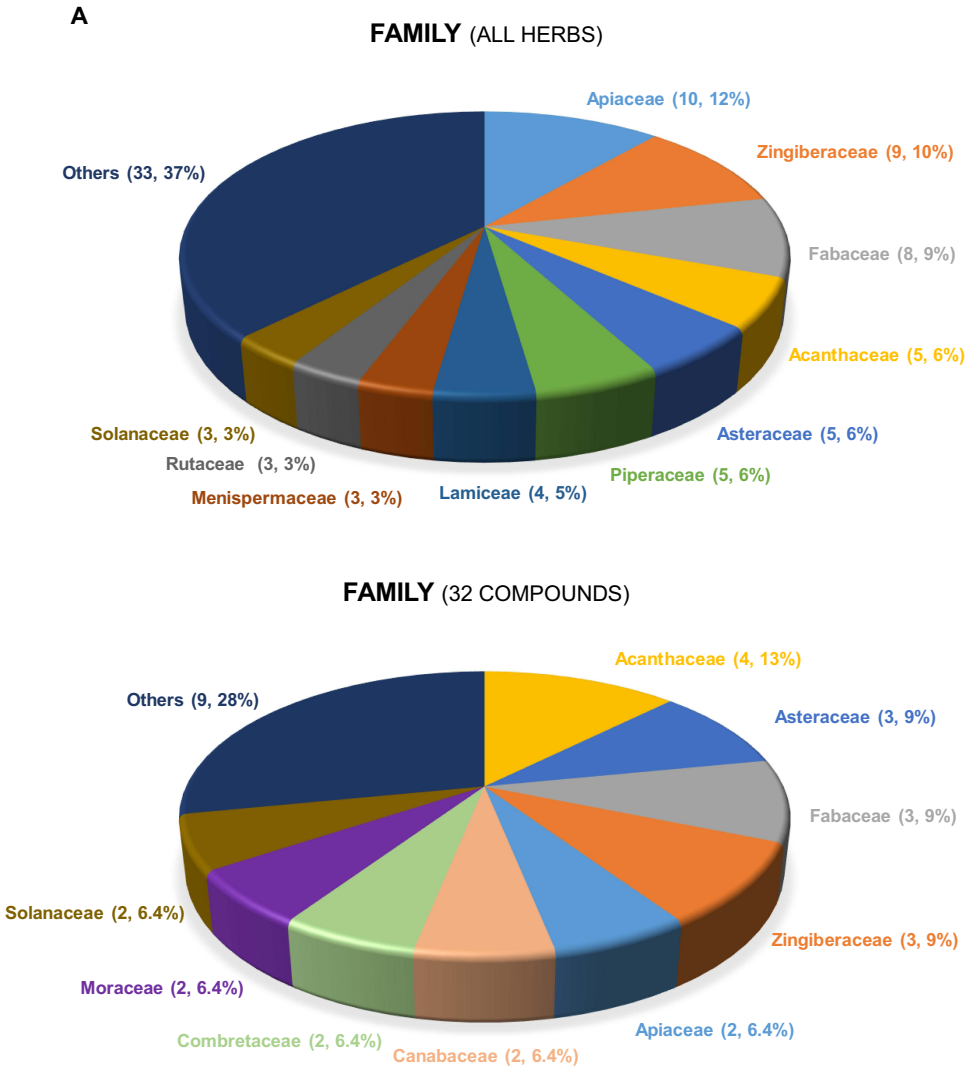

Figure 3 Continued.

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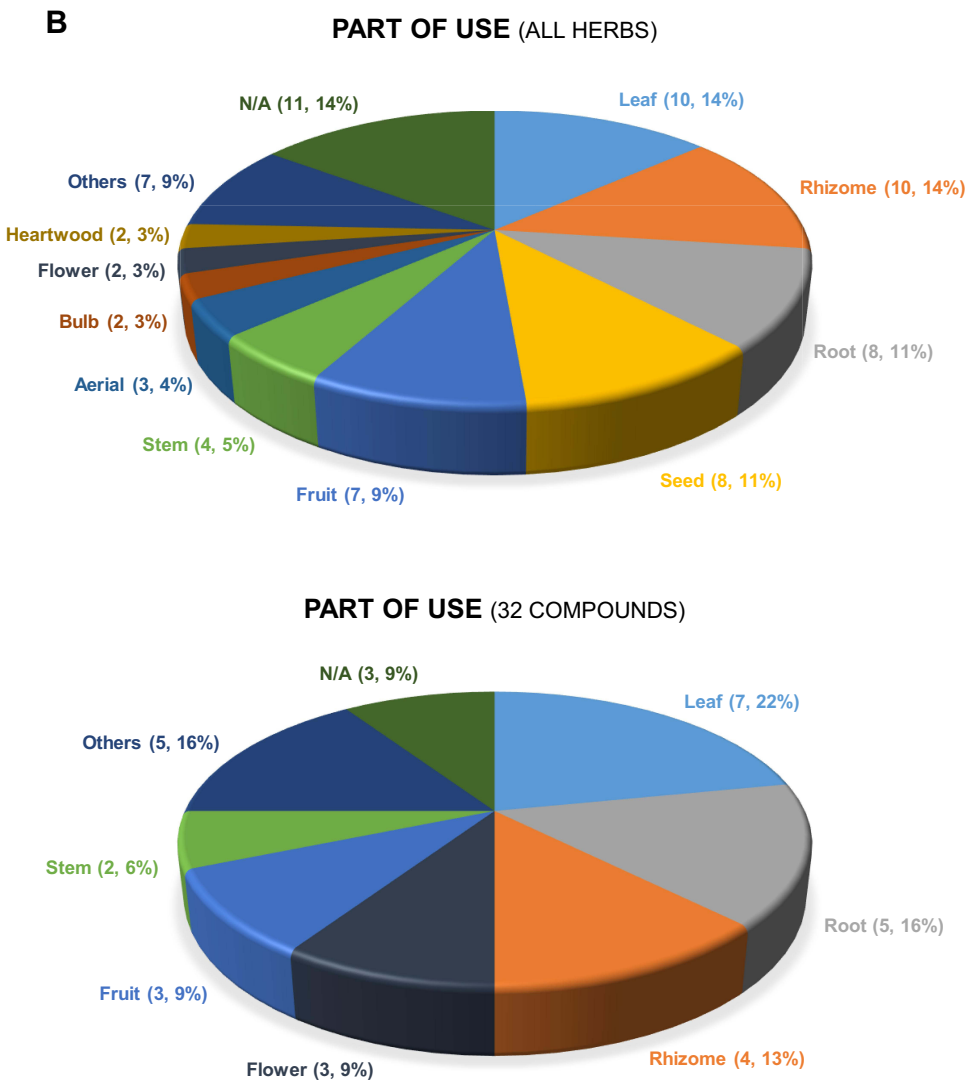

Figure 3 Continued.

druggable bioactive compounds. Most of these herbs are in the families mentioned above but in different amounts, with most belonging to Acanthaceae (13%), followed by Asteraceae (9%), Fabaceae (9%), Zingiberaceae (9%), and Apiaceae (6.4%). Some families considered to have druggable bioactive compounds are not mentioned above; these included Cannabaceae (6.4%), Combretaceae (6.4%), Moraceae (6.4%), and Solanaceae (6.4%) (Figure 3A).

Various parts of the herbs found in the Thai Herbal Pharmacopoeia were used for medication, and these parts included the leaf (14%), rhizome (14%), root (11%), seed (11%), fruit (9%), and stem (5%). Of the 25 herbs included in our examination, the distribution of the parts used in medicine is similar: leaf (22%), root (16%), rhizomes (13%), fruits (9%), and stems (6%). Interestingly, bioactive compounds have also been found in flowers (9%) which are used less often than other parts of the herbs (Figure 3B).

We found many targeted inflammatory mediators of herbs listed in the Thai Herbal Pharmacopoeia, and these included TNF-α (20%), IL-6 (15%), IL-1β (12%), (IFN-γ, 8%), IL-10 (7%), IL-2 (6%), IL-4 (6%), nitric oxide (NO, 5%), and cyclooxygenase-2 (COX-2, 3%). Similarly, the 25 herbs identified as sources of 32 druggable bioactive compounds function as modulators of inflammatory mediators such as TNF-α (19.5%), IL-1β (16%), IL-6 (13%), IL-10 (7%), IFN-γ (6%), NO (4.5%), and COX-2 (4.5%). Interestingly, IL-2 and IL-4 were the main inflammatory mediator targets of the herbs. However, they were not the main target when focusing on bioactive compounds (Figure 3C).

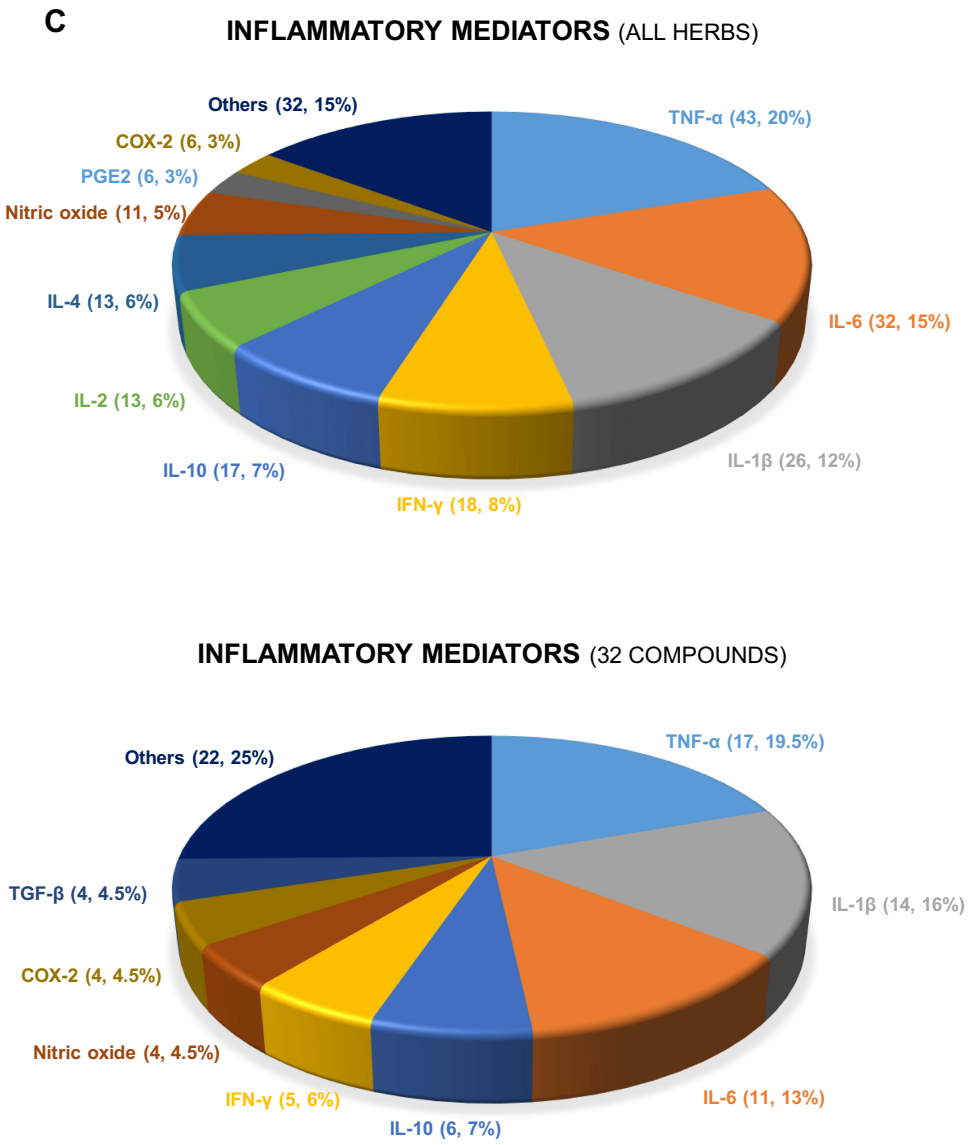

Figure 3 (**A**) Classification of family, (**B**) part of the plant used, and (**C**) inflammatory mediators of all tropical herbs and 32 bioactive compounds in the Thai Herbal Pharmacopoeia 2022.

In vitro, ex vivo, and in vivo Immunomodulatory Activities of Thai Herbs

Immunological activity shown in in vitro and ex vivo studies was reported for 35 herbs listed in the Thai Herbal Pharmacopoeia.[29–63] Many of these herbs, such as *Cannabis sativa, Curcuma longa, Momordica charantia, and Zingiber montanum*, are well known (Table 1). Some of these herbs have an inhibitory effect on inflammatory cytokines, such as *C. sativa*, which can suppress the production of inducible nitric oxide synthase (iNOS) and IL-1β, resulting in decreased potential for inflammatory response.[35] However, some of these herbs enhance the effect of inflammatory cytokines, including *C. longa*, which can induce the production of IL-2, IL-6, IL-10, IL-12, TNF-α, and IFN-γ, resulting in the promotion of pro-inflammatory (IL-2, IL-6, IL-12, TNF-α, and IFN-γ) and anti-inflammatory (IL-10) cytokines, which suggests that this herb can be used for stimulation of the immune system, inflammatory regulation, and disease management.[41] Some of these herbs can both inhibit and induce inflammatory cytokines. For example, *M. charantia* can suppress the production of IL-7 and induce the production of TGF-β and IL-10, thus modulating immune and anti-inflammatory responses.

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Table 1 List of Tropical Herbs in the Thai Herbal Pharmacopoeia 2022 That Showed Immunological Effects in In Vitro and Ex Vivo Studies and Its Evidence Rating

Scientific name	Common name	Family	Part	Concentration	Immunomodulatory Effects	Author/Date	Evidence Rating
Anethum graveolens	Dill (ENG) Thian Ta Takkatan (THAI)	Apiaceae	Leaf	50 ug/mL	IL-6↓, IL-1↓	(Li et al, 2018)[29]	Fair
Angelica dahurica	Bai Zhi (CHINESE) Dahurian angelica (ENG) Kot So (THAI)	Apiaceae	Root	20 uM	TNF-α↓, IL-1β↓, IL-4↓	(Li et al, 2017)[30]	Fair
Angelica sinensis	Female Ginseng (ENG) Dong Quai (CHINESE) Kot Chiang (THAI)	Apiaceae	Root	50-100 ug/mL	IL-6↓, TNF-α↓, IL-10↓	(Kim et al, 2018)[31]	Excellent
Artemisia annua	Sweet Wormwood (ENG) Kot Chula Lampa (THAI)	Asteraceae	N/A	5-100 ug/mL	IL-1β↓, IL-6↓, IL-10↓	(Kim et al, 2015)[32]	Excellent
Atractylodes lancea	Cang Zhu (CHINESE) Kot Kamao (THAI)	Asteraceae	Rhizome	50-2000 ug/mL	TNF-α↓, IL-6↑	(Qin et al, 2019)[33]	Fair
Aucklandia lappa Decne	Costus (ENG) Kot Kraduk (THAI)	Asteraceae	Root	1.25–25 uM	TNF-α↓, IL-8↓, IFN-γ↓	(Seo et al, 2015)[34]	Excellent
Cannabis sativa	Marijuana (ENG) Kancha (THAI)	Cannabaceae	Flower and leaf	0.001–1 uM	iNOS↓, COX-2↓, IL-1β↓	(Romano et al, 2016)[35]	Excellent
Capsicum annuum	Chili Pepper (ENG) Phrik Khinu (THAI)	Solanaceae	Fruit	1-10 ug/mL	IL-2↓, IFN-γ↓, IL-4↓, IL-5↓	(Takano et al, 2007)[36]	Excellent
Chrysopogon zizanioides	Vetivergrass (ENG) Yah Faek Hawm (THAI)	Poaceae	Whole specimens	10 uM	IL-1β↓	(Shih et al, 2012)[37]	Excellent
Cissus quadrangularis	Veldt Grape (ENG) Phet Sangkhat (Thai)	Vitaceae	Stem	10 ng - 50 ug/mL	TNF-α↓, iNOS↓, COX-2↓	(Bhujade et al, 2012)[38]	Fair
Citrus hystrix DC.	Kaffir Lime (ENG) Makrut (Thai)	Rutaceae	Leaf	25 ug/mL	IL-1β↓, IL-6↓, TNF-α↓, NF-κB↓	(Buakaew et al, 2021)[39]	Excellent
Cuminum cyminum	Cumin (ENG) Thian Khao (THAI)	Apiaceae	N/A	10-50 ug/mL	IL-1β↑, TNF-α↑, IL-6↑, IL-12↑	(Tabarsa et al, 2020)[40]	Fair
Curcuma longa	Turmeric (ENG) Khamin Chan (THAI)	Zingiberaceae	Rhizome	0.8–500 ug/mL	IL-2↑, IL-6↑, IL-10↑, IL-12↑, TNF-α↑, IFN-γ↑	(Chandrasekaran et al, 2013)[41]	Fair
Derris scandens	Hog Creeper Vine (ENG) Thaowan Priang (THAI)	Fabaceae	Stem	7-*O*-α-rhamno(1→6)-β-glucosylgenistein [1] Genistein [2] 5,7,4′-trihydroxy-6,5′-diprenylisoflavone [3] Scandenin [4] 1500,100,3,8 uM for [1],[2],[3],[4] 2500,80,6,1.6 uM for [1],[2],[3],[4] 0.22,0.14 uM for [2],[4] 0.3 uM of [2]	 COX↓ 5-lipoxygenase↓ Granular enzyme↓ Superoxide↓	(Laupattarakasem et al, 2004)[42]	Fair
Eurycoma longifolia	Ali's Umbrella Root (ENG) Pla Lai Phueak (THAI)	Simaroubaceae	Root	125-2000 ug/mL	TNF-α↑, IL-6↑	(He et al, 2019)[43]	Fair
Ficus racemosa	Cluster Fig (ENG) Maduea Uthumphon (THAI)	Moraceae	Stem	10-100 uM	PAI1↓, STAT6↓, IL-4↓	(Park et al, 2020)[44]	Excellent

Foeniculum vulgare	Sweet Fennel (ENG) Thian Khao Plueak (THAI)	Apiaceae	Aerial part	10-100 ug/mL	IFN-γ↓, IL-4↓	(Darzi et al, 2018)[45]	Fair
Harrisonia perforata	Khon Tha (THAI)	Rutaceae	Root	2.5–20 uM	Nitric oxide↓	(Choodej et al, 2013)[46]	Good
Hibiscus sabdariffa	Roselle (ENG) Krachiap Daeng (THAI)	Malvaceae	Calyces	50-200 ug/mL	IL-1↓, IL-6↓, TNF-α↓, COX-2↓, nitric oxide↓	(Shen et al, 2016)[47]	Fair
Kaempferia parviflora	Thai Black Ginger (ENG) Krachai Dam (Thai)	Zingiberaceae	Rhizome	3-100 uM	TNF-α↓, PGE_2↓	(Tewtrakul et al, 2008)[48]	Fair
Momordica charantia	Bitter-melon (ENG) Mara Khi Nok (THAI)	Cucurbitaceae	Fruit	0.625–1.875 mg/mL	IL-7↓, TGF-β↑, IL-10↑	(Manabe et al, 2003)[49]	Fair
Moringa oleifera	Horseradish Tree (ENG) Marum (THAI)	Moringaceae	Seed	10 ug/mL	TNF-α↑, IL-2↑, IL-6↑, IL-10↑, nitric oxide↑	(Coriolano et al, 2018)[50]	Fair
Myristica fragrans	Nutmeg Tree (ENG) Dok Chan (THAI)	Myristicaceae	Aril of the fruit	100-500 ug/mL	IL-2↑, IL-4↑, IFN-γ↑	(Checker et al, 2008)[51]	Excellent
Neopicrorhiza scrophulariflora	Kutki (NAPALI) Kot Kan Phrao (THAI)	Plantaginaceae	Root	5-125 ug/mL	IFN-γ↑, IL-2↑, IL-4↑, IL-12↑	(An et al, 2009)[52]	Fair
Orthosiphon aristatus	Java Tea (ENG) Ya Nuat Maeo (THAI)	Lamiaceae	Leaf	12.5–50 ug/mL	iNOS↓, COX-2↓, PGE_2↓, nitric oxide↓	(Hsu et al, 2010)[53]	Excellent
Pimpinella anisum	Aniseed (ENG) Thian Sattabut (THAI)	Apiaceae	Seed	100 ug/mL	IL-1β↑, IL-10↑	(Lee et al, 2011)[54]	Fair
Piper nigrum	Black Pepper (ENG) Phrik Thai Dam (THAI)	Piperaceae	Fruit	2-8 uM	TNF-α↓, IL-6↓, IL-1β↓, PGE_2↓	(Pei et al, 2020)[55]	Fair
Pterocarpus santalinus	Red Sandalwood (ENG) Chan Daeng (THAI)	Fabaceae	Heartwood	31.9 uM	TNF-α↓	(Cho et al, 2001)[56]	Excellent
Santalum album	Indian Sandalwood (ENG) Chan Khao (THAI)	Santalaceae	N/A	50-200 ug/mL	IFN-β↑, IFN-α↑, MxA↑, OAS-1↑, IL-6↓, CXCL8↓, CCL2↓, IP-10↓	(Suganya et al, 2021)[57]	Fair
Senna alata	Candle Bush (ENG) Chumhet Thet (THAI)	Fabaceae	Leaf	5-50 ug/mL	TNF-α↓	(Chomnawang et al, 2007)[58]	Fair
Senna tora	Sickle Senna (ENG) Chumhet Thai (THAI)	Fabaceae	Seed	25-50 uM	TNF-α↓, IL-6↓	(Hou et al, 2018)[59]	Excellent
Terminalia bellirica	Beleric (ENG) Samo Phiphek (THAI)	Combretaceae	Fruit	25-100 ug/mL	TNF-α↓, IL-6↓, NF-κB↓, COX-2↓	(Jayesh et al, 2017)[60]	Fair
Trachyspermum ammi	Ajowan (ENG) Thian Yaowaphani (THAI)	Apiaceae	Seed	1-10 ug/mL	IL-12↑, TNF-α↑, IFN-γ↑	(Shruthi et al, 2017)[61]	Fair
Zingiber montanum	Zingiber Cassumunar (ENG) Phlai (THAI)	Zingiberaceae	Rhizome	0.5–2 uM	IL-1β↓, TNF-α↓, nitric oxide↓, IL-10↑	(Kizukala et al, 2020)[62]	Fair
Zingiber officinale	Ginger (ENG) Khing (Thai)	Zingiberaceae	N/A	50-200 ng/mL	IL-6↓, PGE_2↓, nitric oxide↓	(Han et al, 2013)[63]	Excellent

Abbreviation: N/A, not available.

In in vivo studies, 39 herbs from the Thai Herbal Pharmacopoeia were evaluated as having immunological effects.[64–102] These included well-known herbs such as *Allium sativum L., Boesenbergia rotunda, Centella asiatica, Morus alba*, and *Tinospora crispa* (Table 2). The results of the immunological effects of these herbs in the in vivo studies are in accordance with the results of those in the in vitro and ex vivo studies (ie, in terms of their roles as inhibitors, inducers, and modulators). For example, *A. sativum L.* induces the production of IL-4, IFN-γ, and IL-2. This induction results in immunomodulatory effects that promote Th2 immune responses, which support antibody production, contributing to macrophage activation and stimulating the activation and proliferation of T cells. *B. rotunda*, a well-known herb used in in vitro studies on anti-severe acute respiratory syndrome coronavirus 2 activity, causes a decrease in levels of IL-6 and prostaglandin E2 (PGE_2), which are key pro-inflammatory mediators that have considerable anti-inflammatory properties. *C. asiatica* has also been shown to have various modulating effects, such as anti-inflammatory effects caused by inducing TGF-β and IL-10 levels and immune response modulation activity in the form of suppressing IL-2 levels. Similarly, *M. alba* induces the production of IFN-γ, IL-12, and TNF-α, resulting in macrophage activation by increasing TNF-α levels and enhanced immune responses against bacterial infections by increasing IFN-γ and IL-12, which are Th1 cytokines. *Andrographis paniculata*, a well-known herb for treating the common cold, has the ability to suppress the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, resulting in attenuated inflammatory responses. These well-known herbs are also used for conditions other than those involving inflammation or immune response, such as fever treated using *T. crispa*.

Determination of Druggability of Bioactive Compounds Using Lipinski's Rule of Five

A total of 43 herbs containing bioactive compounds were identified, each supported by sufficient and appropriate data (Table 3). The majority of these herbs contain bioactive constituents that modulate immune responses, primarily through the enhancement or suppression of cytokine production. Examples include, *B. rotunda*, which reduces PGE_2 and IL-6 levels, has panduratin A as a bioactive compound that can be derived from the rhizome of the plant. *C. sativa* considerably reduces iNOS expression, COX-2 protein hyperexpression, and IL-1β levels. The bioactive compounds of *C. sativa* are tetrahydrocannabivarin (THCV) and Δ^9-tetrahydrocannabinol (THC), which can be found in the flowers and leaves. *C. asiatica* increases TGF-β and IL-10 levels and suppresses the production of IL-2, and its bioactive compounds, madecassoside and asiaticoside, can be obtained from the leaf. *A. paniculata* decreases the production of TNF-α, IL-6, and IL-1β, and contains andrographolide, neoandrographolide, and didehydroandrographolide as bioactive compounds, which can be extracted from the leaf. Medicinal products made from *A. paniculata* have appeared on the market in many dosages. Artemisinin, which can be obtained from *Artemisia annua*, inhibits the production of IL-1β, IL-6, and IL-10 and is used to treat malaria.

In this study, we used Lipinski's rule of five to identify bioactive compounds with druggability potential. Thus, we considered a bioactive compound to have druggability potential if its molecular weight was <500 Da (Figure 4A); its partition coefficient was <5 (Figure 4B), which indicates water solubility and membrane permeability; and it had <10 HBAs (Figure 4C) and <5 HBDs (Figure 4D), indicating good molecular interaction. A total of 17 bioactive compounds met all the criteria of Lipinski's rule of five (Figure 4E and Table 4). Andrographolide, neoandrographolide, and didehydroandrographolide (derived from the leaves of *A. paniculata*); tetrahydrocannabivarin (from the leaves and flowers of *C. sativa*); and costunolide, dehydrocostus lactone, alantolactone, capsaicin, rhein, aciculatin, isocyperol, loureirin B, ethyl-p-methoxycinnamate, piceatannol, eugenol, and zerumbone. However, some bioactive compounds did not meet all the criteria but still also showed druggability potential after some modifications. Therefore, Lipinski's rule of five can help guide the selection of bioactive compounds with a high druggability potential or identify bioactive compounds that can be modified to increase their druggability potential. The source code used in this study to apply Lipinski's rule of five can be found in the GitHub repository at https://github.com/44REAM/Thai-herbs-Lipinski.

Discussion

Water Solubility, Metabolic Stability, and Possible Toxicity of the Potential Bioactive Compounds

Lipinski's rule of five is a guideline to determine the potential of lead compounds for oral drug developments that is mainly focused on pharmacokinetics. However, there are other important factors such as water solubility, metabolic

Table 2 List of Tropical Herbs in the Thai Herbal Pharmacopoeia 2022 with Immunological Effects in In Vivo and Its Evidence Rating

Scientific Name	Common Name	Family	Part	Dosage	Immunomodulatory Effects	Author/Date	Evidence Rating
Acanthus ebracteatus	Variegated Sea Holly (ENG) Ngueak plaa mo dok khao (THAI)	Acanthaceae	N/A	125 µg/mL	IL-1α↓, IL-6↓, IL-1β↓, TNF-α↓, NO↓	(Wisuitiprot et al, 2022)[64]	Excellent
Acanthus ilicifolius	Sea Holly (ENG) Ngueak Pla Mo Dok Muang (THAI)	Acanthaceae	N/A	25-100 mg/kg	IL-1β↓, NO↓, iNOS↓, IL-10↑	(Sun et al, 2019)[65]	Excellent
Acorus calamus	Sweet Flag (ENG) Wannam (THAI)	Acoraceae	Rhizome	10 mg/kg	IgE↓, IgG1↓	(Belska et al, 2010)[66]	Fair
Aegle marmelos (L.) Corréa	Bael Fruit Tree (ENG) Matum (THAI)	Rutaceae	Root	50 mg/kg	IL-2↑, IL-6↓, IL-1β↓	(Rajaram et al, 2018)[67]	Fair
Albizia procera	White Siris (ENG) Thing Thon (THAI)	Fabaceae	Bark	100-200 mg/kg/day	TNF-α↓, IFN-α↓, IL-2↓, IL-6↓	(Sangeetha et al, 2020)[68]	Fair
Allium ascalonicum	Shallot (ENG) Hom (THAI)	Amaryllidaceae	Bulb	100 mg/kg	IFN-γ↑, IL-4↓	(Farhadi et al, 2014)[69]	Fair
Allium sativum L.	Garlic (ENG) Krathiam (THAI)	Amaryllidaceae	Bulb	10-100 mg/kg/day	IL-4↑, IFN-γ↑, IL-2↓	(Ota et al, 2012)[70]	Excellent
Andrographis paniculata	Green Chiretta (ENG) Fa Thalai Chon (THAI)	Acanthaceae	Leaf	50-400 mg/kg	TNF-α↓, IL-↓6, IL-1β↓	(Sani et al, 2019)[71]	Excellent
Areca catechu	Nut Palm (ENG) Maksong (THAI)	Arecaceae	Nut	100-300 mg/kg	TNF-α↑, IL-2↑, IFN-γ↑	(Wang et al, 2018)[72]	Fair
Boesenbergia rotunda	Fingerroot (ENG) Krachai (THAI)	Zingiberaceae	Rhizome	1000 mg/kg	IL-6↓, PGE_2↓	(Kongratanapasert et al, 2023)[73]	Excellent
Capsicum oleoresin	(ENG) Chan Namman Phrik Khinu (THAI)	Solanaceae	N/A	10 mg/kg	TNF-α↓, IL-1β↓, IL-10↑,	(Liu et al, 2013)[74]	Excellent
Cassia fistula	Golden Shower (ENG) Khun (Thai)	Fabaceae	Flower	10-40 mg/kg	Nitrite↓, IL-6↓, IL-1β↓, TNF-α↓, MDA↓, iNOS↓, COX-2↓	(Antonisamy et al, 2019)[75]	Excellent
Centella asiatica	Indian Pennywort (ENG) Buabok (THAI)	Apiaceae	Leaf	100 mg/kg	TGF-β↑, IL-10↑, IL-2↓	(Tawinwung et al, 2021)[76]	Excellent
Clinacanthus nutans	Sabah Snake Grass (ENG) Phaya yo (THAI)	Acanthaceae	Aerial part	3-10 mg/kg	IFN-γ↑, IL-2↑	(Huang et al, 2015)[77]	Excellent
Curcuma comosa	Wan Chuk Modlok (THAI)	Zingiberaceae	Rhizomes	0.5–2.0 mg in 20 µL of acetone	IL-1β↓, TNF-α↓, IL-6↓, IL-10↑	(Chuncharunee et al, 2021)[78]	Excellent
Cyperus rotundus	Nut Grass (ENG) Yah Haeo Mu (THAI)	Cyperaceae	Rhizomes	7.5–30 mg/kg	IL-1β↓, IL-6↓, NO↓	(Seo et al, 2016)[79]	Excellent
Dracaena cochinchinensis	Dragon Blood Tree (ENG) Lakkachan (THAI)	Asparagaceae	N/A	25-100 mg/kg	IL-1↓, IL-1β↓, IL-6↓, TNF-α↓, TGF-β↓, IL-10↑	(Sun et al, 2020)[80]	Excellent
Gynostemma pentaphyllum	Jiaogulan (CHINESE) Five-leaf Ginseng (ENG) Pancha Khan (THAI)	Cucurbitaceae	N/A	50-200 mg/kg	IL-2↑, TNF-α↑, IFN-γ↑	(Liu et al, 2014)[81]	Fair
Hyptis suaveolens	Wild Spikenard (ENG) Maenglak Kha (THAI)	Lamiaceae	Aerial part	62.5–125 mg/kg	Nitrite/nitrate↓, MDA↓, MPO↓, IL-1β↓, TNF-α↓	(Machado et al, 2021)[82]	Fair

(*Continued*)

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Table 2 (Continued).

Scientific Name	Common Name	Family	Part	Dosage	Immunomodulatory Effects	Author/Date	Evidence Rating
Kaempferia galanga	Cekur (ENG) Pro Hom (THAI)	Zingiberaceae	Dried and powdered rhizomes	800 mg/kg	IL-1↓, TNF-α↓	(Umar et al, 2014)[83]	Excellent
Lepidium sativum	Garden Cress (ENG) Thian Daeng (THAI)	Brassicaceae	Seed	150-300 mg/kg	IL-6↓, TNF-α↓, IL-10↑	(Raish et al, 2016)[84]	Fair
Mesua ferrea	Ceylon Ironwood (ENG) Bunnak (THAI)	Calophyllaceae	Seed	20-40 mg/kg	Neutrophils↑	(Chahar et al, 2012)[85]	Excellent
Morus alba	White Mulberry (ENG) Mon (THAI)	Moraceae	Fruit	100-500 mg/kg	IFN-γ↑, IL-12↑, TNF-α↑	(Chang et al, 2018)[86]	Good
Nardostachys jatamansi	Spikenard (ENG) Kot Chada Mangsi (THAI)	Caprifoliaceae	N/A	0.05–0.5 mg/kg	IL-1β↓, IL-6↓, TNF-α↓	(Shin et al, 2015)[87]	Excellent
Nelumbo nucifera	Sacred Lotus (ENG) Bua Luang (THAI)	Nelumbonaceae	N/A	0.2–10 ug/kg	IL-10↓, IL-6↓, TNF-α↓	(Liao et al, 2012)[88]	Fair
Nigella sativa	Black Cumin (ENG) Thian Dam (THAI)	Ranunculaceae	Seed	10-250 mg/kg	IL-1β↓, TNF-α↓, IFN-γ↓	(Michel et al, 2011)[89]	Excellent
Ocimum tenuiflorum	Holy Basil (ENG) Kaphrao Daeng (THAI)	Lamiaceae	Leaf	300 mg	IFN-γ↑, IL-4↑	(Mondal et al, 2011)[90]	Fair
Phyllanthus emblica	Indian Gooseberry (ENG) Makham Pom (THAI)	Phyllanthaceae	Fruit	5-10 g/kg/d	TNF-α↓, IL-6↓, IL-1β↓	(Wang et al, 2017)[91]	Excellent
Piper betle	Betel Pepper (ENG) Phlu (THAI)	Piperaceae	Leaf	100 mg/kg (Methanol) 0.3–30 mg/kg (N-hexane) 3-30 mg/kg (Chloroform)	IL-4↑ IFN-γ↑	(Singh et al, 2009)[92]	Fair
Piper sarmentosum	Chavica Sarmentosa (ENG) Chaphlu (THAI)	Piperaceae	Stem leaf	50-200 mg/kg	TNF-α↓, IL-6↓, IL-1β↓, TGF-β↑, IL-4↑, IL-10↑	(Wang et al, 2017)[93]	Fair
Plantago ovata	Blond Plantain (ENG) Thian Klet Hoi (THAI)	Plantaginaceae	Seed	3.5–5%	TNF-α↓, nitric oxide↓	(Rahimi et al, 2010)[94]	Fair
Senna garrettiana	Samae San (Thai)	Fabaceae	Heartwood	40 mg/kg	PGE_2↓, TNF-α↓, IL-1β↓	(Surapanthanakorn et al, 2018)[95]	Excellent
Solanum trilobatum	Thai Nightshade (ENG) Mawaeng Khruea (THAI)	Solanaceae	Root	75 mg/kg	Neutrophil migration↓	(Pandurangan et al, 2011)[96]	Excellent
Syzygium aromaticum	Clove Tree (ENG) Kanplu (THAI)	Myrtaceae	Dried flower bud	0.25% w/v	TNF-α↓, IL-6↓, TGF-β↓, VEGF↓, NO↓, and MDA↓	(Moradi et al, 2023)[97]	Excellent
Terminalia chebula	Myroban (ENG) Samo Thai or Kot Phung Pla (THAI)	Combretaceae	Young Fruit	20-80 mg/kg	TNF-α↓, IL-1β↓, IL-6↓	(Nair et al, 2010)[98]	Fair
Thunbergia laurifolia	Bengal Clockvine (ENG) Rangchuet (THAI)	Acanthaceae	Leaf	2.5–10 mg/kg	IL-17A↓, IL-10↑	(Boonyarikpunchai et al, 2014)[99]	Excellent
Tiliacora triandra	Ya Nang (THAI)	Menispermaceae	Leaf	250-500 mg/kg	TNF-α↓, IL-1β↓, IL-6↓	(Huang et al, 2021)[100]	Fair
Tinospora crispa	Tinospora Crispa (ENG) Boraphet (THAI)	Menispermaceae	Stalk	100-400 mg/kg	IL-2↑, TNF-α↑, IFN-γ↑, IL-4↑	(Ahmad et al, 2015)[101]	Excellent
Zingiber zerumbet	Bitter Ginger (ENG) Krathue (THAI)	Zingiberaceae	Rhizome	0.1–10 mg/kg	IL-4↓, IL-5↓, IL-10↓, IL-13↓	(Tan et al, 2018)[102]	Excellent

Abbreviation: N/A, not available.

Table 3 List of Tropical Herbs with Bioactive Compounds in the Thai Herbal Pharmacopoeia 2022 and Its Evidence Rating

Scientific Name	Bioactive Compounds (Dosage)	Part	Results	Author/Date	Evidence Rating
Acanthus ebracteatus	Verbascoside (125 μg/mL)	N/A	• 95% ethanol extract of *A. ebracteatus* which has verbascoside effects on decreasing release of IL-1β, TNF-α, and NO from RAW 264.7 cells, as well as IL-1α and IL-6 from dermal papilla cells.	(Wisuitiprot et al, 2022)[64]	Excellent
Acanthus ilicifolius	4-hydroxy-2(3H)-benzoxazolone (25–100 mg/kg)	N/A	• 4-hydroxy-2(3H)-benzoxazolone (HBOA) isolated from *A. ilicifolius* decreases IL-1β, NO and iNOS and increases IL-10. Moreover, in liver fibrosis mice, it reduced the mRNA levels of TNF-α and IL-6 by decreasing CCl_4.	(Sun et al, 2019)[65]	Excellent
Acorus calamus	Pectic polysaccharide (20 μg/mL)	Rhizome	• Pectic polysaccharide isolated from the rhizomes by 0.05 mol/L aqueous solution HCl increase 6-fold of IL-12 production, stimulated the production of TNF-α by 1.7 times in human phagocytes in vitro, reduced the concentration of IgE and reduced 2-fold concentration of IgG1 in animals immunized twice.	(Belska et al, 2010)[66]	Fair
Andrographis paniculata	Andrographolide (1.5–12 mg/kg), neoandrographolide (0.9–7.2 mg/kg), and 14-deoxy-11, 12-didehydroandrographolide (0.05–0.44 mg/kg)	Leaf	• Andrographolide, neoandrographolide, and 14-deoxy-11, 12-didehydroandrographolide significantly suppressed the production of all measured PICs (Production of toxic inflammatory cytokines) – include TNF-α, IL-6 and IL-1β producing from hippocampus in dose dependent.	(Sani et al, 2019)[71]	Excellent
Angelica dahurica	Bergapten and phellopterin (20 μM)	Root	• The dried roots of *A. dahurica* were ground and extracted with 95% ethanol. This extract has 15 compounds in which bergapten and phellopterin have the strongest effect to inhibit the secretion of TNF-α, IL-1β and IL-4.	(Li et al, 2017)[30]	Fair
Artemisia annua	Artemisinin (21.1 μg/mL)	N/A	• 80% acetone extracts of *A. annua* 100 μg/mL have the highest inhibitory effect on the various cytokines compared to other extracts methods (water, methanol, and ethanol) including inhibit production of IL-1β, IL-6, and IL-10.	(Kim et al, 2015)[32]	Excellent
Atractylodes lancea	Neutral polysaccharide and acidic polysaccharide (50–2000 μg/mL)	Rhizome	• *A. lancea* polysaccharides increase the production of TNF-α and IL-6 from RAW 264.7 macrophages.	(Qin et al, 2019)[33]	Fair
Aucklandia lappa Decne	Costunolide, dehydrocostus lactone and alantolactone (1.25–10 μM)	Root	• 70% methanolic extract of *A. lappa* contains lactones costunolide, dehydrocostus lactone, and alantolactone have inhibitory effects of the three compounds including TNF-α, IFN-γ, and IL-8.	(Seo et al, 2015)[34]	Excellent
Boesenbergia rotunda	Panduratin A (9.6% w/w)	Rhizome	• EtOH extract of *Boesenbergia rotunda* has Panduratin A which significantly reduces PGE_2 and IL-6 levels.	(Kongratanapasert et al, 2023)[73]	Excellent
Cannabis sativa	Tetrahydrocannabivarin (THCV) and tetrahydrocannabinol (THC) (0.001–1 μM)	Flower and leaf	• THCV (1 μM concentration) significantly reduced the LPS-induced up-regulation of iNOS expression, reduced COX-2 protein hyper-expression, and decreasedIL-1β levels in peritoneal macrophages.	(Romano et al, 2016)[35]	Excellent
Capsicum oleoresin	Capsaicin (6% w/w)	N/A	• Capsaicin from the *C. oleoresin* extract decreased serum TNF-α and IL-1β to PRRSV-infected pigs.	(Liu et al, 2013)[74]	Excellent
Cassia fistula	Rhein (10–40 mg/kg)	Flower	• Administration of rhein inhibited carrageenan-induced paw oedema in rats, croton oil-induced ear oedema in mice, increased the activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) and decreased the levels of nitrite, IL-6, IL-1β, TNF-α, malondialdehyde (MDA) and vascular endothelial growth factor (VEGF). Continual administration to rats using implanted cotton pellets reduced granuloma formation.	(Antonisamy et al, 2019)[75]	Excellent

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Table 3 (Continued).

Scientific Name	Bioactive Compounds (Dosage)	Part	Results	Author/Date	Evidence Rating
Centella asiatica	Madecassoside (50 mg/kg) and asiaticoside (40 mg/kg)	Leaf	• Madecassoside and asiaticoside significantly enhanced the releasing of TGF-β and IL-10 by regulatory T cells but inhibited the production of IL-2.	(Tawinwung et al, 2021)[76]	Excellent
Chrysopogon zizanioides	Aciculatin (10 μM)	Whole specimens	• Aciculatin inhibited IL-1β-stimulated G-CSF expression, suppressing the DNA binding activity of the transcription factors NF-κB and activator protein (AP)-1, inhibited the G-CSF-mediated phosphorylation of Janus kinase-signal transducer and activator of transcription (JAK/STAT) and Akt and neutrophil differentiation from precursor cells.	(Shih et al, 2012)[37]	Excellent
Citrus hystrix DC.	Lupeol (25 μg/mL)	Leaf	• Ethanolic extract of *C. hystrix* leaf contains lupeol which significantly reduced the production of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, NF-κB Signaling, and COX-2 Proteins.	(Buakaew et al, 2021)[39]	Excellent
Curcuma comosa	ASPP 092 [(3S)-1-(3,4-dihydroxy-phenyl)-7-phenyl-(6E)-6-hepten-3-ol]) (0.5–2.0 mg in 20 μL of acetone)	Rhizomes	• Phenolic diarylheptanoid (ASPP 092 [(3S)-1-(3,4-dihydroxy-phenyl)-7-phenyl-(6E)-6-hepten-3-ol]) reduced TNF-α, IL-6, IL-10, IL-1β, and MMP-13	(Chuncharunee et al, 2021)[78]	Excellent
Cyperus rotundus	Isocyperol (7.5–30 mg/kg)	Rhizomes	• 80% EtOH extract of *C. rotundus* has isocyperol which reduces serum level of IL-6, NO and PGE_2 production and mortality in septic mice.	(Seo et al, 2016)[79]	Excellent
Derris scandens (Roxb.) Benth	1. 7-O-α-rhamno(1→6)-β-glucosylgenistein (1500 μM, 2500 μM) 2. Genistein (100 μM, 80 μM) 3. 5,7,4′-trihydroxy-6,5′-diprenylisoflavone (3 μM, 6 μM, 0.3 μM) 4. Scandenin (8 μM, 1.6 μM)	Stem	• 1500 μM, 100 μM, 3 μM and 8 μM for COX inhibition and 2500 μM, 80 μM, 6 μM and 1.6 μM for 5-LOX inhibition for 1, 2, 3 and 4, respectively. • 0.3 μM genistein inhibits the tyrosine kinase activity leading to decreased superoxide production.	(Laupattarakasem et al, 2004)[42]	Fair
Dracaena cochinchinensis	Loureirin B (LB) (25–100 mg/kg)	N/A	• LB in rat could obviously reverse the effect of TNBS (Trinitro-benzene-sulfonic acid), led to a decrease of the production of IL-1, IL-1β, IL-6, TNF-α, IL-6, TGF-β and an increase of the production of IL-10.	(Sun et al, 2020)[80]	Excellent
Ficus racemosa L.	Lupeol (10–100 μM)	Stem	• Lupeol suppresses the chemotaxis of macrophages towards cancer cells by regulating the secretomes of cancer cells. • Lupeol significantly decreased plasminogen activator inhibitor-1 (PAI-1) and Inhibition of PAI-1 secretion from cancer cells mediates the reduced migration of macrophages. Furthermore, lupeol inhibited M2 macrophage polarization by suppression of STAT6 activity which led to reduced migration of lung cancer cells. • Lupeol possesses TAM-regulatory activities.	(Park et al, 2020)[44]	Excellent
Gynostemma pentaphyllum	Neutral polysaccharide fraction (CGPP) (50–200 mg/kg)	N/A	• CGPP was extracted by water extraction and ethanol precipitation significantly increased levels of IL-2, TNF-α and IFN-γ.	(Liu et al, 2014)[81]	Fair
Harrisonia perforata (Blanco) Merr.	Harperfolide (2.5–20 μM)	Dried root	• Harperfolide significantly enhanced the NO production inhibitory activity led to scientific support for the use of *H. perforata* roots for the treatment of inflammatory diseases.	(Choodej et al, 2013)[46]	Good

Hibiscus sabdariffa	*n*-hexadecanoic acid (50, 100, 200 μg/ mL)	Calyces	• n-hexadecanoic acid, accounting for more than 40%, was the most abundant compound in HSO (essential oil isolated from the calyx of *H. sabdariffa*). • HSO 100 μg/mL inhibits 38.57% of NO production rate and makes cell morphological changes in macrophage. • HSO has the strongest inhibition against IL-1 and IL-6 at 200 μg/mL. • mRNA expression of COX-2 was significantly suppressed in a dose-dependent manner (200, 100 and 50 μg/mL of HSO). • The impact on TNF-α presented a moderate inhibitory effect.	(Shen et al, 2016)[47]	Fair
Hyptis suaveolens (L.) Poit.	Hs-HexF (62.5–125 mg/kg)	Aerial part	• Hs-HexF significantly attenuated inflammatory parameters and presented a decrease in nitrite/nitrate, MDA, MPO, IL-1-β and TNF-α and increased levels of SOD, CAT, GSH and IL-10. Furthermore, Hs-HexF significantly reduced positive cells immunostained for PCNA.	(Machado et al, 2021)[82]	Fair
Kaempferia galanga	Ethyl-p-methoxycinnamate (800 mg/kg)	Dried and powdered rhizomes	• Petroleum ether extract of *K. galanga* has ethyl-p-methoxycinnamate which inhibits IL-1 and TNF-α in both in vivo and in vitro models.	(Umar et al, 2014)[83]	Excellent
Mesua ferrea	Mesuol (20 to 40 mg/kg)	Seed	• Mesuol is suggested to have a significant effect increasing neutrophil adhesion and phagocytic index as compared to control group in doses 20 to 40 mg/kg.	(Chahar et al, 2012)[85]	Excellent
Morus alba	Chlorogenic acid (0.354 or 0.59 mg/kg)	Fruit	• The mice fed with hot water extract of *M. alba* (300 or 500 mg/kg) had higher IFN-γ, IL-12, and TNF-α production.	(Chang et al, 2018)[86]	Good
Myristica fragrans	Macelignan (ML) (100–500 ug/mL)	Aril of the fruit	• The production of IL-2, IL-4 and IFN-γ cytokines was significantly inhibited by ML in Con A-stimulated lymphocytes in a dose-dependent manner.	(Checker et al, 2008)[51]	Excellent
Nardostachys jatamansi	Desoxo-narchinol-A (DN) (0.05 mg/kg, 0.1 mg/kg, or 0.5 mg/kg)	N/A	• DN inhibited LPS-induced IL-1β, IL-6, and TNF-α production in a dose-dependent manner (0.05 mg/kg, 0.1 mg/kg, or 0.5 mg/kg).	(Shin et al, 2015)[87]	Excellent
Neopicrorhiza scrophulariflora	Scrocaffeside A (SA) (5–125 μg/mL)	Root	• SA increased the production of cytokines, the CD4+/CD8+ population of splenocytes and the levels of IL-2, IL-4, IL-12, and IFN-γ expressed by cultured splenocytes.	(An et al, 2009)[52]	Fair
Orthosiphon aristatus	Ursolic acid (7.5 μM) and oleanolic acid	Leaf	• Both Ethanol extract from *O. aristatus* and ursolic acid inhibited LPS-stimulated protein and mRNA expression of both iNOS and COX-2 in these cells • Ursolic acid (7.5 μM) significantly inhibited LPS-stimulated NO production.	(Hsu et al, 2010)[53]	Excellent
Piper nigrum	Pipernigramide E, pipernigramide F, and pipernigramide G (2–8 μM)	Fruit	• Pipernigramide E, pipernigramide F, and pipernigramide G concentration-dependently inhibited LPS stimulated IL-1β, TNF-α, IL-6, and PGE_2 release in RAW 264.7 cells	(Pei et al, 2020)[55]	Fair
Pterocarpus santalinus	Savinin (31.9 μM)	Heartwood	• Savinin significantly inhibited TNF-α production in LPS-stimulated RAW264.7 cells, and T cell proliferation elicited by concanavalin, without displaying cytotoxicity.	(Cho et al, 2001)[56]	Excellent
Senna garrettiana	Piceatannol (16 mg/kg)	Heartwood	• Piceatannol-rich extract suppressed the production of PGE_2, TNF-α and IL-1β.	(Surapanthanakorn et al, 2018)[95]	Excellent
Senna tora	Aurantio-obtusin (25 μM, 50 μM)	Seed	• Aurantio-obtusin, an anthraquinone compound, isolated from dried seeds of *S. tora*. At dose 25, 50 μM it significantly suppressed the IL-6 production, while TNF-α was only significantly reduced when the concentration was 25 μM	(Hou et al, 2018)[59]	Excellent

(*Continued*)

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Table 3 (Continued).

Scientific Name	Bioactive Compounds (Dosage)	Part	Results	Author/Date	Evidence Rating
Solanum trilobatum L.	Solasadine (75 mg/kg)	Root	• Solasodine inhibits the arachidonic acid-elicited rat paw oedema and inhibits adjuvant-induced rat paw oedema. • Solasodine exerts anti-inflammatory activity, at least partly through the inhibition of cyclooxygenase and 5-lipoxygenase pathways.	(Pandurangan et al, 2011)[96]	Excellent
Syzygium aromaticum	Eugenol (0.25% w/v)	Dried flower bud	• Ethanol 70% v/v extract of *S. aromaticum* has eugenol which make IL-6, TNF-α, TGF-β1, VEGF, NO, and MDA levels significantly decreased compared with the vehicle group, and the level of GSH was increased.	(Moradi et al, 2023)[97]	Excellent
Terminalia chebula	Tannin (24 mg/kg) and chebulagic acid (8 mg/kg)	Young fruit	• The serum TNF-α level was also found to be reduced in all *T. chebula* hydroalcoholic extract (TCHE)-treated groups as compared with control • Expression of TNF-R1, IL-1β and IL-6 was found to be reduced in the synovium of rats treated with TCHE (80 mg/kg) and indometacin	(Nair et al, 2010)[98]	Fair
Thunbergia laurifolia	Rosmarinic acid (RA) (2.5–10 mg/kg)	Leaf	• Ethanol extracts rosmarinic acid from *T. laurifolia* leaves at low doses (2.5–10 mg/kg) inhibiting leukocytes and decreasing exudation. These effects were associated with a decrease IL-17A and an increase IL-10.	(Boonyarikpunchai et al, 2014)[99]	Excellent
Tinospora crispa	Syringin and magnoflorine (100–400 mg/kg)	Stalk	• *T. crispa* extract 400 mg/kg significantly increase TNF-α almost 2.5-fold, IFN-γ almost threefold, IL-2 almost fourfold, and IL-4 almost fourfold	(Ahmad et al, 2015)[101]	Excellent
Zingiber montanum	Zingiber montanum cysteine protease glycoprotein (ZCPG) (0.5–2 μM)	Rhizome	• ZCPG significantly reduced the production of NO in LPS-induced THP-1 macrophages and inhibited the secretion of TNF-α and IL-1β. Furthermore, ZCPG in LPS-induced THP-1 macrophages also increase production of IL-10.	(Kizukala et al, 2020)[62]	Fair
Zingiber officinale	12-dehydrogingerdione (12-DHGD) (50 ng/mL, 100 ng/mL, 150 ng/mL, 200 ng/mL)	N/A	• 12-DHGD significantly inhibited LPS-stimulated production of NO (at 12-DHGD concentrations of 150 and 200 ng/mL), IL-6 (at 50, 100, 150, and 200 ng/mL), and PGE_2 (at 200 ng/mL)	(Han et al, 2013)[63]	Excellent
Zingiber zerumbet (L.)	Zerumbone (0.1–10 mg/kg)	Rhizome	• Essential oils extracted zerumbone from the rhizomes of *Z. zerumbet* significantly reduced serum anti-OVA IgE levels in mice, which further resulted in the reduction of OVA-induced cytokine secretions (IL-4, IL-5, IL-10, and IL-13) in the BALF collected. • Zerumbone may have an anti-allergic effect on allergic asthma by suppressing Th2-related cytokines (IL-4, IL-5, IL-10, and IL-13) secretion and consequently reducing IgE production by B cells.	(Tan et al, 2018)[102]	Excellent

Abbreviation: N/A, not available.

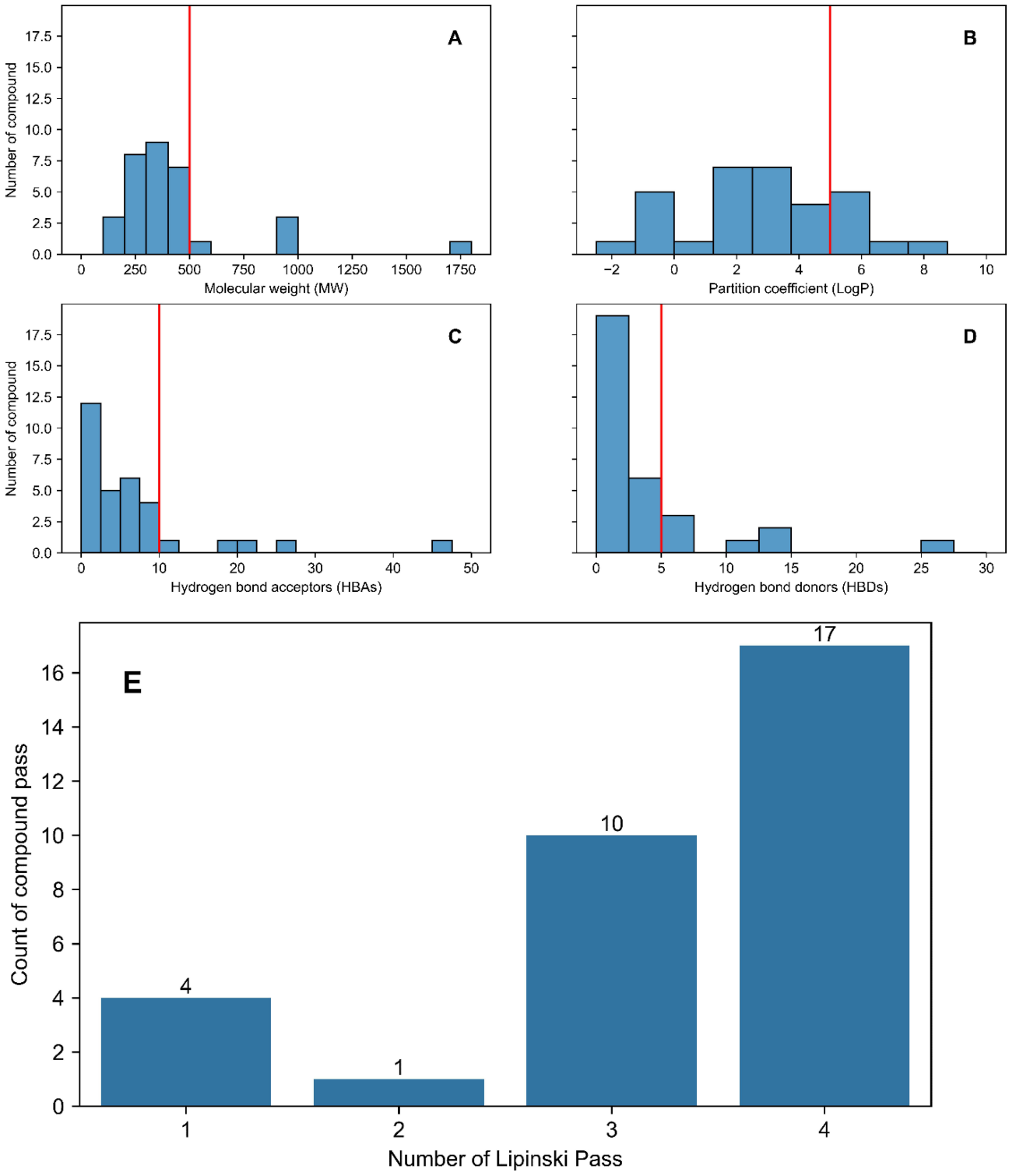

Figure 4 Distributions of drug properties relevant to drug-likeness among 32 bioactive compounds with druggability potential. (**A**) Molecular weight (MW), (**B**) partition coefficient (LogP), (**C**) number of hydrogen bond acceptors (HBAs), and (**D**) number of hydrogen bond donors (HBDs) are shown with red vertical lines indicating Lipinski's thresholds for drug-likeness (MW < 500, LogP < 5, HBAs < 10, HBDs < 5). (**E**) Distribution of compounds based on the number of Lipinski's rule-of-five criteria passed.

stability, and possible toxicity that should also be taken into account during drug development. In Table 5, we report the molecular weight, LogP, HBD, and HBA values for all 17 potential bioactive compounds. In addition, the aqueous solubility value (logS) is a log10 based value that represents the water solubility of the lead compounds.[103] A lower logS value implies low water solubility, and the possible need for solubilizers to improve solubility during formulation

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Table 4 Druggability of the Main Compounds From Thai Herbs That Complied with Lipinski's Rule of Five

Scientific Name	Bioactive Compounds	MW < 500 Dalton	LogP < 5	HBDs < 5	HBAs < 10
Andrographis paniculata	Andrographolide	√	√	√	√
	Neoandrographolide	√	√	√	√
	14-deoxy-11, 12-didehydroandrographolide	√	√	√	√
Aucklandia lappa Decne	Costunolide	√	√	√	√
	Dehydrocostus lactone	√	√	√	√
	Alantolactone	√	√	√	√
Boesenbergia rotunda	Panduratin A	√	x	√	√
Cannabis sativa	Tetrahydrocannabivarin	√	√	√	√
	Tetrahydrocannabinol	√	x	√	√
Capsicum oleoresin	Capsaicin	√	√	√	√
Cassia fistula	Rhein	√	√	√	√
Centella asiatica	Madecassoside	x	√	x	x
	Asiaticoside	x	√	x	x
Chrysopogon zizanioides	Aciculatin	√	√	√	√
Cyperus rotundus	Isocyperol	√	√	√	√
Derris scandens (Roxb.) Benth	Scandenin	√	x	√	√
Dracaena cochinchinensis	Loureirin B	√	√	√	√
Ficus racemosa L.	Lupeol	√	x	√	√
Harrisonia perforata (Blanco) Merr.	Harperfolide	x	√	√	x
Kaempferia galanga	Ethyl-p-methoxycinnamate	√	√	√	√
Mesua ferrea	Mesuol	√	x	√	√
Morus alba	Chlorogenic acid	√	√	x	√
Nardostachys jatamansi	Desoxo-narchinol-A	√	√	√	√
Orthosiphon aristatus	Ursolic acid	√	x	√	√
Senna garrettiana	Piceatannol	√	√	√	√
Solanum trilobatum L.	Solasadine	√	x	√	√
Syzygium aromaticum	Eugenol	√	√	√	√
Terminalia chebula	Tannin	x	√	x	x
	Chebulagic acid	x	√	x	x
Thunbergia laurifolia	Rosmarinic acid	√	√	x	√
Tinospora crispa	Syringin	√	√	x	√
Zingiber zerumbet (L.)	Zerumbone	√	√	√	√

development. Andrographolide derivatives from *Andrographis paniculata* showed low water solubility (logS −3.00 to −3.50), and a wide variety of toxicity classifications from 1 (high toxicity) to 6 (low toxicity).[104] These diterpene lactones were reported to have short half-lives with extensive biotransformation by liver enzymes, especially Phase II conjugations.[105] Sesquiterpene lactones from *Aucklandia lappa* also showed low water solubility (logS −3.00 to −3.50), in a similar manner to the andrographolide derivatives. Their toxicity classifications were in the range 4–5, considered as moderate toxicity. These Sesquiterpene lactones were also reported to have extensive hepatic metabolism and instability in gastrointestinal fluids.[106] Tetrahydrocannabivarin from *Cannabis sativa* had the lowest logS value of −4.82 among 17 potential bioactive compounds, reflecting the very low water solubility of most cannabinoids. This cannabinoid was in toxicity class 4, and can be converted to several metabolites, especially by carboxylation.[107] Capsaicin from *Capsicum oleoresin* also had low solubility in water, with a logS of −3.73. This alkaloid was in toxicity class 2, (moderate to high toxicity) with rapid metabolism via CYP hydroxylation in the liver.[108] Rhein, an anthraquinone from *Cassia fistula* has low water solubility with a logS of −2.95, and low toxicity, in class 5. Rhein undergoes extensive metabolism via phase II conjugation, and is considered to be metabolically unstable, with low oral bioavailability.[109] Aciculatin, a flavone-C-glycoside from *Chrysopogon zizanioides* has a low logS at −4.15, and moderate toxicity, in class

Table 5 Physicochemical Properties of 17 Potential Bioactive Compounds and Its Toxicity Classification

Scientific Name	Bioactive Compounds	MW (Dalton)	LogP	HBDs	HBAs	logS	Toxicity Class
Andrographis paniculata	Andrographolide	350.21	1.96	3	5	−3.05	4
	Neoandrographolide	480.27	1.85	4	8	−3.52	1
	14-Deoxy-11, 12-didehydroandrographolide	332.20	2.77	2	4	−3.45	6
Aucklandia lappa Decne	Costunolide	232.15	3.55	0	2	−3.52	5
	Dehydrocostus lactone	230.13	3.02	0	2	−3.17	4
	Alantolactone	232.15	3.24	0	2	−3.32	5
Cannabis sativa	Tetrahydrocannabivarin	286.19	4.96	1	2	−4.82	4
Capsicum oleoresin	Capsaicin	305.20	3.79	2	3	−3.73	2
Cassia fistula	Rhein	284.03	1.57	3	5	−2.95	5
Chrysopogon zizanioides	Aciculatin	414.13	2.45	4	8	−4.15	4
Cyperus rotundus	Isocyperol	220.18	3.70	1	1	−3.47	5
Dracaena cochinchinensis	Loureirin B	316.13	3.23	1	5	−3.76	4
Kaempferia galanga	Ethyl-p-methoxycinnamate	129.02	0.45	1	2	−0.86	4
Nardostachys jatamansi	Desoxo-narchinol-A	192.12	1.85	1	2	−2.20	6
Senna garrettiana	Piceatannol	244.07	2.68	4	4	−3.40	5
Syzygium aromaticum	Eugenol	164.08	2.13	1	2	−2.37	4
Zingiber zerumbet (L.)	Zerumbone	218.17	4.21	0	1	−3.85	5

Notes: Toxicity classes are defined according to the globally harmonized system of classification of labelling of chemicals (GHS). LD50 values are given in [mg/kg]: Class I: fatal if swallowed (LD50 ≤ 5). Class II: fatal if swallowed (5 < LD50 ≤ 50). Class III: toxic if swallowed (50 < LD50 ≤ 300). Class IV: harmful if swallowed (300 < LD50 ≤ 2000). Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000). Class VI: non-toxic (LD50 > 5000).

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4. Information regarding Aciculatin biotransformation is limited, and further study is needed for this compound. Isocyperol, a sesquiterpene from *Cyperus rotundus* has a low logS of −3.47, and has low toxicity, in class 5. There is limited information on the metabolic stability and pharmacokinetics of isocyperol to date. Loureirin B, a bioactive flavonoid from *Dracaena cochinchinensis* has a low logS of −3.76 and toxicity in class 4. This flavonoid has a short half-life of approximately 2 h with a low Cmax and AUC in rat plasma as determined by LCMS analysis. Extensive metabolism of this compound via CYP hydroxylation and demethylation was reported in rat liver microsomes.[110] Ethyl-p-methoxycinnamate, a cinnamic acid ester had the highest water solubility among the 17 potential compounds with a logS of −0.86. This compound was classified as toxicity class 4. There is limited information of the biotransformation pathways of Ethyl-p-methoxycinnamate. Desoxo-narchinol-A, a diterpenoid from *Nardostachys jatamansi* has a logS of −2.20, and was in the lowest class of toxicity, class 6. This compound was reported to have an oral bioavailability of approximately 20% in rodents, with limited information on its metabolic stability. Piceatannol, a stilbenoid from *Senna garrettiana* has a logS value of −3.40, and was in toxicity class 5. This compound undergoes extensive metabolism by phase II glucuronidation, sulfation, and methylation. Interestingly, *O*-methylation of piceatannol could generate more potent active metabolites with additional pharmacological activities.[111] Eugenol is a phenolic monoterpenoid from *Syzygium aromaticum* with a logS of −2.37 and toxicity class 4. The compound has an approximate oral bioavailability of 4–5%, with extensive metabolism via phase II conjugation by glucuronidation and sulfation.[112] Zerumbone, a sesquiterpenoid from *Zingiber zerumbet* has a logS of −3.85, and is in toxicity class 5. There is limited information regarding zerumbone metabolic pathways; further research concerning its metabolism is required. All the chemical structures of the 17 potential bioactive compounds are shown in Figure 5.

Potential Phytoconstituents with Immunomodulatory Activities and Mechanistic Insights

The discovery of bioactive substances with potential immunomodulatory properties represents an important finding in advancing therapeutics targeting inflammatory and immune-mediated conditions. In our study of Thai herbs with immunomodulatory activities, 17 compounds were found to comply with all criteria of Lipinski's rule of five, indicating their potential for further investigation as bioactive agents. Among these compounds, andrographolide, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide were extracted from *A. paniculata* in the Acanthaceae family. The majority of the active compounds in this plant were found in the leaves.[113–115] The bioactive compounds from *A. paniculata* aqueous extract reverse neuroinflammation and cognitive decline caused by lipopolysaccharide (LPS) in a dose-dependent manner.[71] These findings suggest that these compounds are able to inhibit LPS-induced increases in the levels of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and reactive oxygen species (ROS). It also inhibits the MAPK pathway, reducing inflammation-induced gene expression. Furthermore, extract from *A. paniculata* was shown to enhance endogenous antioxidant systems by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, leading to the upregulation of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and the antioxidant glutathione; it also reduced thiobarbituric acid reactive substances (TBARS), indicating a protective effect against oxidative damage in neurodegenerative conditions.[71] This plant is generally recommended for the treatment of upper respiratory tract infections in ASEAN countries. In addition, an *A. paniculata* extract formulation with a high content of Andrographolide is approved for the treatment of mild COVID in Thailand.

Costunolide, dehydrocostus lactone, and alantolactone are sesquiterpene lactones derived from a 70% methanolic extract of *Aucklandia lappa Decne* root, which is a member of the Asteraceae family. These lactones show considerable anti-allergic effects, primarily through their ability to modulate inflammatory responses by reducing the mRNA levels of chemokines, such as TARC/CCL17 and IL-8 in TNF-α and IFN-γ-stimulated cells.[34] These findings indicate that costunolide, dehydrocostus lactone, and alantolactone may serve as promising candidates for treating inflammatory skin conditions. The extract has also been reported to modulate the MAPK signaling pathway, including key components such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, which are critically involved in the regulation of cytokine production and the expression of pro-inflammatory genes in macrophages and other immune cells.[116] Additionally, *A. lappa Decne* extract has been shown to downregulate the expression of iNOS and

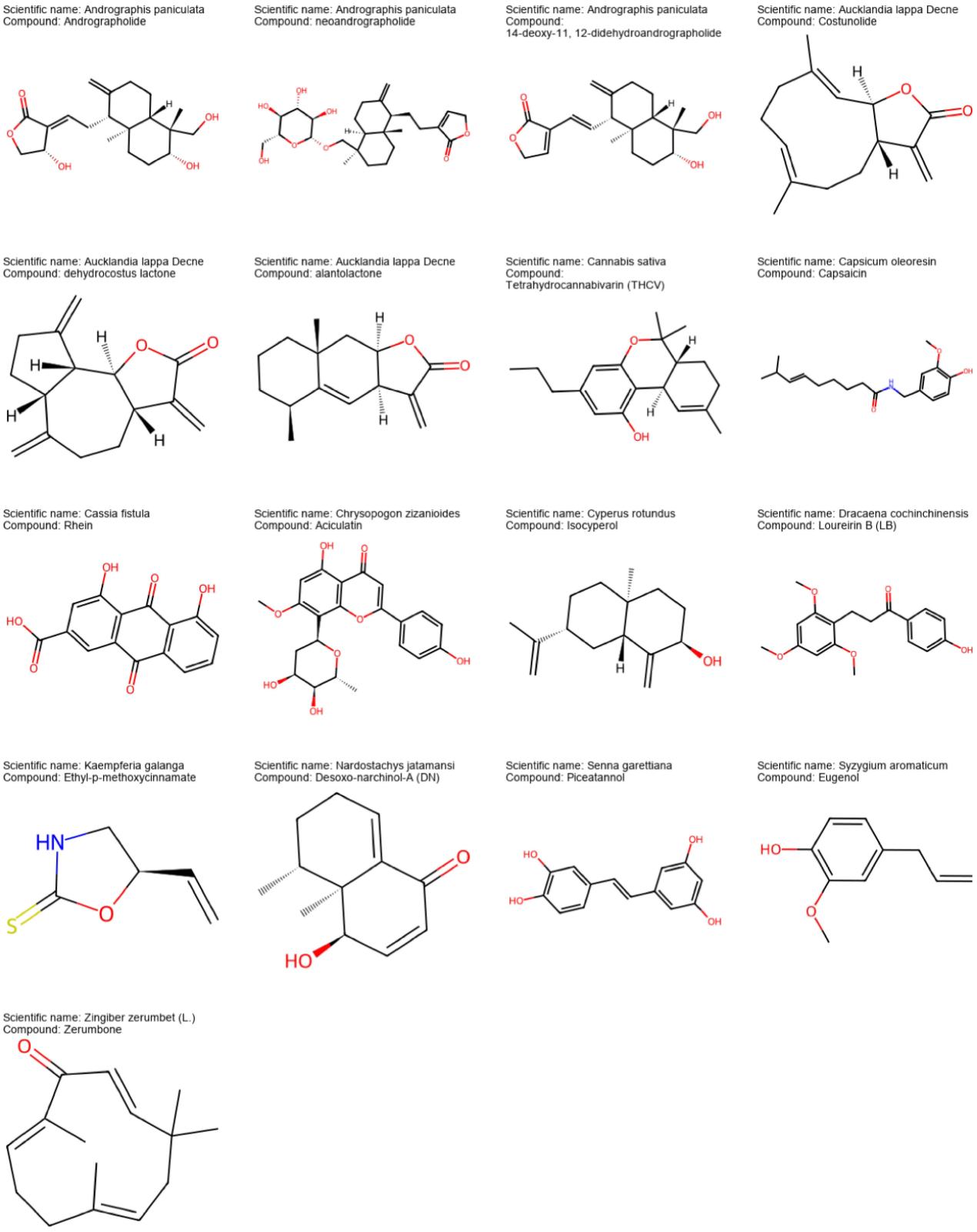

Figure 5 Chemical structures of 17 potential bioactive compounds with immunomodulatory activities.

COX-2 in activated macrophages, resulting in decreased levels of NO and PGE_2.[117] These plant roots are commercially used as major ingredients for heart tonics in Thailand. THCV is a propyl analogue of Δ^9-tetrahydrocannabinol that is found in *C. sativa*.[118] The minor phytocannabinoids are typically extracted from the flowers and leaves of *C. sativa*.[119]

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THCV exhibits distinct dose-dependent pharmacological profiles and demonstrates notable immunomodulatory potential through its interaction with components of the endocannabinoid system. It acts as a partial agonist or antagonist at cannabinoid receptors, depending on the concentration and receptor type. THCV displays CB1 receptor antagonism at low doses and partial agonism at higher doses while also exhibiting agonistic activity at the CB2 receptor, which is prominently expressed in immune cells. Through CB2 activation, it can attenuate pro-inflammatory cytokine release, modulate leukocyte migration, and suppress microglial activation.[120] Prior investigations have examined the potential immunomodulatory and anti-inflammatory effects of THCV, particularly in the context of nitrite production in murine peritoneal macrophages. THCV suppresses the overexpression of certain proteins, such as iNOS, COX-2, and IL-1β, in macrophages that are typically stimulated by LPS. This finding suggests an anti-inflammatory role for THCV.[35]

Capsaicin is a bioactive compound extracted from the oleoresin of Capsicum plants, which are members of the *Capsicum* genus. Capsaicin primarily mediates its biological activity through interaction with the transient receptor potential vanilloid 1 (TRPV1) receptor, a non-selective cation channel expressed in sensory neurons, keratinocytes, and immune cells (including macrophages and T lymphocytes), as well as in epithelial tissues,[121] Upon activation by capsaicin, TRPV1 facilitates calcium influx, thereby initiating intracellular signaling pathways that regulate immune cell function. Furthermore, prolonged or high-dose exposure to capsaicin induces desensitization of sensory neurons, which underlies its sustained anti-inflammatory and analgesic effects.[122] Extracts from *Capsicum oleoresin* have been found to decrease the viral load in serum and reduce inflammatory markers, such as TNF-α and IL-1β, indicating a mitigation of porcine reproductive and respiratory syndrome virus-induced inflammation.[74] Similarly, rhein is a bioactive substance extracted from the flowers of *Cassia fistula* L. that has been studied for its anti-inflammatory properties and shown to have a considerable anti-inflammatory effect in animal models.[75] Rhein inhibits croton oil-induced ear edema in mice and carrageenan-induced paw edema in rats in a dose-dependent manner. Additionally, continuously administered rhein reduces granuloma formation in rats. Rhein increases the activities of antioxidant enzymes, such as CAT, SOD, and glutathione peroxidase (GSH-px), and decreases the levels of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, as well as other inflammatory markers, such as nitrite and malondialdehyde (MDA). In the same study, rhein was found to downregulate COX-2 and iNOS expression, while upregulating the expression of heme oxygenase-1 (HO-1), Nrf2, and peroxisome proliferator-activated receptor gamma (PPAR-γ).[75] Extracts of *Capsicum oleoresin* are developed and marketed as a topical analgesic gel in Thailand.

A natural compound known as aciculatin is derived from the entire plant of *Chrysopogon aciculatus*.[123] Aciculatin shows promise in inhibiting Granulocyte-colony stimulating factor (G-CSF) production and neutrophil differentiation in IL-1β-stimulated fibroblast-like synoviocytes by suppressing key signaling pathways of IL-1β-induction, specifically the IKK/IκB/NF-κB and MAPK pathways. This suppression occurs through the inhibition of the DNA binding activity of the transcription factors NF-κB and activator protein-1.[123] Moreover, this compound inhibits G-CSF-mediated phosphorylation of the JAK/STAT and Akt pathways, which play essential roles in neutrophil differentiation from precursor cells.[37] In one study, sesquiterpene isocyperol was extracted from *Cyperus rotundus* rhizomes using 80% ethanol and was found to have anti-inflammatory properties in the form of inhibiting inflammatory responses by targeting toll-like receptor 4 (TLR4) signaling in RAW 264.7 cells when stimulated with LPS.[79] That study found that treatment with isocyperol reduces the production of NO and PGE_2 by inhibiting iNOS and COX-2 mRNA and protein expression levels in macrophages. Additionally, isocyperol promotes the production of HO-1 and reduces the accumulation of ROS, which are important for combating oxidative stress in cells. In an in vivo model, this compound not only enhanced mouse survival rates but also reduced the serum levels of NO, PGE_2, and IL-6, suggesting that it has anti-inflammatory properties.[79] In our study, we identified loureirin B as a compound that satisfied all of the requirements of Lipinski's rule of five. Loureirin B suppresses the activation of the IL-6/STAT3/NF-κB signaling pathway. This pathway plays a major role in the inflammatory and immune responses in Crohn's disease, suggesting that modulation of this pathway is a key mechanism for the therapeutic effects of loureirin B.[80]

Ethyl-p-methoxycinnamate is the main compound extracted from *Kaempferia galanga* using petroleum ether. This substance shows considerable anti-inflammatory and anti-angiogenic effects, which have been observed in vitro and in vivo. The mechanism of action of ethyl-p-methoxycinnamate involves the suppression of IκBα phosphorylation and degradation, effectively blocking the nuclear translocation of the NF-κB complex. This inhibition leads to a reduction of

pro-inflammatory cytokines, specifically IL-1 and TNF-α, as well as the prevention of angiogenesis by interfering with endothelial cell function.[83] Desoxo-narchinol A, which comes from *Nardostachys jatamansi*, can inhibit the production of inflammatory mediators such as iNOS, NO, COX-2, and PGE_2. Desoxo-narchinol A has also been found to reduce levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in vitro and in vivo in a dose-dependent manner by targeting the NF-κB signaling pathway.[87]

In our study, piceatannol satisfied Lipinski's rule of five. Piceatannol is found in the heartwood of *Senna garrettiana*. The anti-inflammatory effects of piceatannol are attributed to its ability to inhibit leukocyte infiltration and modulate the production of pro-inflammatory mediators such as PGE_2, TNF-α, and IL-1β by suppressing the NF-κB pathway.[95] Piceatannol modulates the MAPK cascade, particularly by inhibiting the phosphorylation of ERK1/2, JNK, and p38 MAPK, which are involved in the regulation of immune cell activation and cytokine production. It also interferes with the JAK/STAT signaling pathway, particularly STAT3, which is associated with chronic inflammation and autoimmune conditions.[124] Eugenol, which also met the criteria of Lipinski's rule of five, is the major compound derived from 70% v/v ethanol from the dried flower buds of *Syzygium aromaticum* L (Myrtaceae family). This compound effectively regulates inflammatory cytokines by lowering the levels of IL-6 and TNF-α via inhibition of the NF-κB signaling pathway and also plays a role in the balance of oxidative stress by neutralizing ROS and enhancing endogenous antioxidant defense systems, including SOD and GSH-px.[97] Eugenol also reduces the levels of oxidative markers, such as NO and MDA while increasing the level of the anti-oxidative factor GSH. This balance is essential in preventing tissue damage and in the formation of adhesion. Eugenol is commercially available as flavoring agents, local antiseptic or anesthetic agents especially in dentistry purposes.

Zingiber zerumbet is a plant from the Zingiberaceae *family.* The essential oils extracted from the rhizomes of this plant are rich in bioactive compounds, especially zerumbone, which met all the criteria of Lipinski's rule of five in our study. These essential oils have been studied for their potential anti-allergic and immunomodulatory effects. Zerumbone has been shown to have the potential to modulate immune responses, particularly through cytokine production. This modulation involves the regulation of pro-inflammatory cytokines, such as TNF-α and IL-1β, and anti-inflammatory cytokines, such as IL-10, which play essential roles in the control of allergic and inflammatory reactions.[102,125,126] Zerumbone also interferes with the MAPK signaling pathways, specifically ERK, JNK, and p38 MAPK, which are involved in immune cell activation and cytokine expression. By suppressing the phosphorylation of these kinases, zerumbone reduces the production of inflammatory mediators in activated macrophages and monocytes.[127]

Conclusion

Some bioactive compounds of Thai herbs have the potential to be developed as immunomodulatory agents in compliance with Lipinski's rule of five, a guideline for identifying bioactive compounds in drug discovery. However, additional factors in drug development such as water solubility, metabolic stability, and toxicity could be big challenges of these bioactive compounds. Most potential bioactive compounds from Thai herbs showed limited water solubility and metabolic instability. Therefore, appropriate strategies to overcome these weaknesses would need to be developed by the additional of solubilizers, bioenhancers, and drug delivery systems. In addition, further molecular work to provide mechanistic insights is needed to ensure a full understanding of their mechanisms of action and potential therapeutic applications.

Abbreviations

12-DHGD, 12-dehydrogingerdione; CAT, Catalase; COVID-19, Coronavirus Disease 2019; COX-2, Cyclooxygenase-2; ERK, Extracellular signal-regulated kinase; GSH-px, Glutathione peroxidase; HBAs, Hydrogen bond acceptors; HBDs, Hydrogen bond donors; HO-1, Heme oxygenase-1; IFN-α, Interferon-alpha; IFN-γ, Interferon-gamma; IkB, Inhibitor of NF-κB; IKK, IκB kinase; IL-1, Interleukin-1; IL-1β, Interleukin-1 beta; IL-2, Interleukin-2; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-7, Interleukin-7; IL-8, Interleukin-8; IL-10, Interleukin-10; IL-12, Interleukin-12; IL-13, Interleukin-13; iNOS, Inducible nitric oxide synthase; JAK/STAT, Janus kinase-signal transducer and activator of transcription; JNK, c-Jun N-terminal kinase; LogP, Partition coefficient; LogS, Aqueous solubility value; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; MDA, Malondialdehyde; MW, Molecular weight; NF-

kB, Nuclear factor-κB; Nrf2, Nuclear factor erythroid 2-related factor 2; NO, Nitric oxide; PGE_2, Prostaglandin E2; PPAR-γ, Peroxisome proliferator-activated receptor gamma; ROS, Reactive oxygen species; SMILES, Simplified Molecular Input Line Entry System; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; TGF-β, Transforming growth factor-beta; THC, Δ^9-tetrahydrocannabinol; THCV, Tetrahydrocannabivarin; TLR4, Targeting toll-like receptor 4; TNF-α, Tumor necrosis factor-alpha; TRPV1, Transient receptor potential vanilloid 1.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

References

1. Spelman K, Burns J, Nichols D, et al. Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. *Altern Med Rev*. 2006;11(2):128–150.
2. Borish LC, Steinke JW. 2. cytokines and chemokines. *J Allergy Clin Immunol*. 2003;111(2 Suppl):S460–475. doi:10.1067/mai.2003.108
3. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. *Int J Mol Sci*. 2019;20(23):6008. doi:10.3390/ijms20236008
4. Banerjee M, Saxena M. Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes. *Clin Chim Acta*. 2012;413(15–16):1163–1170. doi:10.1016/j.cca.2012.03.021
5. Johnson D, O'Keefe R, Grandis J. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol*. 2018;15(4):234–248. doi:10.1038/nrclinonc.2018.8
6. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. *Annu Rev Immunol*. 2009;27:485–517. doi:10.1146/annurev.immunol.021908.132710
7. Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res*. 2007;48(4):751–762. doi:10.1194/jlr.R600021-JLR200
8. Wozniak DJ, Parsek MR, Singh PK, et al. The role of TNF-α in inflammation and endothelial activation. *J Histochem Cytochem*. 2007;55(4):385–392.
9. Zhu J, Paul W. Heterogeneity and plasticity of T helper cells. *Cell Res*. 2010;20(1):4–12. doi:10.1038/cr.2009.138
10. Leonard WJ, Spolski R. Interleukin-21: a modulator of lymphoid proliferation, apoptosis and differentiation. *Nat Rev Immunol*. 2005;5(9):688–698. doi:10.1038/nri1688
11. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol*. 2003;3(2):133–146. doi:10.1038/nri1001
12. Wang P, Wu P, Siegel M, Egan R, Billah M. IL-10 inhibits transcription of cytokine genes in human peripheral blood mononuclear cells. *J Immunol*. 1994;153(2):811–816. doi:10.4049/jimmunol.153.2.811
13. Wang P, Wu P, Siegel M, Egan R, Billah M. Interleukin (IL)-10 inhibits nuclear factor kappa B (NF-κB) activation in human monocytes: IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. *J Biol Chem*. 1995;270(16):9558–9563. doi:10.1074/jbc.270.16.9558
14. Bogdan C, Paik J, Vodovotz Y, Nathan C. Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10. *J Biol Chem*. 1992;267(32):23301–23308. doi:10.1016/S0021-9258(18)50091-0
15. Ozaslan M, Oguzkan SB. Use of plant extracts in alternative medicine. *Pak J Biol Sci*. 2018;21(1):1–7. doi:10.3923/pjbs.2018.1.7
16. Sharma P, Kumar P, Sharma R, et al. Immunomodulators: role of medicinal plants in immune system. *Natl J Physiol Pharm Pharmacol*. 2017;7(6):552–556. doi:10.5455/njppp.2017.7.0203808032017
17. Tiwari R, Latheef SK, Ahmed I, et al. Herbal immunomodulators - a remedial panacea for designing and developing effective drugs and medicines: current scenario and future prospects. *Curr Drug Metab*. 2018;19(3):264–301. doi:10.2174/1389200219666180129125436
18. Zhang J, Onakpoya IJ, Posadzki P, et al. The safety of herbal medicine: from prejudice to evidence. *Evid Based Complement Alternat Med*. 2015;2015:316706. doi:10.1155/2015/316706
19. Pinn G. Herbal medicine in infectious disease. *Aust Fam Physician*. 2001;30(7):681–684.
20. Ying J, Zhang M, Qiu X, et al. The potential of herb medicines in the treatment of esophageal cancer. *Biomed Pharmacother*. 2018;103:381–390. doi:10.1016/j.biopha.2018.04.088
21. World Health Organization. *WHO Traditional Medicine Strategy 2014-2023*. Geneva: WHO Press; 2014.

22. Pongpirul K, Jirathananuwat A, Phutrakool P. Thai herbal medicine research situation: systematic scoping review and policy recommendations. *J Traditl Thai Alter Med*. 2019;17(2):292–304.
23. Kanjanahattakij N, Kwankhao P, Vathesatogkit P, et al. Herbal or traditional medicine consumption in a Thai worker population: pattern of use and therapeutic control in chronic diseases. *BMC Complement Altern Med*. 2019;19:258. doi:10.1186/s12906-019-2652-z
24. Wu JA, Attele AS, Zhang L, et al. Anti-HIV activity of medicinal herbs: usage and potential development. *Am J Chin Med*. 2001;29(1):69–81. doi:10.1142/S0192415X01000083
25. Guo Y, Chen B, Pei X, et al. Radix stephaniae tetrandrine: an emerging role for management of breast cancer. *Curr Pharm Des*. 2020;26(1):25–36. doi:10.2174/1381612826666200110143706
26. Zhao M, Yang Y, Nian Q, et al. Phytochemicals and mitochondria: therapeutic allies against gastric cancer. *Phytomedicine*. 2023;110:154608. doi:10.1016/j.phymed.2022.154608
27. PubChem Database. Available from: https://pubchem.ncbi.nlm.nih.gov/. Accessed May 10, 2023.
28. Lipinski CA, Lombardo F, Dominy BW, et al. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 2001;46(1–3):3–26. doi:10.1016/S0169-409X(00)00129-0
29. Li Z, Xue Y, Li M, et al. The antioxidation of different fractions of dill (*Anethum graveolens*) and their influences on cytokines in macrophages RAW264.7. *J Oleo Sci*. 2018;67(12):1535–1541. doi:10.5650/jos.ess18134
30. Li D, Wu L. Coumarins from the roots of *Angelica dahurica* cause anti-allergic inflammation. *Exp Ther Med*. 2017;14(1):874–880. doi:10.3892/etm.2017.4569
31. Kim YJ, Lee JY, Kim HJ, et al. Anti-inflammatory effects of *Angelica sinensis* (Oliv.) Diels water extract on RAW 264.7 induced with lipopolysaccharide. *Nutrients*. 2018;10(5):647. doi:10.3390/nu10050647
32. Kim WS, Choi WJ, Lee S, et al. Anti-inflammatory, antioxidant and antimicrobial effects of artemisinin extracts from *Artemisia annua* L. *Korean J Physiol Pharmacol*. 2015;19(1):21–27. doi:10.4196/kjpp.2015.19.1.21
33. Qin J, Wang HY, Zhuang D, et al. Structural characterization and immunoregulatory activity of two polysaccharides from the rhizomes of *Atractylodes lancea* (Thunb.) DC. *Int J Biol Macromol*. 2019;136:341–351. doi:10.1016/j.ijbiomac.2019.06.088
34. Seo CS, Lim HS, Jeong SJ, et al. Anti-allergic effects of sesquiterpene lactones from the root of *Aucklandia lappa* decne. *Mol Med Rep*. 2015;12(5):7789–7795. doi:10.3892/mmr.2015.4342
35. Romano B, Pagano E, Orlando P, et al. Pure Δ^9-tetrahydrocannabivarin and a *Cannabis sativa* extract with high content in Δ^9-tetrahydrocannabivarin inhibit nitrite production in murine peritoneal macrophages. *Pharmacol Res*. 2016;113(Pt A):199–208. doi:10.1016/j.phrs.2016.07.045
36. Takano F, Yamaguchi M, Takada S, et al. Capsicum ethanol extracts and capsaicin enhance interleukin-2 and interferon-gamma production in cultured murine peyer's patch cells ex vivo. *Life Sci*. 2007;80(17):1553–1563. doi:10.1016/j.lfs.2007.01.031
37. Shih KS, Wang JH, Wu YW, et al. Aciculatin inhibits granulocyte colony-stimulating factor production by human interleukin 1β-stimulated fibroblast-like synoviocytes. *PLoS One*. 2012;7(7):e42389. doi:10.1371/journal.pone.0042389
38. Bhujade AM, Talmale S, Kumar N, et al. Evaluation of *Cissus quadrangularis* extracts as an inhibitor of COX, 5-LOX, and proinflammatory mediators. *J Ethnopharmacol*. 2012;141(3):989–996. doi:10.1016/j.jep.2012.03.044
39. Buakaew W, Pankla Sranujit R, Noysang C, et al. Phytochemical constituents of *Citrus hystrix* DC. leaves attenuate inflammation via NF-κB signaling and NLRP3 inflammasome activity in macrophages. *Biomolecules*. 2021;11(1):105. doi:10.3390/biom11010105
40. Tabarsa M, You S, Yelithao K, et al. Isolation, structural elucidation and immuno-stimulatory properties of polysaccharides from *Cuminum cyminum*. *Carbohydr Polym*. 2020;230:115636. doi:10.1016/j.carbpol.2019.115636
41. Chandrasekaran CV, Sundarajan K, Edwin JR, et al. Immune-stimulatory and anti-inflammatory activities of *Curcuma longa* extract and its polysaccharide fraction. *Pharmacogn Res*. 2013;5(2):71-79. doi:10.4103/0974-8490.110527
42. Laupattarakasem P, Houghton PJ, Hoult JR. Anti-inflammatory isoflavonoids from the stems of *Derris scandens*. *Planta Med*. 2004;70(6):496–501. doi:10.1055/s-2004-827147
43. He P, Dong Z, Wang Q, et al. Structural characterization and immunomodulatory activity of a polysaccharide from *Eurycoma longifolia*. *J Nat Prod*. 2019;82(2):169–176. doi:10.1021/acs.jnatprod.8b00238
44. Park HJ, Chi GY, Choi YH, et al. Lupeol suppresses plasminogen activator inhibitor-1-mediated macrophage recruitment and attenuates M2 macrophage polarization. *Biochem Biophys Res Commun*. 2020;527(4):889–895. doi:10.1016/j.bbrc.2020.04.160
45. Darzi SE, Khazraei SP, Amirghofran Z. The immunoinhibitory and apoptosis-inducing activities of *Foeniculum vulgare* on human peripheral blood lymphocytes. *Res Pharm Sci*. 2018;13(2):103–110. doi:10.4103/1735-5362.223792
46. Choodej S, Sommit D, Pudhom K. Rearranged limonoids and chromones from *Harrisonia perforata* and their anti-inflammatory activity. *Bioorg Med Chem Lett*. 2013;23(13):3896–3900. doi:10.1016/j.bmcl.2013.04.064
47. Shen CY, Zhang TT, Zhang WL, et al. Anti-inflammatory activities of essential oil isolated from the calyx of *Hibiscus sabdariffa* L. *Food Funct*. 2016;7:4451–4459. doi:10.1039/C6FO00795C
48. Tewtrakul S, Subhadhirasakul S. Effects of compounds from *Kaempferia parviflora* on nitric oxide, prostaglandin E2 and tumor necrosis factor-alpha productions in RAW264.7 macrophage cells. *J Ethnopharmacol*. 2008;120(1):81–84. doi:10.1016/j.jep.2008.07.033
49. Manabe M, Takenaka R, Nakasa T, et al. Induction of anti-inflammatory responses by dietary *Momordica charantia* L. (Bitter Gourd). *Biosci Biotechnol Biochem*. 2003;67(12):2512–2517. doi:10.1271/bbb.67.2512
50. Coriolano MC, de Santana Brito J, de Siqueira Patriota LL, et al. Immunomodulatory effects of the water-soluble lectin from *Moringa oleifera* seeds (WSMoL) on human peripheral blood mononuclear cells (PBMC). *Protein Pept Lett*. 2018;25(3):295–301. doi:10.2174/0929866525666180130141736
51. Checker R, Chatterjee S, Sharma D, et al. Immunomodulatory and radioprotective effects of lignans derived from fresh nutmeg mace (*Myristica fragrans*) in mammalian splenocytes. *Int Immunopharmacol*. 2008;8(5):661–669. doi:10.1016/j.intimp.2008.01.012
52. An N, Wang D, Zhu T, et al. Effects of scrocaffeside A from *Picrorhiza scrophulariiflora* on immunocyte function *in vitro*. *Immunopharmacol Immunotoxicol*. 2009;31(3):451–458. doi:10.1080/08923970902783092
53. Hsu CL, Hong BH, Yu YS, et al. Antioxidant and anti-inflammatory effects of *Orthosiphon aristatus* and its bioactive compounds. *J Agric Food Chem*. 2010;58(4):2150–2156. doi:10.1021/jf903557c
54. Lee JB, Yamagishi C, Hayashi K, et al. Antiviral and immunostimulating effects of lignin-carbohydrate-protein complexes from *Pimpinella anisum*. *Biosci Biotechnol Biochem*. 2011;75(3):459–465. doi:10.1271/bbb.100645

55. Pei H, Xue L, Tang M, et al. Alkaloids from black pepper (*Piper nigrum* L.) exhibit anti-inflammatory activity in murine macrophages by inhibiting activation of NF-κB pathway. *J Agric Food Chem*. 2020;68(8):2406–2417. doi:10.1021/acs.jafc.9b07754
56. Cho JY, Park J, Kim PS, et al. Savinin, a Lignan from *Pterocarpus santalinus* inhibits tumor necrosis factor-.ALPHA. production and T Cell proliferation. *Biol Pharm Bull*. 2001;24(2):167–171. doi:10.1248/bpb.24.167
57. Suganya K, Liu QF, Koo BS. *Santalum album* extract exhibits neuroprotective effect against the TLR3-mediated neuroinflammatory response in human SH-SY5Y neuroblastoma cells. *Phytother Res*. 2021;35(4):1991–2004. doi:10.1002/ptr.6942
58. Chomnawang MT, Surassmo S, Nukoolkarn VS, et al. Effect of *Garcinia mangostana* on inflammation caused by Propionibacterium acnes. *Fitoterapia*. 2007;78(6):401–408. doi:10.1016/j.fitote.2007.02.019
59. Hou J, Gu Y, Zhao S, et al. Anti-inflammatory effects of aurantio-obtusin from seed of *Cassia obtusifolia* L. through modulation of the NF-κB pathway. *Molecules*. 2018;23(12):3093. doi:10.3390/molecules23123093
60. Jayesh K, Helen LR, Vysakh A, et al. Ethyl acetate fraction of *Terminalia bellirica* (Gaertn.) Roxb. fruits inhibits proinflammatory mediators via down regulating nuclear factor-κB in LPS stimulated raw 264.7 cells. *Biomed Pharmacother*. 2017;95:1654–1660. doi:10.1016/j.biopha.2017.09.080
61. Shruthi RR, Venkatesh YP, Muralikrishna G. Structural and functional characterization of a novel immunomodulatory glycoprotein isolated from ajowan (*Trachyspermum ammi* L.). *Glycoconjugate J*. 2017;34(4):499–514. doi:10.1007/s10719-017-9771-x
62. Jamir K, Ganguly R, Seshagirirao K. ZCPG, a cysteine protease from Zingiber montanum rhizome exhibits enhanced anti-inflammatory and acetylcholinesterase inhibition potential. *Int J Biol Macromol*. 2020;163:2429–2438. doi:10.1016/j.ijbiomac.2020.09.097
63. Han YA, Song CW, Koh WS, et al. Anti-inflammatory effects of the *Zingiber officinale* roscoe constituent 12-dehydrogingerdione in lipopolysaccharide-stimulated raw 264.7 cells. *Phytother Res*. 2013;27(8):1200–1205. doi:10.1002/ptr.4847
64. Wisuitiprot V, Ingkaninan K, Chakkavittumrong P, et al. Effects of *Acanthus ebracteatus* Vahl. extract and verbascoside on human dermal papilla and murine macrophage. *Sci Rep*. 2022;12:1491. doi:10.1038/s41598-022-04966-w
65. Sun X, Huang X, Zhu X, et al. HBOA ameliorates CCl4-incuded liver fibrosis through inhibiting TGF-β1/smads, NF-κB and ERK signaling pathways. *Biomed Pharmacother*. 2019;115:108901. doi:10.1016/j.biopha.2019.108901
66. Belska NV, Guriev AM, Danilets MG, et al. Water-soluble polysaccharide obtained from *Acorus calamus* L. classically activates macrophages and stimulates Th1 response. *Int Immunopharmacol*. 2010;10(8):933–942. doi:10.1016/j.intimp.2010.05.005
67. Rajaram A, Vanaja GR, Vyakaranam P, et al. Anti-inflammatory profile of *Aegle marmelos* (L) correa (Bilva) with special reference to young roots grown in different parts of India. *J Ayurveda Integr Med*. 2018;9(2):90–98. doi:10.1016/j.jaim.2017.03.006
68. Sangeetha M, Chamundeeswari D, Saravana Babu C, et al. Attenuation of oxidative stress in arthritic rats by ethanolic extract of *Albizia procera* Benth bark through modulation of the expression of inflammatory cytokines. *J Ethnopharmacol*. 2020;250:112435. doi:10.1016/j.jep.2019.112435
69. Farhadi L, Mohammadi-Motlagh HR, Seyfi P, et al. Low concentrations of flavonoid - rich fraction of shallot extract induce delayed - type hypersensitivity and TH1 cytokine IFNγ expression in BALB/c mice. *Int J Mol Cell Med*. 2014;3(1):16–25.
70. Ota N, Takano F, Muroga S, et al. Garlic extract and its selected organosulphur constituents promote ileal immune responses ex vivo. *J Funct Foods*. 2012;4(1):243–252. doi:10.1016/j.jff.2011.11.003
71. Sani D, Khatab NIO, Kirby BP, et al. A standardised *Andrographis paniculata* Burm. nees aqueous extract prevents lipopolysaccharide-induced cognitive deficits through suppression of inflammatory cytokines and oxidative stress mediators. *J Adv Res*. 2018;16:87–97. doi:10.1016/j.jare.2018.11.005
72. Wang D, Zhou L, Li W, et al. Anticoccidial effects of areca nut (*Areca catechu* L.) extract on broiler chicks experimentally infected with *Eimeria tenella*. *Exp Parasitol*. 2018;184:16–21. doi:10.1016/j.exppara.2017.11.002
73. Kongratanapasert T, Kongsomros S, Arya N, et al. Pharmacological activities of fingerroot extract and its phytoconstituents against SARS-CoV-2 infection in golden Syrian hamsters. *J Exp Pharmacol*. 2023;15:13–26. doi:10.2147/JEP.S382895
74. Liu Y, Che TM, Song M, et al. Dietary plant extracts improve immune responses and growth efficiency of pigs experimentally infected with porcine reproductive and respiratory syndrome virus. *J Anim Sci*. 2013;91(12):5668–5679. doi:10.2527/jas.2013-6495
75. Antonisamy P, Agastian P, Kang CW, et al. Anti-inflammatory activity of rhein isolated from the flowers of *Cassia fistula* L. and possible underlying mechanisms. *Saudi J Biol Sci*. 2019;26(1):96–104. doi:10.1016/j.sjbs.2017.04.011
76. Tawinwung S, Junsaeng D, Utthiya S, et al. Immunomodulatory effect of standardized *C. asiatica* extract on a promotion of regulatory T cells in rats. *BMC Complement Med Ther*. 2021;21(1):220. doi:10.1186/s12906-021-03394-z
77. Huang D, Guo W, Gao J, et al. *Clinacanthus nutans* (Burm. f.) Lindau ethanol extract inhibits hepatoma in mice through upregulation of the immune response. *Molecules*. 2015;20(9):17405–17428. doi:10.3390/molecules200917405
78. Chuncharunee A, Khosuk P, Naovarat R, et al. ASPP 092, a phenolic diarylheptanoid from Curcuma comosa suppresses experimentally-induced inflammatory ear edema in mice. *Saudi J Biol Sci*. 2021;28(10):5937–5946. doi:10.1016/j.sjbs.2021.06.056
79. Seo YJ, Jeong M, Lee KT, et al. Isocyperol, isolated from the rhizomes of *Cyperus rotundus*, inhibits LPS-induced inflammatory responses via suppression of the NF-κB and STAT3 pathways and ROS stress in LPS-stimulated RAW 264.7 cells. *Int Immunopharmacol*. 2016;38:61–69. doi:10.1016/j.intimp.2016.05.017
80. Sun X, Wen K, Xu Z, et al. Effect of Loureirin B on Crohn's disease rat model induced by TNBS via IL-6/STAT3/NF-κB signaling pathway. *Chin Med*. 2020;15:2. doi:10.1186/s13020-019-0282-5
81. Liu J, Zhang L, Ren Y, et al. Anticancer and immunoregulatory activity of *Gynostemma pentaphyllum* polysaccharides in H22 tumor-bearing mice. *Int J Biol Macromol*. 2014;69:1–4. doi:10.1016/j.ijbiomac.2014.05.014
82. Machado FDF, Formiga RO, Lima GRM, et al. *Hyptis suaveolens* (L.) poit protects colon from TNBS-induced inflammation via immunomodulatory, antioxidant and anti-proliferative mechanisms. *J Ethnopharmacol*. 2021;265:113153. doi:10.1016/j.jep.2020.113153
83. Umar MI, Asmawi MZ, Sadikun A, et al. Ethyl-p-methoxycinnamate isolated from *Kaempferia galanga* inhibits inflammation by suppressing interleukin-1, tumor necrosis factor-α, and angiogenesis by blocking endothelial functions. *Clinics*. 2014;69(2):134–144. doi:10.6061/clinics/2014(02)10
84. Raish M, Ahmad A, Alkharfy KM, et al. Hepatoprotective activity of *Lepidium sativum* seeds against D-galactosamine/lipopolysaccharide induced hepatotoxicity in animal model. *BMC Complement Altern Med*. 2016;16(1):501. doi:10.1186/s12906-016-1483-4
85. Chahar MK, Sanjaya Kumar DS, Lokesh T, et al. In-vivo antioxidant and immunomodulatory activity of mesuol isolated from *Mesua ferrea* L. seed oil. *Int Immunopharmacol*. 2012;13(4):386–391. doi:10.1016/j.intimp.2012.05.006
86. Chang B, Koo B, Lee H, et al. Activation of macrophage mediated host defense against *Salmonella typhimurium* by *Morus alba* L. *Food Nutr Res*. 2018;62. doi:10.29219/fnr.v62.1289

87. Shin JY, Bae GS, Choi SB, et al. Anti-inflammatory effect of desoxo-narchinol-A isolated from *Nardostachys jatamansi* against lipopolysaccharide. *Int Immunopharmacol*. 2015;29(2):730–738. doi:10.1016/j.intimp.2015.09.002
88. Liao CH, Lin JY. Purification, partial characterization and anti-inflammatory characteristics of lotus (*Nelumbo nucifera* Gaertn) plumule polysaccharides. *Food Chem*. 2012;135(3):1818–1827. doi:10.1016/j.foodchem.2012.06.063
89. Michel CG, El-Sayed NS, Moustafa SF, et al. Phytochemical and biological investigation of the extracts of *Nigella sativa* L. seed waste. *Drug Test Anal*. 2011;3(4):245–254. doi:10.1002/dta.225
90. Mondal S, Varma S, Bamola VD, et al. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (*Ocimum sanctum* Linn.) leaf extract on healthy volunteers. *J Ethnopharmacol*. 2011;136(3):452–456. doi:10.1016/j.jep.2011.05.012
91. Wang CC, Yuan JR, Wang CF, et al. Anti-inflammatory effects of *Phyllanthus emblica* L on benzopyrene-induced precancerous lung lesion by regulating the IL-1β/miR-101/Lin28B signaling pathway. *Integr Cancer Ther*. 2017;16(4):505–515. doi:10.1177/1534735416659358
92. Singh M, Shakya S, Soni VK, et al. The n-hexane and chloroform fractions of *Piper betle* L. trigger different arms of immune responses in BALB/c mice and exhibit antifilarial activity against human lymphatic filarid Brugia malayi. *Int Immunopharmacol*. 2009;9(6):716–728. doi:10.1016/j.intimp.2009.02.012
93. Wang DF, Zhou LL, Zhou HL, et al. Effects of *Piper sarmentosum* extract on the growth performance, antioxidant capability and immune response in weaned piglets. *J Anim Physiol Anim Nutr*. 2017;101(1):105–112. doi:10.1111/jpn.12517
94. Rahimi R, Shams-Ardekani MR, Abdollahi M. A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. *World J Gastroenterol*. 2010;16(36):4504–4514. doi:10.3748/wjg.v16.i36.4504
95. Surapanthanakorn S. Assessment of the anti-inflammatory activity of piceatannol-rich extract from *Senna Garrettiana* heartwood. Chiang Mai University digital collections. Science Faculty of Chiang Mai University; 2021. Available from: https://cmudc.library.cmu.ac.th/frontend/Info/item/dc:48430. Accessed April 28, 2023.
96. Pandurangan A, Khosa RL, Hemalatha S. Anti-inflammatory activity of an alkaloid from *Solanum trilobatum* on acute and chronic inflammation models. *Nat Prod Res*. 2011;25(12):1132–1141. doi:10.1080/14786410903370783
97. Moradi E, Rakhshandeh H, Rahimi Baradaran V, et al. HPLC/MS characterization of *Syzygium aromaticum* L. and evaluation of its effects on peritoneal adhesion: investigating the role of inflammatory cytokines, oxidative factors, and fibrosis and angiogenesis biomarkers. *Physiol Rep*. 2023;11(2):e15584. doi:10.14814/phy2.15584
98. Nair V, Singh S, Gupta YK. Anti-arthritic and disease modifying activity of *Terminalia chebula* Retz. in experimental models. *J Pharm Pharmacol*. 2010;62(12):1801–1806. doi:10.1111/j.2042-7158.2010.01193.x
99. Boonyarikpunchai W, Sukrong S, Towiwat P. Antinociceptive and anti-inflammatory effects of rosmarinic acid isolated from *Thunbergia laurifolia* Lindl. *Pharmacol Biochem Behav*. 2014;124:67–73. doi:10.1016/j.pbb.2014.05.004
100. Huang Y, Liu C, Song X, et al. Antioxidant and anti-inflammatory properties mediate the neuroprotective effects of hydro-ethanolic extract of *Tiliacora triandra* against cisplatin-induced neurotoxicity. *J Inflamm Res*. 2021;14:6735–6748. doi:10.2147/JIR.S340176
101. Ahmad W, Jantan I, Kumolosasi E, et al. Immunostimulatory effects of the standardized extract of *Tinospora crispa* on innate immune responses in Wistar Kyoto rats. *Drug Des Devel Ther*. 2015;9:2961-2973. doi:10.2147/DDDT.S85405
102. Tan JW, Israf DA, Tham CL. Major bioactive compounds in essential oils extracted from the Rhizomes of *Zingiber zerumbet* (L) smith: a mini-review on the Anti-allergic and immunomodulatory properties. *Front Pharmacol*. 2018;9:652. doi:10.3389/fphar.2018.00652
103. Ali J, Camilleri P, Brown MB, et al. Revisiting the general solubility equation: in silico prediction of aqueous solubility incorporating the effect of topographical polar surface area. *J Chem Inf Model*. 2012;52(2):420–428. doi:10.1021/ci200387c
104. Occupational Safety and Health Administration. *HAZARD COMMUNICATION, Hazard Classification Guidance for Manufacturers, Importers, and Employers*. DC: OSHA Press; 2016.
105. Songvut P, Boonyarattanasoonthorn T, Nuengchamnong N, et al. Enhancing oral bioavailability of andrographolide using solubilizing agents and bioenhancer: comparative pharmacokinetics of *Andrographis paniculata* formulations in beagle dogs. *Pharm Biol*. 2024;62(1):183–194. doi:10.1080/13880209.2024.2311201
106. Zhang J, Hu X, Gao W, et al. Pharmacokinetic study on costunolide and dehydrocostuslactone after oral administration of traditional medicine *Aucklandia lappa Decne*. by LC/MS/MS. *J Ethnopharmacol*. 2014;151(1):191–197. doi:10.1016/j.jep.2013.10.024
107. Sempio C, Campos-Palomino J, Klawitter J, et al. Pharmacokinetics of oral cannabinoid Δ8-Tetrahydrocannabivarin and its main metabolites in healthy participants. *Pharmaceuticals*. 2024;17(12):1603. doi:10.3390/ph17121603
108. Peng Z, Zhang W, Zhang X, et al. Recent advances in analysis of capsaicin and its effects on metabolic pathways by mass spectrometry. *Front Nutr*. 2023;10:1227517. doi:10.3389/fnut.2023.1227517
109. Dahms M, Lotz R, Lang W, et al. Elucidation of Phase I and phase II metabolic pathways of rhein: species differences and their potential relevance. *Drug Metab Dispos*. 1997;25(4):442–452.
110. Paul LD, Springer D, Staack RF, et al. Cytochrome P450 isoenzymes involved in rat liver microsomal metabolism of californine and protopine. *Eur J Pharmacol*. 2004;485(1–3):69–79. doi:10.1016/j.ejphar.2003.11.051
111. Al-Jaber HI, Shakya AK, Al-Qudah MA, et al. Piceatannol, a comprehensive review of health perspectives and pharmacological aspects. *Arabian J Chem*. 2024;17(1):105939. doi:10.1016/j.arabjc.2024.105939
112. Mohammadi Nejad S, Özgüneş H, Başaran N. Pharmacological and toxicological properties of eugenol. *Turk J Pharm Sci*. 2017;14(2):201–206. doi:10.4274/tjps.62207
113. Li X, Yuan W, Wu J, et al. Andrographolide, a natural anti-inflammatory agent: an update. *Front Pharmacol*. 2022;13:920435. doi:10.3389/fphar.2022.920435
114. Jayakumar T, Hsieh CY, Lee JJ, et al. Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent andrographolide. *Evid Based Complement Alternat Med*. 2013;2013:846740. doi:10.1155/2013/846740
115. Rajanna M, Bharathi B, Shivakumar BR, et al. Immunomodulatory effects of *Andrographis paniculata* extract in healthy adults - an open-label study. *J Ayurveda Integr Med*. 2021;12(3):529–534. doi:10.1016/j.jaim.2021.06.004
116. Lee SH, Cho YC, Lim JS. Costunolide, a sesquiterpene lactone, suppresses skin cancer via induction of apoptosis and blockage of cell proliferation. *Int J Mol Sci*. 2021;22(4):2075. doi:10.3390/ijms22042075
117. Lim JS, Lee SH, Lee SR, et al. Inhibitory effects of *Aucklandia lappa* decne. extract on inflammatory and oxidative responses in LPS-treated macrophages. *Molecules*. 2020;25(6):1336. doi:10.3390/molecules25061336

118. Gill EW, Paton WD, Pertwee RG. Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature*. 1970;228(5267):134–136. doi:10.1038/228134a0
119. Croxford JL, Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *J Neuroimmunol*. 2005;166(1–2):3–18. doi:10.1016/j.jneuroim.2005.04.023
120. Basavarajappa BS, Subbanna S. Unveiling the potential of phytocannabinoids: exploring marijuana's lesser-known constituents for neurological disorders. *Biomolecules*. 2024;14(10):1296. doi:10.3390/biom14101296
121. Ramírez-Barrantes R, Córdova C, Gatica S, et al. Transient receptor potential vanilloid 1 expression mediates capsaicin-induced cell death. *Front Physiol*. 2018;9:682. doi:10.3389/fphys.2018.00682
122. Fattori V, Hohmann MS, Rossaneis AC, et al. Capsaicin: current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. *Molecules*. 2016;21(7):844. doi:10.3390/molecules21070844
123. Shen CC, Cheng JJ, Lay HL, et al. Cytotoxic apigenin derivatives from *Chrysopogon aciculatis*. *J Nat Prod*. 2012;75(2):198–201. doi:10.1021/np2007796
124. Rah B, Rather RA, Bhat GR, et al. JAK/STAT signaling: molecular targets, therapeutic opportunities, and limitations of targeted inhibitions in solid malignancies. *Front Pharmacol*. 2022;13:821344. doi:10.3389/fphar.2022.821344
125. Akhtar NMY, Jantan I, Arshad L, et al. Standardized ethanol extract, essential oil and zerumbone of *Zingiber zerumbet* rhizome suppress phagocytic activity of human neutrophils. *BMC Complement Altern Med*. 2019;19(1):331. doi:10.1186/s12906-019-2748-5
126. Gandhi G, Vasconcelos A, Haran G, et al. Essential oils and its bioactive compounds modulating cytokines: a systematic review on anti-asthmatic and immunomodulatory properties. *Phytomedicine*. 2020;73:152854. doi:10.1016/j.phymed.2019.152854
127. Haque MA, Jantan I, Harikrishnan H. Zerumbone suppresses the activation of inflammatory mediators in LPS-stimulated U937 macrophages through MyD88-dependent NF-κB/MAPK/PI3K-Akt signaling pathways. *Int Immunopharmacol*. 2018;55:312–322. doi:10.1016/j.intimp.2018.01.001