Journal of Experimental Pharmacology

Dovepress
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REVIEW

Anti-Inflammatory Activities of Some Plants of Genus *Alpinia*: Insights from In Vitro, In Vivo, and Human Studies

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Abstract: This narrative review intends to provide thorough information on the anti-inflammatory activities of *Alpinia* plants, the largest genus of the family Zingiberaceae. The articles were searched on the PubMed database using 'Alpinia AND anti-inflammatory activity' as the keywords, filtered to articles published from 2020 to 2024 and free full-text. Of the approximately 248 members of the genus *Alpinia* plants, the most commonly studied for their anti-inflammatory activities are *A. galanga*, *A. officinarum*, *A. zerumbet*, and *A. oxyphylla*. Only *A. galanga*, *A. officinarum*, and *A. zerumbet* have been studied in humans. Studies in animal models revealed that the plants contributed as exogenous antioxidants, reduced proinflammatory cytokines, inhibited proinflammatory enzymes, improved gastric acid and gastrointestinal motility, and promoted ulcer healing. The terpenoids, flavonoids (such as kaempferol, quercetin, and galangin), and diarylheptanoids obtained from the rhizomes of these plants may crucially play important roles in their anti-inflammatory activities. These plants did not show toxicity toward numerous normal cell lines (RAW 264.7, IEC-6, HepG2, MT-4, NIH-3T3, Vero cells, human peripheral blood mononuclear cells, and HaCaT) but were toxic to cancer cell lines (HT29). In humans, *A. galanga* was studied for its effects as psychostimulants improving mental health, improving sperm motility, and erectile dysfunction. Similarly, *A. officinarum* could improve sperm morphology and idiopathic infertility, whereas *A. zerumbet* worked as a cardiomyorelaxant in patients with cardiovascular diseases.

Keywords: cytokines, flavonoids, interleukins, polyphenols, secondary metabolites, *Alpinia* genus

Introduction

Alpinia, the largest genus of the Zingiberaceae family, was designated by Prospero Alpino, the Italian botanist. The *Alpinia* genus covers approximately 248 species distributed in tropical and subtropical regions of Asia and the Pacific Ocean.[1–4] Rosemary Margaret Smith, a Scottish botanist who specializes in the taxonomy of Zingiberaceae, proposed that *Alpinia* genus plants should be subdivided into two subgenera, *Alpini*a and *Dieramalpinia*.[5] The rhizome of these plants has a spicy flavor and pungent aromatic odor distinct from other Zingiberaceae plants. *Alpinia* plants, often called galangal (derived from *Gao-Liang-Jiang*, a Chinese word), are greater galangal or *Alpinia galanga* (L). Willd. and lesser galangal or *Alpinia officinarum* Hance.[6] Approximately 200 metabolites have been isolated and authenticated from plants of the genus *Alpinia*, including diarylheptanoids, terpenes, flavonoids, phenylpropanoids, volatile oils, and lignin. We searched for relevant scientific information to understand why these plants can cure disease.

In their phytochemical studies, Zhang and co-workers have confirmed that diterpenoids, flavonoids, and diarylheptanoids, obtained from the rhizomes, are the most prominent metabolites of the *Alpinia* genus.[7] Diarylheptanoids (characterized by a 1.7-diphenyl heptane skeleton) are categorized into linear, cyclic, and dimeric diarylheptanoids, or

Received: 3 October 2024
Accepted: 17 December 2024
Published: 24 January 2025

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diarylheptanoids bearing special moieties or in conjugation with monoterpenes or sesquiterpenes.[8] Diarylheptanoids were reported for their anti-inflammatory activities by modulating several pathways, for example, by inhibiting the production of nitric oxide (NO) and downregulating tumor necrosis factor (TNF-α) in murine macrophage RAW 264.7 and microglial N-11 cells,[9] by decreasing neutrophil and eosinophil counts and malondialdehyde levels, and elevating interferon (IFN)-γ, catalase (CAT), and lymphocyte values in sensitized rats.[10] In addition, flavonoids (phenolic compounds with a chemical structure of C6–C3–C6 that consist of two benzene rings (A and B) connected with heterocycle pyrene ring (C), and oxygen) are subcategorized into flavone, flavonol, flavanone, flavanonol, isoflavone, chalcone, and flavonoid glycosides. The anti-inflammatory mechanism of flavonoids was announced, for example, by inhibiting the overproduction of NO, and reducing pro-inflammatory cytokines such as TNF-α, interleukin (IL)-Iβ, IL-6, and IF-γ in lipopolysaccharide (LPS)-stimulated RAW 264.7.[11] Generally, flavonoids are responsible for the antioxidant activity, due to carbonyl, aldehyde, or hydroxyl moieties. The presence of a B-ring catechol group contributes to the donation of hydrogen (electron) to stabilize a radical species. Flavonoids could alter several protein kinase and lipid kinase signaling cascades such as phosphoinositide 3-kinase (PI3-kinase), Akt/PKB, tyrosine kinases, protein kinase C (PKC), and MAP kinases signaling pathways.[12]

Considering that plants of the genus *Alpinia* are abundant in diarylheptanoids and flavonoid content, this article discusses in vitro, in vivo, and human studies on the anti-inflammatory activity of these plants. The role of cytokines in the pathogenesis of inflammation and the effects of the *Alpinia* plants on pro-inflammatory and anti-inflammatory cytokines are also described.

Methods

This narrative review is intended to provide thorough information on the anti-inflammatory activities of *Alpinia* plants, the largest genus of the family Zingiberaceae. The articles were searched on the PubMed database using the keywords "Alpinia AND anti-inflammatory activity" filtered to free full-text, article language English, and publication period from 2020 to 2024 was used and resulted in 46 articles. Articles were further screened through titles and abstracts. Articles not related to the topic of interest, articles not written in English, reviews, and duplicate articles, were excluded. Additional searches were carried out to comprehend the review.

Botanical and Phytochemical Aspects

The *Alpinia* genus of the family Zingiberaceae are perennial flowering plants with tuberous rhizomes native to Asia and the Pacific islands.[1–4] According to Plants of the World Online, an online database published by the Royal Botanic Gardens, Kew (https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:328388-2), there are 248 species of the *Alpinia* genus plants. The botanical names of the *Alpinia* plants are listed in alphabetical order as follows:

A: *Alpinia abundiflora* Burtt and R. M. Sm., *A. acuminata* R. M. Sm., *A. adana* C. K. Lim, *A. aenea* B. L. Burtt and R. M. Sm., *A. albipurpurea* (P. Royen) R. M. Sm., *A. amentacea* R. M. Sm., *A. apoensis* Elmer, *A. aquatica* (Retz). Roscoe, *A. arctiflora* (F. Muell). Benth., *A. arfakensis* K. Schum., *A. argentea* (B. L. Burtt and R.M. Sm). R. M. Sm., *A. arundelliana* (F. M. Bailey) K. Schum., *A. asmy* C. K. Lim, *A. assimilis* Ridl., *A. athroantha* Valeton, *A. austrosinense* (D. Fang) P. Zou and Y. S. Ye.

B: *A. bambusifolia* C. F. Liang and D. Fang, *A. beamanii* R. M. Sm., *A. biakensis* R. M. Sm., *A. bodenii* R. M. Sm., *A. boia* Seem., *A. boninsimensis* Makino, *A. borraginoides* K. Schum., *A. brachyantha* Merr., *A. brevilabris* C. Presl, *A. breviligulata* (Gagnep). Gagnep, *A. brevis* T. L. Wu and S. J. Chen.

C: *A. caerulea* (R. Br). Benth., *A. calcarata* (Andrews) Roscoe, *A. calcicola* Q. B. Nguyen and M. F. Newman, *A. calycodes* K. Schum., *A. capitellata* Jack, *A. carinata* Valeton, *A. carolinensis* Koidz., *A. celebica* K. Schum., *A. chaunocolea* K. Schum., *A. chinensis* (Retz). Roscoe, *A. chrysorachis* K. Schum., *A. coeruleoviridis* K. Schum., *A. conchigera* Griff., *A. condensata* Valeton, *A. conferta* B. L. Burtt and R. M. Sm., *A. congesta* Elmer, *A. conghuaensis* J. P. Liao and T. L. Wu, *A. conglomerata* R. M. Sm., *A. copelandii* Ridl., *A. coriacea* T. L. Wu and S. J. Chen, *A. coriandriodora* D. Fang, *A. corneri* (Holttum) R. M. Sm., *A. cumingii* K. Schum., *A. cylindrocephala* K. Schum.

D: *A. dasystachys* Valeton, *A. dekockii* Valeton, *A. densibracteata* T. L. Wu and S. J. Chen, *A. densiflora* K. Schum., *A. denticulata* (Ridl). Holttum, *A. diffissa* Roscoe, *A. divaricata* Valeton, *A. diversifolia* (Elmer) Elmer, *A. domatifera* Valeton.

E: *A. elegans* (C. Presl) K. Schum., *A. elmeri* R. M. Sm., *A. emaculata* S. Q. Tong, *A. epiphytica* Meekiong, Ipor and Tawan, *A. eremochlamys* K. Schum., *A. euastra* K. Schum., *A. eubractea* K. Schum.

F: *A. fax* B. L. Burtt and R. M. Sm., *A. flabellata* Ridl., *A. flagellaris* (Ridl). Loes., *A. formosana* K. Schum., *A. foxworthyi* Ridl., *A. fusiformis* R. M. Sm.

G: *A. gagnepainii* K. Schum., *A. galanga* (L). Willd., *A. gigantea* Blume, *A. glabra* Ridl., *A. glabrescens* Ridl., *A. glacicaerulea* R. M. Sm., *A. globosa* (Lour). Horan., *A. gracillima* Valeton, *A. graminea* Ridl., *A. guinanensis* D. Fang and X. X. Chen.

H: *A. haenkei* C. Presl, *A. hagena* R. M. Sm., *A. hainanensis* K. Schum., *A. hansenii* R. M. Sm., *A. havilandii* K. Schum., *A. hibinoi* Masam., *A. himantoglossa* Ridl., *A. hirsuta* (Lour). Horan., *A. hoangviet* D. D. Nguyen and V. C. Nguyen, *A. hongiaoensis* Tagane, *A. horneana* K. Schum., *A. hulstijnii* Valeton, *A. hylandii* R. M. Sm.

I: *Alpinia* × *ilanensis* S. C. Liu and J. C. Wang, *A. illustris* Ridl., *A. inaequalis* (Ridl). Loes., *A. intermedia* Gagnep.

J: *A. janowskii* Valeton, *A. japonica* (Thunb). Miq., *A. javanica* Blume, *A. jianganfeng* T. L. Wu, *A. jingxiensis* D. Fang, *A. juliformis* (Ridl). R. M. Sm.

K: *A. kawakamii* Hayata, *A. kiungensis* R. M. Sm., *A. klossii* (Ridl). R. M. Sm., *A. koidzumiana* Kitam., *A. koshunensis* Hayata, *A. kusshakuensis* Hayata, *A. kwangsiensis* T. L. Wu and S. J. Chen.

L: *A. lalashanensis* S. S. Ying, *A. laosensis* Gagnep., *A. latilabris* Ridl., *A. lauterbachii* Valeton, *A. laxisecunda* B. L. Burtt and R. M. Sm., *A. leptostachya* Valeton, *A. ligulata* K. Schum., *A. ludwigiana* R. M. Sm.

M: *A. maclurei* Merr., *A. macrocephala* K. Schum., *A. macrocrista* Ardiyani and Ardi, *A. macroscaphis* K. Schum., *A. macrostaminodia* Chaveer and Sudmoon, *A. macrostephana* (Baker) Ridl., *A. macroura* K. Schum., *A. malaccensis* (Burm. f). Roscoe, *A. manii* Baker, *A. manostachys* Valeton, *A. martini* R. M. Sm., *A. maxii* R. M. Sm., *A. melichroa* K. Schum., *A. menghaiensis* S. Q. Tong and Y. M. Xia, *A. mesanthera* Hayata, *A. microlophon* Ridl., *A. modesta* F. Muell. ex K. Schum., *A. mollis* C. Presl., *A. mollissima* Ridl., *A. monopleura* K. Schum., *A. multispica* (Ridl). Loes., *A. murdochii* Ridl., *A. musifolia* Ridl., *A. mutica* Roxb., *A. myriocratera* K. Schum.

N: *A. nantoensis* F. Y. Lu and Y. W. Kuo, *A. napoensis* H. Dong and G. J. Xu, *A. nelumboides* Nob. Tanaka, T. T. K. Van and V. Hoang, *A. newmanii* N. S. Lý., *A. nidus-vespae* A. Raynal and J. Raynal, *A. nieuwenhuizii* Valeton, *A. nigra* (Gaertn). Burtt., *A. nobilis* Ridl., *A. novae-hiberniae* B. L. Burtt and R. M. Sm., *A. novae-pommeraniae* K. Schum., *A. nutans* (L). Roscoe.

O: *A. oblongifolia* Hayata, *A. odontonema* K. Schum., *A. officinarum* Hance, *A. okinawaensis* Tawada, *A. oligantha* Valeton, *A. orientalis* Docot and Banag, *A. orthostachys* K. Schum., *A. oui* Y. H. Tseng and Chih C. Wang, *A. ovata* Z. L. Zhao and L. S. Xu, *A. ovoidocarpa* H. Dong and G. J. Xu, *A. oxymitra* K. Schum., *A. oxyphylla* Miq.

P: *A. padacanca* Valeton ex K. Heyne, *A. pahangensis* Ridl., *A. papuana* Scheff., *A. parksii* (Gillespie) A. C. Sm., *A. penduliflora* Ridl., *A. petiolata* Baker, *A. pinnanensis* T. L. Wu and S. J. Chen, *A. platychilus* K. Schum., *A. platylopha* (Ridl). Loes., *A. polyantha* D. Fang, *A. porphyrea* R. M. Sm., *A. porphyrocarpa* Ridl., *A. pricei* Hayata, *A. psilogyna* D. Fang, *A. ptychanthera* K. Schum., *A. pubiflora* (Benth). K. Schum., *A. pulchella* (K. Schum). K. Schum., *A. pulcherrima* Ridl., *A. pulchra* (Warb). K. Schum., *A. pumila* Hook.f., *A. purpurata* (Vieill). K. Schum., *A. pusilla* Ardi & Ardiyani.

R: *A. rafflesiana* Wall. ex Baker, *A. regia* K. Heyne ex R. M. Sm., *A. rigida* Ridl., *A. romblonensis* Elmer, *A. romburghiana* Valeton, *A. rosacea* Valeton, *A. rosea* Elmer, A. roxburghii Sweet, *A. rubricaulis* K. Schum., *A. rubromaculata* S. Q. Tong, *A. rufa* (C. Presl) Náves, *A. rufescens* (Thwaites) K. Schum., *A. rugosa* S. J. Chen and Z. Y. Chen.

S: *A. salomonensis* B. L. Burtt and R. M. Sm., *A. samoensis* Reinecke, *A. sandsii* R. M. Sm., *A. scabra* (Blume) Náves, *A. schultzei* Lauterb. ex Valeton, *A. seimundii* Ridl., *A. sericiflora* K. Schum., *A. sessiliflora* Kitam., *A. shimadae* Hayata, *A. shoukaensis* S. S. Ying, *A. siamensis* K. Schum., *A. sibuyanensis* Elmer, *A. singuliflora* R. M. Sm., *A. smithiae* M. Sabu and Mangaly, *A. stachyodes* Hance, *A. stenobracteolata* R. M. Sm.,

A. stenostachys K. Schum., *A. strobilacea* K. Schum., *A. strobiliformis* T. L. Wu and S. J. Chen, *A. subfusicarpa* Elmer, *A. submutica* K. Schum., *A. subspicata* Valeton, *A. subverticillata* Valeton, *A. superba* (Ridl). Loes., *A. suriana* C. K. Lim.

T: *A. tamacuensis* R. M. Sm., *A. tonkinensis* Gagnep., *A. tonrokuensis* Hayata, *A. trachyascus* K. Schum., *A. tristachya* (Ridl). Loes.

U: *A. unilateralis* B. L. Burtt and R. M. Sm., *A. uraiensis* Hayata

V: *A. valetoniana* Loes., *A. velutina* Ridl., *A. velveta* R. M. Sm., *A. versicolor* K. Schum., *A. vietnamica* H. Đ. Trần, Luu and Škorničk., *A. vitellina* (Lindl). Ridl., *A. vitiensis* Seem., *A. vittata* W. Bull, *A. vulcanica* Elmer.

W-Z: *A. warburgii* K. Schum., *A. wenzelii* Merr., *A. werneri* Lauterb. ex Valeton, *A. womersleyi* R. M. Sm., and *A. zerumbet* (Pers). B. L. Burtt and R. M. Sm.

Different parts of the *Alpinia* genus plants possess significant bioactive metabolites for plant-based drug candidate development, such as diarylheptanoids, terpenes, flavonoids, phenylpropanoids, volatile oil, and lignin, with flavonoids, diterpenoids, and diarylheptanoids, as the most common contributors for their bioactivity.[7] It was described that *A. galanga* is abundant in phenolic compounds and essential oils, with a total phenolic content (TPC) ranging from 26.83 to 252.36 mg gallic acid equivalence (GAE)/g and total flavonoid content (TFC) ranging from 14.12 to 143.13 mg quercetin equivalence (QE)/g extract.[13–16] The most abundant phenolic compounds in the extract were, respectively, gallic acid, catechin, quercetin (a flavonoid), catechol, isorhamnetin, trans-cinnamic acid, and protocatechuic acid.[13] The variety in TPC and TFC values was caused by the differences in plant sources, with the highest values belonging to *A. galanga* collected from West Java, Indonesia.[16] *A. officinarum* is rich in flavonoids and diarylheptanoids.[8,17] The water extract of *A. officinarum* rhizome contains protocatechuic acid, epicatechin, and kaempferide.[18,19] *A. oxyphylla* collected in South Korea was reported to include essential oils, sesquiterpenes, flavones, diarylheptanoids, glycosides, and steroids. Among those, nootkatone is the most abundant metabolite.[20] The dried fruits of *A. oxyphylla* collected from Qiongzhong county, Hainan province, China, were assessed under the optimized extraction and UFLC-MS/MS analytical conditions and resulted in nootkatone, diphenylheptanes, and flavones.[21] Conversely, little is known about the phytochemistry of *A. purpurata*,[22] opening opportunities for further exploration. The metabolites isolated from the plants of the *Alpinia* genus are listed in Table 1.

The Role of Cytokines in the Pathogenesis of Inflammation

Inflammation occurs when tissue injury and inflammation-inducing factors, such as histamines and cytokines, lead to blood vessel dilatation and vascular permeability, opening the entry for inflammatory components.[35] Inflammatory responses play a crucial role in the host defense mechanism against threats and typically present with signs such as redness, swelling, pain, and fever. When the host encounters external triggers or tissue injury, it responds by producing pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), IL-6, NO, and prostaglandins (PGs).[36] TNF-α and IL-1β are important in initiating inflammation following tissue damage from various causes. In addition, NO and PGs contribute to inflammation via the actions of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), respectively. Arachidonic acid (AA), a substrate of COX, is converted to PGs by both COX-1 and COX-2, leading to the stimulation of inflammation. COX-2 is absent in healthy tissue and is only expressed in response to cellular stress or damage, triggered by the activation of growth factor pathways. Inflammation also impacts AA metabolism through lipoxygenase (LOX) activity, which promotes the synthesis of pro-inflammatory cytokines such as IL-1, IL-6, and IL-8.[37] Furthermore, the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-kappaB) has a particular function in inflammation through controlling how inflammatory genes, such as IL-6 and TNF-α, are expressed.[38] The NF-kappaB-IkappaB complex exists in an inactive state in the cytoplasm. Upon stimulation by TNF-α, the β-subunit of the IkappaB kinase (IKK) complex, phosphorylates IkappaB proteins, and free NF-kappaB dimers will translocate to the nucleus, and begin the transcription.[39] In addition to NF-kappaB, which is an activator of inflammatory genes, this protein also works by limiting the NOD-like receptor protein 3 (NLRP3) inflammasome activation and IL-1β production. The production of inflammatory mediators and cytokines, T-cell differentiation, and cell proliferation, lead to the initiation of the inflammatory pathways, such as the NF-kB pathway and JAK-STAT, and complete the inflammatory responses.[40] Therefore,

Table 1 Metabolites Isolated from Alpinia Genus Plants

Name of the Active Metabolite (IUPAC name or Synonym)	Chemical Structure or Molecular Formula (PubChem CID)	Part of the Plant, the Botanical Name of the *Alpinia* Plant, Collected in, and the Isolation Method	Reference
Diarylheptanoids			
Alpinin B Synonym: 5-[(3R,5R)-7-(3,4-dihydroxyphenyl)-3,5-dihydroxyheptyl]-3-methoxybenzene-1,2-diol	$C_{20}H_{26}O_7$ (PubChem CID 168013546)	The rhizomes of *Alpinia officinarum* Hance were collected in China. Compounds were isolated by repeated CC and their structures were elucidated based on extensive spectral analysis (1D and 2D NMR, HRTOFMS, IR).	[23,24]
Alpinin C	The chemical structure is not available in the PubChem database		
Alpinin D	The chemical structure is not available in the PubChem database		
Alpinoid A	The chemical structure is not available in the PubChem database	The rhizomes of *Alpinia officinarum* Hance collected in Chiba, Japan, were extracted using MeOH, followed by bioassay-guided fractionation of the MeOH extract, and led to the isolation of diarylheptanoids (alpinoid A, alpinoid D, alpinoid E, and diarylheptanoids). The structures were elucidated by applying extensive spectroscopic analyses and the modified Mosher method.	[25]
Alpinoid D Synonym: 2-methoxy-4-[[5-(2-phenylethyl) furan-2-yl] methyl] phenol	$C_{20}H_{20}O_3$ (PubChem CID 38363343)	The rhizomes of *Alpinia officinarum* Hance collected in Chiba, Japan, were extracted using MeOH, followed by bioassay-guided fractionation of the MeOH extract, and led to the isolation of diarylheptanoids (alpinoid A, alpinoid D, alpinoid E, and diarylheptanoids). The structures were elucidated by applying extensive spectroscopic analyses and the modified Mosher method.	[26]
Alpinoid E Synonym: (E,2S)-2-hydroxy-1,7-diphenylhept-4-en-3-one	$C_{19}H_{20}O_2$ (PubChem CID 163184099)	The rhizomes of *Alpinia officinarum* Hance collected in Chiba, Japan, were extracted using MeOH, followed by bioassay-guided fractionation of the MeOH extract, and led to the isolation of diarylheptanoids (alpinoid A, alpinoid D, alpinoid E, and diarylheptanoids). The structures were elucidated by applying extensive spectroscopic analyses and the modified Mosher method.	

(*Continued*)

https://doi.org/10.2147/JEP.S499115

Table 1 (Continued).

Name of the Active Metabolite (IUPAC name or Synonym)	Chemical Structure or Molecular Formula (PubChem CID)	Part of the Plant, the Botanical Name of the *Alpinia* Plant, Collected in, and the Isolation Method	Reference
Blepharocalyxin B Synonym: [2,4-dihydroxy-3-[(E,1R,5S)-5-hydroxy-1,7-bis (4-hydroxyphenyl) hept-2-enyl]-6-methoxyphenyl]-[(2R,3R,4S,6S)-2-(4-hydroxyphenyl)-4-[(E)-2-(4-hydroxyphenyl) ethenyl]-6-[2-(4-hydroxyphenyl) ethyl] oxan-3-yl]methanone	$C_{54}H_{54}O_{11}$ (PubChem CID 10677118)	The seeds of *Alpinia blepharocalyx* K. Schum. were collected in the southwest of China. The seeds were extracted with 95% EtOH and the extract was further fractionated with hexane and ether. The diarylheptanoids were isolated from the ether and residual fractions of the ethanol extract by chromatographic separations afforded 44 diarylheptanoids, 2 diarylheptanoid derivatives, 11 phenolic compounds, and beta-sitosterol glucoside.	[27]
Blepharocalyxin D Synonym: 4-[2-[(2S,4S,4aS,5S,7S,8aR)-5-(4-hydroxyphenyl)-4-[(E)-2-(4-hydroxyphenyl) ethenyl]-7-[2-(4-hydroxyphenyl) ethyl]-2,3,4,4a,5,7,8,8a-octahydropyrano[3,2-c] pyran-2-yl] ethyl] phenol	$C_{38}H_{40}O_6$ (PubChem CID 9985898)		
Calyxin K Synonym: 7-hydroxy-2-(4-hydroxyphenyl)-8-[(2S,6S)-2-(4-hydroxyphenyl)-6-[2-(4-hydroxyphenyl) ethyl] oxan-4-yl]-5-methoxy-2,3-dihydrochromen-4-one	$C_{35}H_{34}O_8$ (PubChem CID 42608061)		
Epicalyxin K Synonym: 7-hydroxy-2-(4-hydroxyphenyl)-8-[(2S,4R,6S)-2-(4-hydroxyphenyl)-6-[2-(4-hydroxyphenyl) ethyl] oxan-4-yl]-5-methoxy-2,3-dihydrochromen-4-one	$C_{35}H_{34}O_8$ (PubChem CID 10348279)		
Officinaruminane A	The chemical structure is not available in the PubChem database	The dried rhizomes of *A. officinarum* Hance were collected in October 2002 from Xu-Wen County, Guangdong province of China. The plant specimen was identified by Prof. Shou-Quan Lin, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, China. Dried rhizomes of *A. officinarum* Hance were extracted with 95% EtOH. The EtOH extract was further extracted with petroleum ether, $CHCl_3$, EtOAc, and *n*-BuOH, respectively. The $CHCl_3$ extract was separated by CC on silica gel, MPLC, and preparative TLC. The structures were elucidated based on mass spectrometry, 1H-NMR, 13C-NMR, HMQC, and HMBC data.	[28]
Officinaruminane B Synonym: 1-[4-(4-methylpent-3-enyl)-6-(2-phenylethyl) cyclohex-3-en-1-yl]-3-phenylpropan-1-one	$C_{29}H_{36}O$ (PubChem CID 102004698)		
Officinin A	The chemical structure is not available in the PubChem database	The compound was isolated from the rhizomes of *Alpinia officinarum* Hance collected in Nanjing, China. The structure elucidation was accomplished by HR-ESIMS, 1D, and 2D NMR methods.	[29]

Officinin B	The chemical structure is not available in the PubChem database	The compound was isolated from the rhizomes of *Alpinia officinarum* Hance collected in Nanjing, China. The structure was elucidated by spectral methods (1H NMR, 13C NMR, 1H–1H COSY, HMBC, and HR-ESI-MS).	[30]
Flavonoids			
Alpinetin Synonym: (2S)-7-hydroxy-5-methoxy-2-phenyl-2,3-dihydrochromen-4-one	$C_{16}H_{14}O_4$ (PubChem CID 154279)	The compound was isolated from *Alpinia katsumadai* Hayata, purchased in Qingdao, China. Extraction was done by using orthogonal experiments L16 in a microwave-assisted extraction, followed by an HSCC chromatography to separate and isolate alpinetin using a two-phase solvent system of n-hexane-EtOAc-EtOH-water (5:6:5:5, v/v) in one-stepseparation. From 158.4 mg of the crude extract, 14.47 mg of alpinetin (99.01%) was obtained. The structure elucidation was accomplished by melting points, UV, IR,1H NMR, and 13C NMR.	[31] [32]
Cardamomin Synonym: (E)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenylprop-2-en-1-one	$C_{16}H_{14}O_4$ (PubChem CID 641785)	Extraction was done by using orthogonal experiments L16 in a microwave-assisted extraction, followed by an HSCCC to separate and isolate alpinetin using a two-phase solvent system of n-hexane-EtOAc-EtOH-water (5:6:5:5, v/v) in one-step separation. From 158.4 mg of the crude extract, 1.72 mg of cardamomin (97.71%)was obtained. The structure elucidation was accomplished by melting points, UV, IR,1H NMR, and 13C NMR.	[31]
Chrysin Synonym: 5.7-dihydroxy-flavone or 5.7-dihydroxyflavone or chrysin	$C_{15}H_{10}O_4$ (PubChem CID 5281607)	The fruits of *A. oxyphylla* (Yizhi) were collected in Yangjiang, Guangdong province of China, in August 2010 and identified by Dr Sibao Chen, Institute of Medicinal Plant Development, Peking Union Medical College & Chinese Academy of Medical Sciences. The air-dried and powdered Yizhi (10 kg) was percolated in 95% EtOH (3 x 100 L) for 48 h at 60°C. The combined extracts were concentrated in a vacuum and the residue was suspended in water and partitioned successively with petroleum ether (60–90°C), EtOAc, and n-BuOH. EtOAc-soluble fraction (275 g) was subjected to CC on silica gel with the mixtures of petroleum ether–EtOAc in a gradient from 100:0 to 0:100. Fractions were combined based on their TLC patterns to get E1–E6. Chrysin was obtained from E2 (28 mg).	[33]

(*Continued*)

Table 1 (Continued).

Name of the Active Metabolite (IUPAC name or Synonym)	Chemical Structure or Molecular Formula (PubChem CID)	Part of the Plant, the Botanical Name of the *Alpinia* Plant, Collected in, and the Isolation Method	Reference
Galangin Synonym: 3,5,7-trihydroxy flavone or 3,5,7-trihydroxy-2-phenyl-4H-chromene-4-one	$C_{15}H_{10}O_5$ (PubChem CID 5281616)	The compound was isolated from the rhizomes of *Alpinia officinarum* Hance collected at Haikou City, Hainan Province, China. Extraction was done by refluxing 1 kg of the rhizomes with 80% EtOH for 1 h and concentrated to 40% under reduced pressure. The extract was purified with AB-8 macroporous. The ethanol elution fraction was subjected to silica gel CC and eluted with a petroleum ether-ethyl acetate gradient. The fractions were subjected to gel CC and eluted with MeOH, UHPLC diode array detector, and MS analysis.	[20]
3-methyl galangin Synonym: Galangin 3-methyl ether or 3-O-methylgalangin	$C_{16}H_{12}O_5$ (PubChem CID 5281946)		
Kaempferide Synonym: 4'-methylkaempferol or 4'-O-methylkaempferol	$C_{16}H_{12}O_6$ (PubChem CID 5281666)		
Quercetin Synonym: Sophoretin or Meletin or Xanthaurine or 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromene-4-one	$C_{15}H_{10}O_7$ (PubChem CID 5280343)	*Alpinia galanga* rhizomes were obtained from the local market in Riyadh, Saudi Arabia. The rhizomes were cleaned and milled to powder. 5 g of the powder was extracted using 50 mL of MeOH: water (80:20, v/v), stirred for 3 h, filtered through Whatman No. 1 filter paper, and the solvent was evaporated using a rotary evaporator. The extract was filtered using a microporous filter (0.45 m) before HPLC injection. An HPLC system (Shimadzu) was connected to a PDA detector with an Inertsil ODS-3 column (5 mm, 4.6 mm, 3250 mm). The mobile phase consisted of 0.05% acetic acid in water (A) and acetonitrile (B), and the flow rate was set at 1 mL/min. The gradient profile was 0.0–0.1 min 8% B; 0.1–2.0 min 10% B; 2.0–27.0 min 30% B; 27.0–37.0 min 56% B; 37.0–37.1 min 8% B; 37.1–45.0 min 8% B and 20 mL acetic acid, at 30°C. The wavelengths of the detector were set at 280 and 330 nm. Phenolic compounds were determined according to the retention time and absorption spectra of standard compound peaks, resulting in quercetin levels of 105.34 ± 2.80 mg/100 g extract.	[13]

https://doi.org/10.2147/JEP.S499115

Tectochrysin Synonym: 5-hydroxy-7-methoxy flavone; 5-Hydroxy-7-methoxy-2-phenyl-4H-chromene-4-one; or techtochrysin	$C_{16}H_{12}O_4$ (PubChem CID 5281954)	The fruits of *A. oxyphylla* (Yizhi) were collected in Yangjiang, Guangdong province of China, in August 2010 and identified by Dr Sibao Chen, Institute of Medicinal Plant Development, Peking Union Medical College & Chinese Academy of Medical Sciences. The air-dried and powdered Yizhi (10 kg) was percolated in 95% EtOH (3 x 100 L) for 48 h at 60°C. The combined extracts were concentrated in a vacuum and the residue was suspended in water and partitioned successively with petroleum ether (60–90°C), EtOAc, and n-BuOH. The petroleum ether-soluble fraction was CC over silica gel with a petroleum ether–EtOAc gradient system. Fractions were combined based on their TLC patterns to yield P1–P5. Further separation of P2 (9 g), P3 (25 g), and P4 (18 g) was performed by silica gel CC eluting by petroleum ether–EtOAc solvent system with different ratios of 15:1, 10:1, and 9:1, respectively. Tectochrysin was obtained from P2 (23 mg).	[33]
Terpenoids			
α-terpineol Synonym: 2-(4-methylcyclohex-3-en-1-yl)propan-2-ol	$C_{10}H_{18}O$ (PubChem CID 17100)	The compounds were isolated from the rhizome and leaves of *A. calcarata* collected from the Western province of Sri Lanka in 2015 during the flowering season. The rhizome and leaves were chopped separately. Each part (450 g) was separately hydro-distilled for 4 h using 500 mL distilled water in a Clevenger-type apparatus to obtain the essential oils (ACEOs). Oil samples were dried with anhydrous Na_2SO_4 and stored at 4°C before analysis. The ACEOs from rhizome and leaf were analyzed by Thermo Scientific TRACE 1300 Series GC operated with a split mode injector, Thermo Scientific AI/AS 1310 Series autosampler, and Thermo Scientific ISQ Series GC-Single Quadrupole MS.	[34]
Eucalyptol Synonym: Cineole or 1.8-cineole	$C_{10}H_{18}O$ (PubChem CID 2758)		

(*Continued*)

Table 1 (Continued).

Name of the Active Metabolite (IUPAC name or Synonym)	Chemical Structure or Molecular Formula (PubChem CID)	Part of the Plant, the Botanical Name of the *Alpinia* Plant, Collected in, and the Isolation Method	Reference
Nootkatone	$C_{15}H_{22}O_6$ (PubChem CID 1268142)	The compound was isolated from the rhizomes of *Alpinia oxyphylla* obtained at Kyung-Dong Market in Seoul, Korea. Extraction was done by using EtOH 70% at 70°C for 48 h with stirring at 500 rpm. The extract was filtered using Toyo No. 4 filter paper, concentrated using a vacuum evaporator, and diluted in DMSO to obtain a final concentration of 100 mg/mL.	[21]
Fenchyl acetate Synonyms: Fenchyl acetate 13851–11-1 Fenchylacetate 4057–31-2 2-Norbornanol, 1,3,3-trimethyl-, acetate	$C_{12}H_{20}O_2$ (PubChem CID 107217)	Whole plants of *A. calcarata* were collected from the Western province of Sri Lanka in 2015 during the flowering season. The plants were authenticated by NPT Gunawardena, and voucher specimens were deposited at the National Herbarium, Peradeniya, Sri Lanka. The whole plant was washed, and the rhizome and leaves were chopped separately. Each part (450 g) was separately hydrodistilled for 4 h using 500 mL distilled water in a Clevenger-type apparatus to obtain the essential oils. After decanting, oil samples (ACEOs) were dried with anhydrous Na_2SO_4 and stored at 4°C before analysis. ACEOs were analyzed using GC-MS.	[34]

Abbreviations: BuOH, butanol; CC, column chromatography; $CHCl_3$, chloroform; DMSO, dimethyl sulfoxide; 1H–1H COSY, homonuclear correlation spectroscopy; EtOAc, ethyl acetate; EtOH, ethanol; GC, gas chromatography; GC-MS, gas chromatography–mass spectroscopy; HMBC, heteronuclear multiple bond coherence; HMQC, heteronuclear multiple quantum coherence; HPLC, high performance liquid chromatography; HR-ESI-MS, high-resolution electrospray ionization mass spectrometry; HRTOFMS, high resolution time-of-flight mass spectrometry; HSCCC, high-speed counter-current chromatography; IR, infrared; MeOH, methanol; MPLC, medium pressure liquid chromatography; MS, mass spectrometry; 1H NMR, proton nuclear magnetic resonance; 13C NMR, carbon nuclear magnetic resonance; TLC, thin layer chromatography; UHPLC, ultra-high performance liquid chromatography; UV, ultra-violet.

https://doi.org/10.2147/JEP.S499115

Table 2 In Vitro and In Vivo Studies of Anti-Inflammatory Activity of Alpinia Genus Plants

Botanical name	Part of the plant, collected in and authenticated by	Extraction method	Phytochemical analysis	Type of cell	Model category, methods, inducer, and parameter assessed	Control drug and dosage	Statistical analysis	Results	Reference
In Vitro Studies									
Alpinia officinarum	Rhizomes of *A. officinarum* were collected from Haikou County, Hainan Province, China, in October 2017. The plant was identified by Professor Niankai Zeng of Hainan Medical University.	The fresh rhizomes were refluxed with eightfold 80% EtOH for 1 h. The residue was extracted twice under the same conditions. The EtOH extracts were combined and concentrated to 40% under reduced pressure, and purified with AB-8 macroporous resin by 80% EtOH. The EtOH fraction was subjected to silica gel CC and eluted with a PE-EtOAc gradient to obtain six crude components (1–6), with components 4 and 5 being subjected to gel CC and eluted with MeOH.	The UHPLC-DAD-MS data were obtained from an Agilent 1290 Infinity series with a DA detector and quadrupole MS. The MS contained a dual APCI and ESI interface. The LC column was an Agilent ZORBAX Eclipse Plus C18 (2.1 × 100 mm, 1.8 μm), set at 30°C. The flow rate was 0.25 mL/min. The mobile phase eluent was isopropanol with 5 mm ammonium formate (B) and water (A), both containing 0.05% formic acid. Ionization and detection of compounds were carried out on the MS using the ESI positive mode at m/z 100–800. The DAD was set at 254, 280, and 325 nm.	GES-1 cell line was obtained from Procell Life Science & Technology, Wuhan, China.	GES-1 cells were seeded on a 96-well plate at a density of 1×10^4 cells per well for 4 h and then treated with flavonoids of *A. officinarum* extract (16, 8, 4, 2, and 1 μg/mL), while the normal group and the EtOH group were cultured in a serum-free medium, followed by incubation at 37°C for 16 h. The normal group was stimulated with an equal volume of serum-free medium, while 7% alcohol was added and co-incubated for 4 h; 10 μL CCK-8 and 90 μL serum-free medium were added into each well. After incubation for 2 h in a cell culture incubator, the OD value was then measured on a microplate reader at 450 nm.	Not described.	All experimental results were expressed as mean ± SD and analyzed with SPSS 25.0 using a one-way ANOVA followed by Fisher's LSD test for multiple comparisons. p values < 0.05 indicated statistical significance.	In GES-1 cells, the inhibition of proinflammatory factor levels was suppressed by flavonoids of *A. officinarum* extract (4 μg/mL), thus suggesting that the flavonoids in the extract significantly inhibited the upregulation of TNF-α, IL-1β, and IL-6 inflammatory factors (p < 0.01).	[17]

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Table 2 (Continued).

Alpinia officinarum	The dried rhizome of *A. officinarum* was collected from an Ayurvedic pharmacy in Chennai, India. The plant was authenticated by a botanist from the Institute of Herbal Botany Plant Anatomy Research Centre, Chennai, India.	The rhizome was shade-dried and ground to a fine powder. The powder was successfully extracted in n-hexane and filtered. The filtered extracts were dried under reduced pressure in a rotary flash evaporator and used for further studies.	Not described.	HT29 cell line was obtained from NCCS, Pune.	HT29 cells were plated in 96-well plates with 100 μL medium and were exposed to various concentrations of *A. officinarum* hexane extract (0.5, 1, 2.5, 5, 7.5, 10 μg) for 3, 6, 24, and 48 h in triplicate. The parameters assessed were the mRNA expression of NF-kappaB and COX-2 in *A. officinarum* hexane extract-treated HT29 as compared to untreated cells.	Not described.	The data obtained were evaluated with SPSS 16 including one-way ANOVA followed by LSD test. *p*-values < 0.05 indicated statistical significance.	*A. officinarum* hexane extract downregulated the mRNA expression of NF-kappaB and COX-2 in HT29 cells, thus suggesting its promising anti-oxidant and anti-inflammatory agent.	[18]
Alpinia officinarum	Dried *Alpinia officinarum* was purchased from KOCBiotech (Daejeon, Korea).	Dried *A. officinarum* (1 kg) was extracted in 10 L of distilled water under circumfluence for 3 h at 100 ± 2°C and lyophilized after filtration (53 μm mesh). The dried powder was stored at – 20°C until further use.	The HPLC analysis of galangin, protocatechuic acid, and epicatechin in the extract was performed with a Waters e2695 liquid chromatography system, equipped with a Waters 2998 PDA detector. The separation was carried out using the Phenomenex Luna C18 column (250 mm × 4.6 mm; particle size 5 μm) and detected at 270 nm. The mobile phase consisted of 0.1% aqueous formic acid (A) and acetonitrile (B) in gradient elution. The flow rate was 1.0 mL/min and the injection volume was 20 μL.	HaCaT cell line was obtained from Elabscience (Houston, TX, USA).	HaCaT cells were pre-incubated with *A. officinarum* water extract for 1 h and treated with 10 ng/mL of the inducers (IFN-γ/TNF-α) for 24 h at 37°C. Parameters assessed were the levels of secreted MDC protein, RANTES, IP-10, and I-TAC in HaCaT cells. The levels of secreted MDC protein in HaCaT cells were detected using the Human CCL22/MDC Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA). The levels of released RANTES, IP-10, and I-TAC were evaluated using the LEGENDplex™ Proinflammatory Chemokine panel bead-based immunoassay (BioLegend, San Diego, CA, USA).	Not described.	Data were analyzed using the GraphPad Prism version 8.0 (GraphPad Software, USA). The data were represented as means ± SEM and calculated using the ordinary one-way ANOVA. A *p*-value of < 0.05 indicates statistical significance.	The secretion of MDC, RANTES, IP-10, and I-TAC were markedly inhibited upon treatment with 50, 100, and 300 μg/mL *A. officinarum* extract, thus confirming the anti-inflammatory effects of *A. officinarum* water extract. This activity was due to its inhibitory action on MAPK phosphorylation, NF-kappaB, and STAT1.	[19]

Alpinia officinarum	Rhizomes of *A. officinarum* were collected from Haikou County, Hainan Province, China, in October 2017. The plant was identified by Professor Niankai Zeng of Hainan Medical University.	The fresh rhizomes were refluxed with eightfold 80% EtOH for 1 h. The residue was extracted twice under the same conditions. The EtOH extracts were concentrated to 40% under reduced pressure, and purified with AB-8 macroporous resin by 80% EtOH.	The EtOH fraction was subjected to silica gel CC and eluted with a PE-EtOAc gradient. UHPLC-DAD-MS data were obtained from an Agilent 1290 Infinity series with a DA detector and an Agilent 6120 quadrupole MS containing a dual APCI and ESI interface.	GES-1 cell line was obtained from Procell Life Science & Technology, Wuhan, China.	GES-1 cells were seeded on a 96-well plate at a density of 1 × 10^4 cells per well for 4 h and then treated with flavonoids of *A.officinarum* extract (16, 8, 4, 2, and 1 μg/mL), while the normal group and the EtOH group were cultured in aserum-free medium, followed by incubation at 37°C for 16 h. A transwell assay was performed to evaluate the cell migration ability. In the Transwell experiment, 1 × 10^5 GES-1 cells were inoculated into the upper compartment of the transwell. After incubation for 24 h, 7% EtOH was added for 4 h to induce GES-1 cell damage. The upper chamber was then transferred to a new 24-well plate. First, the lower chamber was added to a serum-free medium and incubated for 8 h. Then, the upper chamber was transferred to a medium containing 15% FBS for further incubation for 16 h. During this period, a 200 μL serum-free medium was added to the upper chamber of the normal and EtOH groups, and 200 μL flavonoids of *A. officinarum* extract (2, 4, and 8 μg/mL) and ranitidine (100 μg/mL) were added to the drug groups, respectively. After a total of 24 h culture, residual cells that failed to pass through the pore membrane in the upper chamber were wiped gently. The GES-1 cells below the upper chamber were fixed with MeOH and stained with crystal violet. The number of cells passing through the polycarbonate membrane was observed under a fluorescence microscope.	Ranitidine 100 μg/mL.	All experimental results were expressed as mean ± SD and analyzed with SPSS 25.0 using a one-way ANOVA followed by Fisher's LSD test for multiple comparisons. *p* values < 0.05 indicated statistical significance.	Treatment with flavonoids of *A. officinarum* extract significantly resisted the damage degree of EtOH-exposed GES-1 cells and increased the number of cells passing through the polycarbonate membrane. The results indicated significant advantages over ranitidine in EtOH-induced gastric ulcer treatment.	[20]
Alpinia oxyphylla and its bioactive compound nootkatone	*A. oxyphylla* was purchased from Kyung-Dong Market in Seoul, Korea. The plant was identified at least twice through morphological analysis by Dr. Jaeyoon Cha, Department of Food Science and Nutrition, Dong-A University, Busan, Republic of Korea.	The plants were washed and ground using a laboratory mill to a particle size of 100 mesh. EtOH 70% was added to the powder and extracted at 70°C for 48 h with stirring at 500 rpm. The extract was filtered and concentrated using a vacuum evaporator.	Not described.	HCT-116, SW480, DLD-1, and HT-49 colorectal cancer cell lines were purchased from the American Type Culture Collection (ATCC).	The parameters assessed were the expression of pro-apoptotic protein NAG-1 and cell proliferative protein cyclin D1.	Not described.	Data are expressed as mean ± SD from at least three independent experiments. Statistical analyses were performed using a one-way ANOVA test. Significant differences have been indicated as **p* < 0.05; ***p* < 0.01; ****p* < 0.001.	The extract and nootkatone increased the expression of NAG-1 and suppressed cyclin D1 expression levels in various human colon cancer cell lines (HCT-116, SW480, DLD-1, and HT-49).	[21]

(*Continued*)

https://doi.org/10.2147/JEP.S499115

Table 2 (Continued).

Alpinia oxyphylla	*A. oxyphylla* fruits were purchased from Ulsan, South Korea.	The fruits were reflux-extracted twice with 50% EtOH for 4 h. The extract was passed through filter paper, concentrated under reduced pressure, dried, and stored at 4°C.	An Agilent HPLC 1200 series system equipped with a quaternary pump, autosampler, and PDA detector with a Phenomenex® Luna C18 column (250 × 4.6 mm, 5 μm) was used for analysis. The column temperature was maintained at 30°C, and the injection volume was 10 μL. Elution with solvent A (deionized water) and solvent B (MeOH) in a gradient elution at a flow rate of 1 mL/min was carried out. The detection was set at 245 nm.	The murine macrophage cell line RAW264.7 was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).	Parameters assessed were NO, PGE2, IL-1β, IL-6, and TNF-α production. LPS was used as the inducer. Cells were cultured in DMEM supplemented with 5.5% heat-inactivated FBS, penicillin (100 U/mL), and streptomycin (100 μg/mL) and maintained in a 37°C humidified incubator containing 5% CO_2. The medium was replaced with serum-free DMEM, and 0.5 μg/mL LPS was added with or without the ethanol extract of A. oxyphylla fruits (25, 50, and 100 μg/mL) for 24 h.	Not described.	The results are expressed as the mean ± SEM and analyzed using one-way ANOVA followed by Dunnett's tests for multiple comparisons or unpaired Student's t-tests for two-group comparisons. All analyses were performed using Prism 7.0 (GraphPad Software, San Diego, USA). *p*-values < 0.05 were considered statistically significant.	The ethanol extract of *A. oxyphylla* fruits significantly decreased the production of NO (68.2%), PGE_2 (92.8%), IL-1β (77.2%), IL-6 (39.9%), and TNF-α (20.7%) and showed the activation of ERK, JNK, and p38 MAPK in LPS-treated RAW264.7 cells at a dose of 100 μg/mL.	[41]
Alpinia zerumbet	Fresh leaves were collected from Zoo Garden, Giza, Egypt in May 2014. The plant was identified by Dr. Tearse Labib, Department of Flora and Taxonomy, El-Orman Botanical Garden, Giza, Egypt.	Dry powdered leaves were macerated in MeOH at room temperature. The extract was concentrated using a rotatory evaporator at 40 ± 2°C. The crude MeOH extract was defatted by PE at 60–80°C, and freeze-dried.	HPLC-ESI-MS/MS was employed to investigate the chemical constituents of the extract. The LC system was Thermo Finnigan coupled with an LCQ Duo ion trap MS with an ESI source. A silica gel C18 reversed-phase column (Zorbax Eclipse XDB-C18, rapid resolution, 4.6 × 150 mm, 3.5 μm, Agilent, USA) was used. Water with a gradient increase from 5% to 50% of acetonitrile (with 1% formic acid each in the positive mode) was applied in 60 min, with a flow rate of 1 mL/min, and then increased to 90% acetonitrile in the next 30 min. The ions were detected in a full scan mode at 50–2000 m/z.	No cell lines were used.	The parameters assessed were the inhibition of bovine COX-1 and COX-2 using an EIA kit. A lipoxygenase inhibitor screening assay kit was used to evaluate lipoxygenase inhibition activity.	Not described.	Data were analyzed using statistical software Graph Pad Prism version 5 (GraphPad Software, San Diego, USA). ANOVA or repeated-measures analysis of variance (RM-ANOVA), after which Tukey's post hoc test and Student's *t*-test were used to state the differences between groups. Data are expressed as mean ± SEM.	The methanol extract of *A. zerumbet* leaves successfully inhibited COX-1 as comparable to that of diclofenac, inhibited COX-2 with half the potency of celecoxib, and inhibited LOX with nearly double the potency of zileuton, a LOX inhibitor.	[42]

Alpinia zerumbet	The fruits of *Alpinia zerumbet* were collected in Zhenfeng County, Guizhou province, China, in October 2013. The fruits were identified by Professor Zuyun Chen at the Department of Pharmacognosy and Medico-botany at Guizhou Medical University.	The essential oils were extracted by steam distillation.	Not described.	Primary HAEC cells were purchased from ScienCell Research Laboratories (San Diego, CA, USA). HAEC cells at passages 3–5 were used in this study.	The parameters assessed were mRNA and protein levels of ICAM-1 and VCAM-1.	HAEC was cultured in ECM and incubated in a humidifier at 37°C and 5% CO_2. Cells were assigned to one of the following groups: (i) control group: cells were cultured in ECM complete media with an equal volume of vehicle (PBS and DMSO); (ii) LPS group: cells were treated with LPS (1 μg·mL^{-1}, dissolved in PBS) for 12 h; (iii) essential oils (L) (50 ng·mL^{-1},) plus LPS; (iv) essential oils (100 ng·mL^{-1},) plus LPS.	Statistical significance was calculated by one-way ANOVA and multiple comparisons were carried out by Dunnett's post hoc test (2-sided). A value of $P < 0.05$ was considered significant. Data are expressed as mean ± SD.	The essential oils of *A. zerumbet* completely prevented LPS-induced HAEC activation and inflammation in vitro, as assessed by the expression of endothelial adhesion molecules, ICAM-1 and VCAM-1. It was demonstrated that TLR4-dependent NF-kappaB signaling may be involved in the process.	[43]
Alpinia zerumbet	The essential oil of the dried and ripe fruit of *A. zerumbet* The plant was identified by Associate Professor Qing-De Long at the Herbarium of Traditional Chinese Medicine and Ethnic Medicine, Guizhou Medical University (Guizhou, China).	The extraction process was not described in detail.	Not described.	Human monocytic THP-1 derived macrophages.	The inducer used was cholesterol. The parameter assessed was ox-LDL level.	In both THP-1-derived macrophages with and without oxLDL, the cytotoxicity of the essential oil treatment was evaluated across varying concentrations (1–25 μg/L) over 24 h. The results indicated that there was no apparent toxicity was found compared to the control group, respectively.	Data were expressed as the mean ± SD of at least three independent experiments. GraphPad Prism 8 software (San Diego, CA, USA) was utilized for data analysis. A two-tailed Student's t-test was performed to analyze the differences between the two groups. Difference among various groups was determined utilizing one-way ANOVA and Tukey method. *p*-value < 0.05 indicates a significant difference.	The essential oil of *A. zerumbet* fruits could restrain the formation of MFCs by increasing cholesterol efflux via the activation of the PPARγ-LXRα-ABCA1/G1 pathway, and decreasing the ubiquitination degradation of PPARγ. This activity was thought due to the direct interaction of phytochemicals to the PPARγ protein, thereby increasing the stability of the protein.	[34]

(*Continued*)

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Table 2 (Continued).

Alpinia calcarata	Whole plants were collected from the Western province of Sri Lanka in 2015 during the flowering season. The plants were authenticated by N. P. T. Gunawardena at National Herbarium, Peradeniya, Sri Lanka.	The whole plant was washed, and the rhizome and leaves were chopped separately. Each part was separately hydrodistilled for 4 h using 500 mL distilled water in a Clevenger-type apparatus to obtain the essential oils.	The essential oils from rhizome and leaf were analyzed by Thermo Scientific™ TRACE™ 1300 Series GC operated with a split mode injector, Thermo Scientific AI/AS 1310 Series autosampler, and Thermo Scientific™ ISQ™ Series GC-Single Quadrupole MS, injection volume: 1.0 µL; flow rate: 1.0 mL/min; MS mode: EI; mass range: 40–450 m/z.	RAW 264.7, HepG2, IEC-6, and HaCaT cells.	RAW 264.7 cells were treated with LPS (1 µg/mL) in the presence of various concentrations of essential oils 0.5, 5, and 50 µg/mL and compounds (0.32–1.25 µg/mL) for 4 h. After 20 h, the concentration of nitrite, the stable product of NO, was quantified in the culture supernatant by Griess reagents (1% sulfanilamide and 0.1% NED.2HCl).	L-NMMA was used as a specific inhibitor of iNOS enzyme activity (positive control) at 250 µM.	The raw data were analyzed by *T*-tests and one-way ANOVA followed by Tukey's test and Dunnett's comparison test using GraphPad Prism version 5.0. Differences were considered to be significant when $p < 0.05$.	The essential oil demonstrated a concentration-dependent reduction in NO generation. At 50 µg/mL, the rhizome oil displayed a maximum inhibition of 85%, whereas the leaf oil displayed 81% inhibition. After treating LPS-exposed RAW 264.7 cells with L-NMMA for 24 h, 87% NO inhibition was observed.	[44]
Alpinia galanga	*Alpinia galanga* rhizomes were collected from Tawangmangu in Central Java Indonesia in May 2021.	The dried *Alpinia galanga* rhizomes were rinsed with water, ground, and sieved. The powder was extracted in a maceration apparatus with 500 mL of 98% EtOH for 24 h. The filtrate was collected and rotary evaporated.	Not described.	PMBC obtained from female healthy subjects.	The isolated PBMCs were cultured in 12-well plates with the TNF-α 100 pg/ mL for 72 h in RPMI, supplemented with 100 U/mL penicillin-streptomycin and 10% FBS as a treatment group. The untreated group was a PMBC group without TNF-α induction and only received 100 U/mL penicillin-streptomycin and 10% FBS. After being induced by TNF-α, the PBMCs were treated with *A. galanga* extract for 24 h, and the total RNA from PMBC culture was extracted with TRIzol.	Not described.	Data were presented as the mean ± SD. The statistical significance of differences between the groups was examined using ANOVA with post-hoc Fisher's LSD analysis. The statistical significance of differences between the two groups was examined using paired *T*-test analysis. Differences were considered to be significant when $p < 0.05$.	Treatment with *A. galanga* extract significantly increased the anti-inflammatory cytokine IL-10 and transforming growth-factor-beta (TGF-β) in a concentration-dependent manner. This result indicated that the secondary metabolite compounds of *A. galanga* extract could suppress inflammation through the induction of anti-inflammatory cytokines and growth factors.	[45]

https://doi.org/10.2147/JEP.S499115

Alpinia galanga	*A. galanga* was acquired from local areas of Thiruvananthapuram, India. The plant was identified by a taxonomist at CSIR-NIIST, Thiruvananthapuram, India.	Air-dried plant rhizomes were ground to powder and extracted with hexane, followed by 70% EtOH at 27 ± 1°C for 6 h, and repeated until the solvent turned colorless. The supernatant obtained after filtration was concentrated in a vacuum rotavapor under minimal pressure, and lyophilized.	Polyphenol profiling in the extract was done using HPLC. 0.45 μM PTFE filter was used to filter the extract and standards before injection. The study was done on a Prominence UFLC system (Shimadzu, Japan) containing an LC-20AD system controller, Phenomenex Gemini C18 column (250 x 4.6 mm, 5 μm), a column oven (CTO-20A), a Rheodyne injector (USA) having a loop of 20 μL volume and a diode array detector (SPD-M20A). The flow rate was 1 mL/min, and the fractions were monitored at 280 nm.	RAW 264.7 cell lines were obtained from the American Type Culture Collection (ATCC).	Six well plates were seeded with RAW 264.7 cells at a density of 3 × 10^5 cells/cm [2] overnight. Cell-free culture supernatants after subsequent treatments were used for the detection of cytokines (TNF-α, IL-6, and IL-10) using an ELISA kit.	Dexamethasone 10 μM.	The results are represented as mean ± SD of three independent experiments. Statistical comparisons between the groups were analyzed by one-way ANOVA using GraphPad Prism 8 software (GraphPad Software, Inc). $p < 0.05$ was considered statistically significant.	Pretreatment with *A. galanga* extract (12.5, 25, 50, 100, and 200 μg/mL) significantly decreased the production of cytokines in a dose-dependent manner. IL-10 level was significantly increased upon pretreatment with *A. galanga* extract or dexamethasone (10 μM) under inflammatory conditions.	[46]
Alpinia katsumadai	The ethanol extracts of *Alpinia katsumadai* seeds were provided by COSMAX Inc. R&I Center (Seongnam, Korea).	*Alpinia katsumadai* seeds were ground to a fine powder and extracted material in 70% EtOH.	Not described.	Immortalized human gingival fibroblasts (IGFs) and immortalized human oral keratinocytes (IHOKs) were kindly provided by the Yonsei University College of Dentistry, Oral Cancer Institute (Seoul, Korea).	The inducer used was LPS extracted from dental plaque bacteria. Parameters assessed were prostaglandin E2 (PGE2) and human cyclooxygenase-2 (COX2).	Cells were cultured in Dulbecco's modified Eagle's medium (DMEM)/F-12 medium (3:1 ratio) with 10% fetal bovine serum.	InStat GraphPad Prism ver. 5.01 statistical software (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical analysis. Non-parametric Kruskal–Wallis tests with Dunn's post hoc analysis were employed for multiple comparisons. The data are expressed as the mean ± SEM. $p < 0.05$ was considered statistically significant.	The extracts revealed potential anti-inflammatory activity by significantly decreasing the high levels of PGE2 and COX-2 induced by dental plaque bacteria–fLPS (DPB-LPS) and *Porphyromonas gingivalis*–LPS (PG-LPS). The dose variations used were 1 μg/mL, 5 μg/mL, and 10 μg/mL, where a higher decreasing ability was indicated by the 10 μg/mL treatment in IGF, IHOK, and RAW264.7 macrophage cells.	[47]

(*Continued*)

https://doi.org/10.2147/JEP.S499115

Table 2 (Continued).

Botanical name	Part of the plant, collected in and authenticated by	Extraction method	Phytochemical analysis	Animals, ethical approval committee	Model category, inducer, and parameter assessed	Control drug and dosage	Statistical analysis	Results and statistical difference	Reference
In Vivo Studies									
Alpinia officinarum	The dried root was collected from an Ayurvedic pharmacy, in Chennai, India. The plant was authenticated by a botanist from the Institute of Herbal Botany Plant Anatomy Research Centre, Chennai.	The rhizome of *A. officinarum* was shade-dried and ground to a fine powder. The powder obtained was successfully extracted in n-hexane, filtered, and dried under reduced pressure in a rotary flash evaporator.	Not described.	Male Wistar rats weighing 150–200 g were obtained from The King Institute of Preventive Medicine, Chennai. The animals were housed in a well-aerated room under 12 h light/dark cycle for 1 week, before the experiment. Food and water was provided ad libitum. All experiments were approved by the Institute Animal Ethics Committee (IAEC) No.15/01/2012.	The animals were randomly divided into four groups (n = 6). Acute colitis was induced by administration of 5% DSS in drinking water for 5 days. Chronic colitis was induced by the administration of 5% DSS for the first 9 days and was subsequently decreased to 2% for the next 18 days. At the end of the experimental period, the rats were fasted overnight and were anesthetized the next morning with ketamine hydrochloride, intravenously (30 mg/kg BW). Blood was collected in heparinized tubes and serum was separated by centrifugation at 4000 rpm for 10 min at 4°C to analyze the hematological profile. The colon and liver tissue samples were collected. The length and weight of the colon were measured. Colonic damage was assessed for indirect (DAI score) and direct measures (macroscopic and microscopic damage) and MPO activity.	Not described.	All results were expressed as mean ± SD for six animals in each group. The data obtained were evaluated with SPSS 16 software. Hypothesis testing methods included one-way ANOVA followed by an LSD test. $p < 0.05$ was considered to indicate statistical significance.	All rats with DSS-induced colitis progressively showed weight loss and manifested with bloody diarrhea. Administration of *A. officinarum* extract during DSS induction prevented this weight loss. DSS induced animals, co-treated with the hexane extract of *A. officinarum* (200 mg/kg body wt), effectively suppressed colonic injury that was evidenced by the reduced DAI score, colon weight/length ratio, histological damage, proinflammatory markers and MPO activity. Further, it restored the colonic antioxidants near to normal levels by regulating the oxidative stress via attenuation of lipid peroxidation.	[18]
Alpinia officinarum	Dried *Alpinia officinarum* was purchased from KOCBiotech (Daejeon, Korea).	Dried *A. officinarum* (1 kg) was extracted in 10 L of distilled water under circumfluence for 3 h at 100 ± 2°C and lyophilized after filtration (53 μm mesh). The dried powder was stored at – 20°C until further use.	The HPLC analysis of galangin, protocatechuic acid, and epicatechin in the extract was performed with a Waters e2695 liquid chromatography system, equipped with a Waters 2998 PDA detector. The separation was carried out using the Phenomenex Luna C18 column (250 mm × 4.6 mm; particle size 5 μm) and detected at 270 nm. The mobile phase consisted of 0.1% aqueous formic acid (A) and acetonitrile (B) in gradient elution. The flow rate was 1.0 mL/min and the injection volume was 20 μL.	Male NC/Nga mice (8 weeks old) were obtained from Central Lab Animal Inc. (Seoul, Korea). The mice were housed under specific pathogen-free and controlled conditions (6 mice/cage). The mice were given access to a standard laboratory diet and tap water ad libitum and provided with corncob natural bedding material. All animal experiments were approved by the Institutional Animal Care and Use Committee at the Korea Institute of Oriental Medicine (KIOM).	After acclimatization for 7 d, the mice were randomly divided into different experimental groups: normal (untreated), AD (*Dermatophagoides farina* extract/DfE only), AD-*A. officinarum* (30, 100, and 300 mg/kg), and AD-Dexamethasone. The shaved dorsal skin and ear barrier of NC/Nga mice were disrupted by 150 μL of 4% SDS, and after 3 h, 100 mg of DfE was applied. Mice were treated with DfE twice per week for a total of 3 weeks. Seven days after the final DfE application, each dose of *A. officinarum* or dexamethasone was orally administered daily for 14 d. The blood samples were collected on the 23rd day, and the total levels of IgE, MDC, and RANTES were measured.	Dexamethasone.	Data were analyzed using the GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). The data are represented as means ± SEM and calculated using the one-way ANOVA. A p-value of < 0.05 was considered to indicate statistical significance. All experiments were performed at least in triplicate.	Serum levels of MDC, RANTES, and IgE were considerably higher following DfE treatment than in the non-induced group. The water extract of *A. officinarum* or dexamethasone, when administered orally, significantly reduced MDC, RANTES, and IgE blood levels.	[19]

Alpinia officinarum	The rhizomes of *A. officinarum* (Chinese origin) were collected and authenticated by a botanist at KPEB (Korea Plant Extract Bank https://portal.kribb.re.kr/kpeb, Daejeon, Korea), where the voucher specimen was deposited.	The rhizomes were dried, powdered, and extracted with distilled water for 2.5 h at 100°C. The supernatant was filtered, concentrated, and lyophilized using a freeze-dryer.	HPLC/MS analysis was performed on an AQUITY Ultra Performance LC system (Waters, San Jose, CA, USA) coupled with a Micromass Q-Tof Premier mass spectrometer (Waters). The extract was separated on an ACQUITY UPLC™ BEH C18 column (100 mm × 2.10 mm, 1.7 µm, Thermo Fisher Scientific) by using a flow rate of 0.4 mL/min at 40°C. The mobile phase of eluent A (aqueous formic acid solution, 0.1% v/v) and eluent B (acetonitrile with formic acid, 0.1%, v/v). The Micromass Q-Tof Premier MS and spray chamber conditions were a capillary temperature of 350°C and a source voltage of 2.3 kV.	Six-week-old hairless mice (SKH-1, female) were obtained from Orientbio Inc. (Seoul, Korea). The mice were housed under pathogen-free conditions with a temperature of 23 ± 2°C, humidity of 50 ± 10%, and 12 h light/dark cycle.	The mice were divided into four groups (n = 5 per group): nontreated (control), UVB-irradiated (UVB), UVB-irradiated with pretreatment using *A. officinarum* extract 25 µg/mL, and UVB-irradiated with pretreatment using *A. officinarum* extract 50 µg/mL. *A. officinarum* extract was dissolved in propylene glycol/ethanol (7:3) at a concentration of 25 µg/mL and 50 µg/mL. 100 µL of each solution was treated to the dorsal areas of the hairless mice, and UVB was irradiated using a microprocessor-controlled UV irradiation system (BIO-LINK 312, VILBER).	Not described.	All experiments were performed in triplicate and repeated three times. All data are presented as mean ± SD. Two-tailed, unpaired Student's *T*-test and ANOVA and Tukey's post hoc multiple comparisons using Prism 5 (Graph-Pad Software, San Diego, CA, USA) were used for statistical analysis. $p < 0.05$ was considered statistically significant.	The water extract of *A. officinarum* rhizomes when applied on the dorsal skin of UVB-irradiated hairless SKH-1 mice was found to dramatically attenuate the wrinkle formation and epidermal thickening in the skin, and to attenuate the expression of MMP-1a and COL1A1, and recovered the reduction of collagen content.	[48]
Alpinia oxyphylla	*A. oxyphylla* was purchased from Kwangmyoungdang Pharms (Ulsan, South Korea). The plant was authenticated at the Korean Herbarium of Standard Herbal Resources of Korea Institute of Oriental Medicine (2–17–0580, Daejeon, South Korea).	The plant material was extracted twice with 50% EtOH with a 4 h reflux. The extract was passed through filter paper, concentrated under reduced pressure, dried, and stored at 4°C. The yield was 12%.	An Agilent HPLC 1200 series system equipped with a quaternary pump, autosampler, and PDA detector with a Phenomenex® Luna C18 column (250 × 4.6 mm, 5 µm) was used for analysis. Gradient elution with solvent A (deionized water, E-Pure ≥18.0 MΩ/cm) and solvent B (MeOH) at a flow rate of 1 mL/min was carried out. The detection was set at 245 nm. The column temperature was maintained at 30°C, and the injection volume was 10 µL.	Male Sprague-Dawley rats (7 weeks old, 190–210 g) were purchased from Orient Bio, Seongnam, Korea. After acclimation, the rats were housed separately in cages and were familiarized with the testing procedures.	The rats were then divided randomly into six groups of five animals each: (1) control group, (2) MIA group with MIA injection, (3–5) *A. oxyphylla* extract-treated group (150 and 300 mg/kg) with MIA injection, and (6) indomethacin (IM)-treated group (1 mg/kg) with MIA injection. The MIA solution (3 mg/50 µL of 0.9% saline) was injected directly into the intra-articular space of the right knee while the rats were under anesthesia with a mixture of ketamine (25 mg/0.5 mL) and xylazine (20 mg/0.2 mL). The rats received 2 mL of *A. oxyphylla* extract orally and IM 3 days before MIA injection and then once daily for 21 days. After treatment with *A. oxyphylla* extract, no evidence of systemic adverse effects was observed in any study group. Blood samples were centrifuged at 1500 g for 10 min at 4°C, and the serum was collected and stored at −70°C until use.	Indomethacin 1 mg/kg.	The results are expressed as the mean ± SEM and analyzed using one-way ANOVA followed by Dunnett's tests for multiple comparisons or unpaired Student's t-tests for two-group comparisons. All analyses were performed using Prism 7.0 (GraphPad Software, San Diego, CA, USA). *p*-values < 0.05 were considered statistically significant.	When *A. oxyphylla* extract was administered to rats with osteoarthritis induced by MIA, serum levels of pro-cytokines LTB4, IL-1β, and IL-6 were considerably reduced. *A. oxyphylla* extract therapy resulted in a decrease in serum TNF-α levels but was not statistically significant. Furthermore, the control group exhibited significantly higher mRNA levels of IL-6, TNF-α, iNOS, COX-2, MMP-2, and MMP-9 in the cartilage, as well as higher expression levels of all cytokines, whereas the *A. oxyphylla* extract-treated groups tended to have lower values, thus suggesting that *A. oxyphylla* extract modulated inflammatory cytokines, lowered inflammation, and preserved cartilage in MIA-induced osteoarthritis models.	[41]

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https://doi.org/10.2147/JEP.S499115

https://doi.org/10.2147/JEP.S499115

Table 2 (Continued).

Alpinia oxyphylla, known as Yi Zhi Ren (YZR), is a traditional Chinese herb	The extract powder was obtained from Chuang Song Zong Pharmaceutical Co., Ltd. (Kaohsiung, Taiwan).	2 g of the extract powder was dissolved with 8 mL of double-distilled water. The final concentration of the aqueous extract was maintained at 0.1 g/mL.	The standards of protocatechuic acid, chrysin, and nootkatone were precisely weighed and dissolved in absolute MeOH. 2 g of the extract powder was dissolved in 100 mL of absolute MeOH and the solution was ultrasonic-shaken at room temperature for 30 min, and filtered. Subsequently, HPLC measurements were conducted using 20 μL of the standard or sample solution, injected into the Waters HPLC system, which consists of the Waters 2690 Separations Module and Waters 2996 Photodiode Array Detector. The HPLC profile of the extract was determined using a C18 column (Cosmosil 5C18-AR-II, 4.6 mm I.D. × 250 mm, 5 μm). The mobile phase consisted of water with 0.1% phosphoric acid (A) and acetonitrile with 0.1% phosphoric acid (B) in gradient elution processes. The flow rate of the mobile phase was 1.0 mL/min, and the total run time was 85 min. The effluent was monitored by a PDA detector at 254 nm.	151 adult male Sprague–Dawley rats, 8–9 weeks old and weighting 290–330 g were purchased from BioLASCO Co., Ltd., Yilan, Taiwan. The animals were housed under the conditions of controlled temperature (22–24°C), humidity (50–55%), and lighting cycle (12/12-h light/dark). All experimental procedures were approved by the Institutional Animal Care and Use Committee of China Medical University (CMUIACUC-2019-312).	The rats were randomly divided into 5 groups (n = 5–6): Sham, Control, YZR-0.2 g, YZR-0.4 g, and YZR-0.8 g groups. The rats in the YZR-0.2 g, YZR-0.4 g, and YZR-0.8 g groups were IP injected with the YZR extract at the doses of 0.2, 0.4, and 0.8 g/kg, respectively, after the initiation of MCAo. After 90 min of ischemia followed by 1 day of reperfusion, the rats were euthanized by CO_2 inhalation, and their brains were immediately removed. The rats in the Control group were subjected to the identical protocols of the YZR-0.8 g group, except that the rats were injected with normal saline instead of the YZR extract. The rats in the Sham group were subjected to the identical protocols of the Control group, except that the MCA was not occluded. All rats were anesthetized with isoflurane (5% and 2% isoflurane for induction and maintenance, respectively). The head was fixed in the stereotaxic frame and a burr hole was drilled into the skull (2.0 mm posterior and 2.5 mm lateral to the right from the bregma) to expose the distal territory of the middle cerebral artery (MCA). A 3-cm midline neck incision was made to expose the right external carotid artery (ECA) and internal carotid artery (ICA). A 3–0 nylon suture with a heat-blunted tip was carefully inserted into the lumen of the right ICA through the stump of the ECA and was advanced up to the origin of the MCA. After 90 min, the suture was withdrawn to permit reperfusion. Blood flow in the MCA was monitored using a Laser-Doppler flowmetry. Successful establishment of MCAo was defined as a reduction in the MCA blood flow to 20–30% of baseline in the ischemic period and an increase in MCA blood flow to 60% of baseline in the reperfusion period. The rats subjected to incomplete MCAo were excluded from the study.	Not described.	The normality test was performed on all data by Kolmogorov–Smirnov test with a significance level of 0.05. All numeric data, except for neurological function scores, follow the normal distribution ($p > 0.05$). The data were evaluated using one-way ANOVA followed by Bonferroni post-hoc test, and the data were expressed as mean ± standard deviation. p values < 0.05 were considered as statistically significant.	The extracts of *A. oxyphilla* doses of 0.4 g and 0.8 g significantly reduced cerebral infarction (both $p < 0.05$), attenuated neurological deficits, and suppressed the expression of phospho-apoptosis signal-regulating kinase 1 (p-ASK1)/ASK1, tumor necrosis factor receptor-associated factor 3 (TRAF3), TRAF3-interacting JNK-activating modulator (T3JAM), ionized calcium-binding adapter molecule 1 (Iba1), p-JNK/JNK, iNOS, COX-2, TNF-α, TLR4, glial fibrillary acidic protein (GFAP), NF-kappaB, and IL-6 in the penumbral cortex at 1 day after reperfusion.	[49]

Alpinia oxyphylla, known as Yi Zhi Ren (YZR), is a traditional Chinese medicine	The decoction pieces of YZR fructus (Beijing Greenfield Pharmaceutical Co., Ltd.; Lot. Number 20122801) were identified by Prof. JIN Shiyuan, Master of National Physician and Professor of Capital Medical University, as the dried fruits of *A. oxyphylla* Miq processed with salt-water.	The decoction pieces were soaked in 10 x water (v/w) for 30 min and then reflux-extracted for 1 h. The extraction process was repeated twice. Subsequently, the extraction solution was filtered, combined, vacuum-concentrated, and freeze-dried into powder with an approximate extraction rate of 10%.	The extract was dissolved in water while the chrysin and tectochrysin were dissolved in 50% MeOH-water (v/v). All the solutions were filtered by 0.22 µm filters and analyzed in the Agilent 1260 hPLC system with an Alltima HPLC C18 column (250 mm × 4.6 mm, 5 µm) at room temperature, and the mobile phase consisted of 0.1% formic acid (A) and acetonitrile (B) in gradient elution. The UV absorbance was detected at 254 nm. The injection volume was 10 µL and the flow rate was 0.6 mL/min.	9-week-old male spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats were provided by Beijing Vital River Laboratory Animal Technology Co., Ltd (SCXK 2021–0006). The rats were housed in the National Standard Laboratory of Capital Medical University (SYXK 2021–0030) under standard conditions (a 12 h on/12 h off light cycle, 20–25°C room temperature, and 40–50% relative humidity). During the whole experimental period, the animals were given soybean-free chow and allowed to drink water ad libitum. All experimental protocols were approved by the animal ethics committee of Capital Medical University (Approval No. AEEI-2021–249).	SHR rats were randomly divided into five groups: a model group, a positive control group (darifenacin, 3 mg/kg/day), and low- (10 mg/kg/day), middle- (30 mg/kg/day), and high-dose (90 mg/kg/day) groups of YZR water extract, respectively (p.o). Approximate 9 g of crude material per day is close to the highest recommended clinical dose in Chinese Pharmacopoeia v.2020; the water extraction yield of YZR was approximately 10%, and 90 mg/kg/day of YZR was approximately equivalent to the human dose of 9 g crude herbs/day, as calculated based on body surface area. The WKY rats served as the normal control and received an equal volume of distilled water. After a 3-week administration, some rats in each group were sacrificed with CO_2 for the collection of abdominal aortic blood, bladder, and prostate tissues immediately. Other rats were subjected to conscious free-moving cystometry and transcriptomics.	Darifenacin 3 mg/kg/day, the first-line M3 receptor inhibitor for OAB treatment, was used as the control drug.	All data were expressed as mean ± SEM. The statistical analysis was carried out in GraphPad prism v.8. The unpaired *t*-test was used to compare the means between the WKY and SHR groups while the means among SHR and YZR groups were compared by one-way ANOVA. *p* value < 0.05 was set for statistical significance.	The water extract of *A. oxyphylla* fructus administered orally for 3 weeks to a vascular disorder-related OAB spontaneous hypertensive rats, significantly improved the bladder storage parameters, tightened the detrusor layer, reduced inflammatory infiltration, and decreased collagen proportion in the rats' bladder. These effects were caused by the reduction of TGFβ1, p-SMAD3, collagen III, Gq, and PLCβ1, involved in collagen synthesis and calcium signaling pathways. It was predicted that sitosterol, chrysin, and nootkatone were responsible for these pharmacological activities.	[50]

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https://doi.org/10.2147/JEP.S499115

Table 2 (Continued).

Alpinia zerumbet (Pers). B. L. Burtt and R. M. Smith	Fresh leaves were collected from Zoo Garden, Giza, Egypt in May 2014. Plant identity was confirmed by Dr. Tearse Labib, Department of Flora and Taxonomy, El-Orman Botanical Garden, Giza, Egypt.	Dry powdered leaves were macerated in MeOH. The extract was concentrated using a rotatory evaporator at 40 ± 2°C. The crude MeOH extract (150 g) was defatted by petroleum ether (60–80°C), yielding 115 g after freeze-drying.	Not described.	The animals used were rats and Swiss Albino mice. All animals were obtained from the Faculty of Veterinary Medicine, (Zagazig, Egypt), and acclimatized to the experimental conditions for 1 week before starting each experiment. Animals were housed in a light-controlled room with a 12 h light/dark cycle and constant ambient humidity. They were allowed free access to food and water. All experimental procedures and animal care methods in this study were approved by the Ethical Committee of the Faculty of Pharmacy, Zagazig University for Animal Use, Egypt.	Anti-inflammatory activity determined with carrageenan-induced hind-paw edema in rats, recruitment of leukocytes to the peritoneal cavity in mice, acetic acid-induced vascular permeability in mice, anti-nociceptive activity by hot plate test in mice, induction of pyrexia in mice using brewer's yeast, anti-nociceptive activity by acetic acid-induced abdominal writhing in mice.	Diclofenac 20 mg/kg per oral.	ANOVA or repeated-measures analysis of variance (RM-ANOVA), after which Tukey's post hoc test and Student's *t*-test were used to state differences between groups using Graph Pad Prism version 5. Data are expressed as mean ± SEM.	The methanol leaf extract elicited an inflammatory response in rats, as evidenced by an increase in paw thickness evaluated hourly for 5 h and 24 h after injection. Rats pretreated with the extract (200 and 400 mg/kg, per oral) 1 h earlier showed a dose-dependent reduction in edema thickness values by 33 and 55% of the control values, respectively. The treatment of the latter dose was stronger than that shown in rats given with the usual anti-inflammatory drug, diclofenac (20 mg/kg, per oral), which only reduced edema thickness by 40% compared to control rats. Thirty-seven compounds were characterized in compound profiling using HPLC-ESI-MS/MS. These compounds consist of flavonoids (aglycones and glycosides) and benzoic and cinnamic acid derivatives.	[42]
Alpinia zerumbet (Pers). B. L. Burtt and R. M. Smith	The plants were collected in Zhenfeng County, Guizhou Province, China, in October 2013. The fruit was identified by Professor Zuyun Chen at the Department of Pharmacognosy and Medico-botany at Guizhou Medical University.	The essential oils were extracted by steam distillation.	Not described.	Twenty-four adult male Konmin mice, weighing 18–22 g, were purchased from Guizhou Laboratory Animal Engineering Technology Center (Guiyang, China) and housed in a temperature- and humidity-controlled environment (12-h light/dark cycle) with unlimited access to water and standard chow. All animal experiments were approved by an independent Animal Care and Use Committee of Guizhou Medical University (Guiyang, China) and all animal experimental procedures were performed following the Guide for the Care and Use of Laboratory Animals.	Mice were randomly divided into four groups as follows: two groups were treated with varying doses of essential oils of *A. zerumbet* and the other two groups were treated with 0.5% Tween-80 solution in saline for 7 days by intragastrical administration daily. After 7 days of treatment, the vehicle control group received saline, mice in the other three groups were administered with LPS by intraperitoneal injection. 24 hours later, the mice were sacrificed. Aorta tissue was collected and frozen immediately in liquid N_2, stored at −80°C	Not described.	Statistical significance was calculated by one-way ANOVA and multiple comparisons were carried out by Dunnett's post hoc test (2-sided). A value of $p < 0.05$ was considered significant. Data are expressed as mean ± SD. Each experiment was performed in triplicate	The essential oils of *A. zerumbet* reduced the expression of ICAM-1 and VCAM-1 produced by endothelial cells and activated NF-kappa B signaling, making it an effective anti-inflammatory drug.	[43]

https://doi.org/10.2147/JEP.S499115

Alpinia zerumbet (Pers). B. L. Burtt & R. M. Smith	The dried and ripe fruits were authenticated and deposited at the Herbarium of Traditional Chinese Medicine and Ethnic Medicine, Guizhou Medical University (Guizhou, China).	The extraction procedure was not described in detail. The total yield of the extract was approximately 1.3%.	Not described.	C57BL/6J male mice 8 weeks, including wild-type (WT) and ApoE−/− mice. All animal protocols were approved by the Ethical and Welfare Committee of Guizhou Medical University. The mice were maintained in an environment (25°C) under a 12 h light/12 h dark cycle with sufficient food and water. WT mice (control) were maintained with a standard diet. ApoE−/− mice were treated with an HFD (1.25% cholesterol, 40% fat).	The ApoE−/− mice were injected every 4 weeks with lentivirus carrying short hairpin RNA (shRNA) targeting PPAR-γ via the tail vein for PPAR-γ knockdown.	Atorvastatin and rosiglitazone.	Statistical significance was calculated by one-way ANOVA and multiple comparisons were carried out by Dunnett's post hoc test (2-sided). $p < 0.05$ was considered significant. Data are expressed as mean ± SD. Each experiment was performed in triplicate.	Essential oil of fructus *A. zerumbet* attenuated atherosclerosis progression in HFD ApoE−/− mice which manifested by the reduced aortic intima plaque development, increased collagen content in aortic plaques, notable improvement in lipid profiles, and decreased levels of inflammatory factors. Essential oil of *A. zerumbet* inhibited the formation of MFCs by enhancing cholesterol efflux by activating the PPARγ-LXRα-ABCA1/G1 pathway. Essential oil of *A. zerumbet* indicates the reduction of the ubiquitination degradation of PPARγ, and its chemical composition directly bound to the PPARγ protein, thereby increasing its stability. Finally, PPARγ knockdown mitigated the protective effects of Essential oil of *A. zerumbet* on atherosclerosis HFD ApoE−/− mice.	[34]
Alpinia purpurata	The leaves were collected from Kanyakumari, Tamil Nadu, India. The plant specimen was authenticated by Dr. G. V. S. Murthy, Botanical Survey of India, Coimbatore, TNAU campus, India.	The leaves of *A. purpurata* were washed thoroughly in tap water, shade-dried, and powdered. Pre-weighted plant powder (100 g) was exhaustively extracted with EtOAc in the ratio of 1:5 for 24 h by using a Soxhlet apparatus. The extract was completely evaporated to dryness using a rotary flash evaporator at 40°C. The dried EtOAc extract was dissolved in sterile water and pre-treated in rats using an oral gavage tube.	Not described.	Adult male Wistar Strain of albino rats weighing about 160–180 g was procured from Karpagam University, Animal House, Coimbatore, India. The rats were housed in large spacious polyurethane cages under hygiene conditions with 12 h light–dark cycle and were allowed to consume an adequate amount of standard diet for 16 weeks and water given ad libitum. The guidelines prescribed by CPCSEA were strictly followed and the study was approved by the Institutional Animal Ethical Committee of Karpagam University (No. KU/IAEC/Ph.D/123 dated 21.09.2013).	The animals were divided into five groups, (1) normal healthy rats; (2) rats in the negative control, were intraperitoneally injected with testosterone (T) at a daily dose of 100 mg/kg for 3 days to induce prostate cancer; (3) rats in the positie control group, were treated as group 2 along with finasteride at a dose of 25 mg/kg, supplemented for 2 months; (4) rats at dose 1 of ethyl acetate extract of *A. purpurata*, were treated as group 2 and simultaneously treated with a daily dose of 200 mg/kg of the extract through oral gavage for 2 months; and (5) rats at dose 2 of ethyl acetate extract of *A. purpurata* received a daily dose of 200 mg/kg of the extract through oral gavage for 2 months.	Finasteride at a dose of 25 mg/kg.	Results are expressed as the Mean ± SD. Statistical significance was evaluated by one-way ANOVA using SPSS version 16.0 and the individual comparisons were obtained by the Duncan multiple range test (DMRT). A value of $p < 0.05$ was considered to indicate a significant difference between groups.	Histopathological observation of hepatic tissue in the normal group demonstrated normal morphology of hepatocytes surrounding periportal lobules. Rats in group 2 (prostate cancer-induced) showed periportal inflammatory cell infiltration with sinusoidal congestion and the regeneration of fatty cell changes with hepatic cell necrosis. Rats treated with the standard drug finasteride (group 3) confirmed minimal hemorrhagic necrosis in focal areas of hepatocytes. Rats in group 4 showed minimal congestion in focal areas with minimal inflammatory sites of hepatocytes. This confirms that rats treated with *A. purpurata* showed normal morphological appearances when compared to the negative control group.	[51]

(*Continued*)

https://doi.org/10.2147/JEP.S499115

https://doi.org/10.2147/JEP.S499115

Table 2 (Continued).

Alpinia galanga	The rhizomes were collected from herbal medicine raw material supplier in Chennai, India. The rhizomes were authenticated by Siddha Central Research Institute, Chennai, India.	Not described.	Not described.	Inbred male Wistar-Lewis rats were selected for the study. The animals were maintained on a 12 h/12 h day/night cycle with free access to food and water. The procedures were approved by the Institutional Animal Ethical Committee (Meenakshi Medical College and Research Institute).	Various doses of the ethanolic extract of *A. galanga* (100–400 mg/kg) were prepared as a fine suspension in 0.5% CMC and given per oral 30 min before the testing procedure. The animals were given 0.25 mL of an intrapleural injection of 1% carrageenan on the right side of the thorax. The animals were sacrificed 3 h after carrageenan injection by ether inhalation. 1 mL of heparinized Hank's solution was injected into the pleural cavity and gently massaged to mix its contents. The fluid was aspirated out of the cavity, and the exudates were collected. The number of migrating leukocytes in the exudate was determined with Neubauer chamber.	Indomethacin 10 mg/kg.	The results were analyzed using one-way ANOVA followed by paired *t*-test utilizing GraphPad Instat software version 3.1. $p < 0.05$ was considered to be statistically significant.	The extract of *A. galanga* rhizome reduced the exudation effect in the inflammatory edema in a dose-dependent manner (100–400 mg/kg) and *A. galanga* 200 mg/kg and 400 mg/kg significantly inhibited the total leukocyte influx.	[52]

Abbreviations: ABCA1, ATP-binding cassette transporters A1; ANOVA, analysis of variance; APCI, atmospheric pressure chemical ionization; CC, column chromatography; CCK-8, cell counting kit-8; COL1A1, procollagen type-1; DAI, disease activity index; DMEM, Dulbecco's modified eagle medium; DMSO, dimethyl sulfoxide; DSS, dextran sulfate sodium; ECM, endothelial cell medium; EIA, enzyme immunoassay; ERK, extracellular signal-regulated kinase; ESI, electrospray ionization; EtOAc, ethyl acetate; EtOH, ethanol; FBS, fetal bovine serum; GES-1, human gastric mucosal epithelial cells; HaCaT, an immortalized human keratinocyte cell line; HAEC, primary human aortic endothelial cells; HPLC, high-performance liquid chromatography; HT29, human colon tumor cell line; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-gamma; IP-10, interferon-induced protein of 10 kDa; I-TAC, interferon-induced T cell α-chemoattractant; JNK, Jun N-terminal kinase; LC, liquid chromatography; L-NMMA, N-methyl-L-arginine acetate salt; LSD, least significant difference; LPS, lipopolysaccharide; LXRα, liver X receptor alpha; MAPK, mitogen-activated protein kinase; MDC, macrophage-derived chemokine; MFC, macrophage-derived foam cells; MIA, monosodium iodoacetate; MMP-1a, metalloproteinase-1a; MPO, myeloperoxidase; NAG-1, nonsteroidal anti-inflammatory drug-activated gene; OAB, overactive bladder; OD, optical density; PDA, photodiode array; PE, petroleum ether; PBMC, peripheral blood mononuclear cells; PPARγ, peroxisome proliferator-activated receptor gamma; RANTES, regulated on activation, normal T-cell expressed and secreted; SD, standard deviation; SDS, sodium dodecyl sulfate; SEM, standard error of the mean; STAT1, signal transducer and activator of transcription 1; TNF-α, tumor necrosis factor-alpha; UHPLC-DAD-MS, ultra-high performance liquid chromatography-diode array detector-mass spectrometry; VCAM-1, vascular cell adhesion molecule-1.

understanding various proteins and cytokines involved in the pathogenesis of inflammation will provide a broader insight into how immunomodulatory activity studies of plant extracts were designed.

In vitro Anti-Inflammatory Activities of Alpinia

The anti-inflammatory activities of *Alpinia* have been broadly reported in numerous in vitro studies, with the most reported being *A. officinarum*, *A. oxyphylla*, *A. zerumbet*, *A. calcarata*, *A. galanga*, and *A. katsumadai* (Table 2).

Alpinia officinarum

Alpinia officinarum, known as lesser galangal, is used to treat a wide range of symptoms including stomach ache, swelling, inflammation, and gastrointestinal ailments. The primary active phytochemical of *A. officinarum* is a flavonol named galangin (synonym: 3,5,7-trihydroxy flavone or 3,5,7-trihydroxy-2-phenyl-4H-chromene-4-one; molecular formula $C_{15}H_{10}O_5$; PubChem CID 5281616).[40,53] Galangin works at multiple target sites such as nitric oxide synthase (NOS), COX-1 and COX-2, androgen, peroxisome proliferator-activated receptor, dipeptidyl peptidase-IV, and serine/threonine-protein kinase,[41] and suppresses extracellular signal-regulated kinase (ERK) and NF-kappaB-p65 phosphorylation, which leads to anti-inflammatory activity.[53]

Bioactive metabolites in *A. officinarum*, such as galangin, 3-methyl galangin (synonym: 3-O-methyl galangin or galangin 3-methyl ether; molecular formula $C_{16}H_{12}O_5$; PubChem CID 5281946), and kaempferide (synonym: 4'-methyl kaempferol or 4'-O-methyl kaempferol; molecular formula $C_{16}H_{12}O_6$; PubChem CID 5281666), contributed to anti-inflammatory responses.[8,17] An in vitro experiment of the ethanol extract of *A. officinarum* rhizome, collected from Haikou County, Hainan Province, China, in October 2017, was conducted on ethanol-exposed human gastric epithelial cells (GES-1). The apoptosis rate of GES-1 cells induced by ethanol was considerably greater compared with that of the normal group. In this study, the flavonoids significantly lowered the apoptosis rate compared with that of the ethanol model group. Western blotting and quantitative polymerase chain reaction (qPCR) techniques revealed that the flavonoids increased the expression of Bcl-2 protein and gene while lowering that of Bax and caspase-3 proteins and genes. Furthermore, the results showed that the flavonoids of *A. officinarum* enhanced the number of cells that passed through the polycarbonate membrane and considerably reduced the degree of damage caused by ethanol in GES-1 cells.[17]

The effects of n-hexane extract of *A. officinarum*, collected from an Ayurvedic pharmacy in Chennai, India, were studied on the mRNA expression of NF-kappaB and COX-2 in cultured human colon tumor cell line HT29 (obtained from NCCS, Pune). The cells were treated with different concentrations of the extract (0.5, 1, 2.5, 5, 7.5, 10 μg), and the treated cells showed a significant decrease in the mRNA expression levels of NF-kappaB and COX-2 as compared to untreated cells.[18]

A. officinarum, purchased from KOCBiotech (Daejeon, Korea), was studied on human epidermal keratinocyte (HaCaT) cells. Dried *A. officinarum* was extracted in distilled water under circumfluence for 3 h at 100 ± 2°C, and lyophilized after filtration to obtain the water extract. The cells were stimulated with interferon-gamma (IFN-γ) and TNF-α (each 10 ng/mL). When treated with nontoxic doses of 50, 100, and 300 μg/mL of *A. officinarum* water extract, there was a noticeable inhibition of macrophage-derived chemokine (MDC), regulated on activated normal T-cell expressed and secreted (RANTES), interferon-induced protein of 10 kDa (IP-10), and interferon-induced T cell α-chemoattractant (I-TAC) secretion. Furthermore, the IFN-γ/TNF-α exposure on the cells which activated the STAT1 and NF-kappaB subunits (p65 and p50) in the nucleus, was inhibited by *A. officinarum* extract, thus suggesting that the water extract of *A. officinarum* exhibited anti-inflammatory effects due to its inhibitory action on MAPK phosphorylation, NF-kappaB, and STAT1.[19]

Alpinia oxyphylla

A. oxyphylla is abundantly grown in Asia and is widely utilized in oriental medicine. A study reported the plants, purchased from Kyung-Dong Market in Seoul, Korea, that were extracted with ethanol 70% at 70°C for 48 h with stirring at 500 rpm. The resulting *A. oxyphylla* extract was filtered and vacuum-concentrated, and the concentrate was diluted in dimethyl sulfoxide to obtain a final concentration of 100 mg/mL. The extract was reported could increase the

nonsteroidal anti-inflammatory drug-activated gene (NAG-1) expression and suppress cyclin D1 expression levels in various human colon cancer cell lines (HCT-116, SW480, DLD-1, and HT-49).[21]

The ethanol extract of *A. oxyphylla* fruits, purchased from Ulsan, South Korea, significantly decreased the production of NO (68.2%), PGE_2 (92.8%), IL-1β (77.2%), IL-6 (39.9%), and TNF-α (20.7%) and showed the activation of extracellular signal-regulated kinase (ERK), Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) in lipopolysaccharide-treated RAW264.7 cells at a dose of 100 µg/mL.[41]

Alpinia zerumbet

A. zerumbet grows widely from East Asian countries to South America. The leaves, rhizomes, fruits, seeds, and flowers have been exploited to treat various ailments.[54]

The methanol extract of *A. zerumbet* leaves, collected from Zoo Garden, Giza, Egypt in May 2014, was reported to be successfully inhibiting COX-1 comparable to that of diclofenac, inhibiting COX-2 with half the potency of celecoxib, and inhibiting LOX with nearly double the potency of zileuton, a LOX inhibitor.[42]

The essential oil of *A. zerumbet* fruits, collected in Zhenfeng County, Guizhou province, China, in October 2013, completely prevented LPS-induced human aortic endothelial cells (HAEC) activation and inflammation in vitro, as assessed by the expression of endothelial adhesion molecules, ICAM-1 and VCAM-1. It was demonstrated that TLR4-dependent NF-kappaB signaling may be involved in the process.[43]

A recent study by Wang et al (2024) reported that the essential oil of *A. zerumbet* fruits could restrain the formation of macrophage-derived foam cells by increasing cholesterol efflux via the activation of the peroxisome proliferator-activated receptor gamma (PPARγ)-liver X receptor alpha (LXRα)-ATP-binding cassette transporters A1 (ABCA1)/G1 pathway, and decreasing the ubiquitination degradation of PPARγ. This activity was thought to be due to the direct interaction of phytochemicals to the PPARγ protein, thereby increasing the stability of the protein.[34]

Alpinia calcarata

The anti-inflammatory potential of *A. calcarata* essential oil, derived from the leaves and rhizomes, was evaluated by examining their impact on LPS-exposed NO generation in murine macrophages. Whole plants of *A. calcarata* were collected from the Western province of Sri Lanka in 2015 during the flowering season. The plants were washed, and the rhizomes and leaves were cut separately. Each part was separately hydro-distilled for 4 h using 500 mL distilled water to obtain the essential oils. After decanting, water in the oil samples was removed with anhydrous Na_2SO_4, and the essential oil was evaluated for its inhibitory towards NO production and nitrite scavenging potential in LPS-exposed RAW 264.7 cells. The essential oil demonstrated a concentration-dependent reduction in NO generation. At 50 µg/mL, the rhizome-derived essential oil displayed a maximum inhibition of 85%, whereas the leaf oil displayed 81% inhibition. L-NMMA (N-monomethyl-L-arginine acetate; empirical formula $C_7H_{16}N_4O_2.C_2H_4O_2$), an NO inhibitor, was utilized as a positive control at a dosage of 250 µM, and after treating LPS-exposed RAW 264.7 cells with L-NMMA for 24 h, 87% NO inhibition was observed.[44]

NO suppresses Th1 and increases Th2 cytokine response by boosting COX activity and synthesizing proinflammatory eicosanoids. This way, NO works a role as an inflammatory mediator. In addition, NO suppresses the expression of several cytokines in different immune cells, including lymphocytes, eosinophils, and monocytes, including IL-1β, TNF-α, IL-6, and INF-γ. However, excess NO can rapidly be oxidized to reactive nitrogen oxide species and damage numerous proteins and enzymes critical for cell survival and signaling, such as JAK/STAT proteins, NF-kappaB /IkappaB pathway, MAPK, G proteins, and transcription factors. Nitration of cysteines by reactive nitrogen oxide species to these proteins may lead to their activation or inactivation.[55,56]

Alpinia galanga

A. galanga rhizomes, collected from Tawangmangu in Central Java Indonesia in May 2021, were reported to have strong anti-inflammatory activity in an in vitro study. The rhizomes were extracted in a maceration apparatus with 500 mL of 98% ethanol for 24 h. The ethanol extract of *A. galanga* rhizomes was assayed on peripheral blood mononuclear cells (PBMCs), isolated from three healthy female participants who did not receive anti-inflammatory, antioxidant, vitamins,

and immunosuppressant therapy for a certain period. PBMC acute inflammation cells were stimulated by TNF-α 100 pg/mL and treatment with *A. galanga* significantly increased the anti-inflammatory cytokine IL-10 and transforming growth-factor-beta (TGF-β) in a concentration-dependent manner. The physiological expression levels of IL-10 might be necessary to control the inflammatory process induced by TNF-α. IL-10 inhibits the expression of pro-inflammatory cytokines including IL-6, IL-12, and TNF-α via the signal transducer and activator of the transcription 3 (STAT3) pathway. TGF-β inhibits inflammatory cytokine-induced iNOS expression in an SMAD3-dependent manner (SMAD3 proteins are mothers against decapentaplegic homolog 3 also known as SMAD family member 3).[45]

Hydroalcoholic extract of *A. galanga* downregulated the release of pro-inflammatory mediators (IL-6, TNF-α, NO, and ROS) and stimulated the release of IL-10 in LPS-exposed RAW 264.7 cells. The vital enzymes involved in inflammation (iNOS, COX-2, and MMP-9) were also downregulated by pre-treatment with hydroalcoholic extract of *A. galanga*. Pretreatment with hydroalcoholic extract of *A. galanga* significantly inhibited the phosphorylation of JNK and p38 at the protein level. Further, the extract also inhibited the nuclear translocation of NF-kappa B, thus confirming the specific inhibition of the TLR4 and JAK/STAT pathways. It is well known that the inactive form of NF-kappaB is localized in the cytosol bound to IkB, an inhibitor of NF-kappaB activation. In response to an external stimulus like LPS, IκB is phosphorylated, subsequently causing the proteasomal degradation of IκB. This is followed by the translocation of free NF-kappaB-p65 from the cytoplasm to the nucleus.[46]

Alpinia katsumadai

The anti-inflammatory activity of *A. katsumadai* was evaluated using the seed extracts. The extracts revealed potential anti-inflammatory activity by significantly decreasing the high levels of PGE2 and COX-2 induced by dental plaque bacteria–fLPS (DPB-LPS) and *Porphyromonas gingivalis*–LPS (PG-LPS). The dose variations used were 1 µg/mL, 5 µg/mL, and 10 µg/mL, where a higher decreasing ability was indicated by the 10 µg/mL treatment in immortalized gingival fibroblast (IGF), immortalized human oral keratinocyte (IHOK), and RAW264.7 macrophage cells.[47]

Vivo Anti-Inflammatory Activities of Alpinia

The anti-inflammatory activities of *Alpinia* plants have been reported in numerous in vivo studies presented in Table 2, with the most common being *A. officinarum*, *A. oxyphylla*, and *A. zerumbet.*

Alpinia officinarum

Hexane extract of *A. officinarum* dried rhizomes, collected from Ayurvedic pharmacy, Chennai, India, exhibited the ability to decrease the expression of inflammatory mediators in dextran sulfate sodium (DSS)-induced acute and chronic ulcerative colitis (UC) male Wistar rats. Both histological and immunological abnormalities observed in animal models of colitis are similar to those observed in human inflammatory bowel disease (IBD). UC is a chronic IBD linked to an immune-mediated gut problem. It arises in genetically susceptible individuals owing to dysregulated immune responses brought on by several environmental factors. The findings demonstrated that DSS-induced rats had higher expressions of pro-inflammatory mediators TNF-α and NF-kappaB, and serum levels of C-reactive proteins (CRP). When the hexane extract of *A. officinarum* co-treated rats was compared to DSS-induced acute and chronic UC rats, there was a decrease in the expression of these inflammatory mediators, and CRP levels, indicating a beneficial therapeutic effect on UC.[18]

A. officinarum water extract was tested for anti-inflammatory effects in atopic dermatitis (AD) in NC/Nga mice (an inbred mouse model bred in Japan at Nagoya University in 1957, frequently used as a human AD model for its biological properties). Following *Dermatophagoides farina* extract (DfE)-induced AD-like symptoms twice per week for 3 weeks, ear thickness was observed to be increased in NC/Nga mice. Ear thickness was evaluated twice per week using a digital caliper. The dermatitis score was determined based on edema, scarring/dryness, erythema/hemorrhage, and excoriation/erosion of the dorsal skin and ear lesions. However, oral treatment with water extract or dexamethasone (the control drug) effectively alleviated the skin complaints. Serum levels of proinflammatory chemokines, such as macrophage-derived chemokine (MDC), regulated on activation normal T-cell generated and secreted (RANTES), and IgE were considerably higher following DfE treatment than in the non-induced group. The water extract of *A. officinarum* or dexamethasone, when administered orally, significantly reduced MDC, RANTES, and IgE blood levels.[19]

 https://doi.org/10.2147/JEP.S499115

Moreover, the water extract of *A. officinarum* rhizomes (Chinese origin) when applied on the dorsal skin of UVB-irradiated hairless SKH-1 mice, was found to dramatically attenuate the wrinkle formation and epidermal thickening in the skin, and to attenuate the expression of metalloproteinase-1a (MMP-1a) and procollagen type-1 (COL1A1), and recovered the reduction of collagen content.[48]

Alpinia oxyphylla

When *A. oxyphylla* extract was administered to rats with osteoarthritis induced by monosodium iodoacetate (MIA), serum levels of pro-cytokines LTB4, IL-1β, and IL-6, were considerably reduced. *A. oxyphylla* extract therapy resulted in a decrease in serum TNF-α levels but was not statistically significant. Furthermore, the control group exhibited significantly higher mRNA levels of IL-6, TNF-α, iNOS, COX-2, MMP-2, and MMP-9 in the cartilage, as well as higher expression levels of all cytokines, whereas the *A. oxyphylla* extract-treated groups tended to have lower values, thus suggesting that *A. oxyphylla* extract modulated inflammatory cytokines, lowered inflammation, and preserved cartilage in MIA-induced osteoarthritis models.[41]

A. oxyphylla Miq, a traditional Chinese herb, is known as Yi Zhi Ren. The extract powder of Yi Zhi Ren, obtained from Chuang Song Zong Pharmaceutical Co., Ltd. (Kaohsiung, Taiwan), was dissolved with 8 mL of double-distilled water. The aqueous extracts at the doses of 0.2 g/kg, 0.4 g/kg, and 0.8 g/kg were investigated on rats' cerebral infarction at 1 day after 90 min of transient middle cerebral artery occlusion (MCAo) and the molecular mechanisms underlying the regulation of c-Jun N-terminal kinase (JNK)-mediated inflammatory cascades in the penumbral cortex was observed. The extracts of *A. oxyphilla* doses of 0.4 g and 0.8 g significantly reduced cerebral infarction (both $p < 0.05$), attenuated neurological deficits, and suppressed the expression of phospho-apoptosis signal-regulating kinase 1 (p-ASK1)/ASK1, tumor necrosis factor receptor-associated factor 3 (TRAF3), TRAF3-interacting JNK-activating modulator (T3JAM), ionized calcium-binding adapter molecule 1 (Iba1), p-JNK/JNK, iNOS, COX-2, TNF-α, TLR4, glial fibrillary acidic protein (GFAP), NF-kappaB, and IL-6 in the penumbral cortex at 1 day after reperfusion.[49]

The water extract of *A. oxyphylla* fructus administered orally for 3 weeks to a vascular disorder-related overactive bladder spontaneous hypertensive rats, significantly improved the bladder storage parameters, tightened the detrusor layer, reduced inflammatory infiltration, and decreased collagen proportion in the rats' bladder. These effects were caused by the reduction of TGFβ1, p-SMAD3, collagen III, Gq, and PLCβ1, involved in collagen synthesis and calcium signaling pathways. It was predicted that sitosterol, chrysin, and nootkatone were responsible for these pharmacological activities.[50]

Alpinia zerumbet

Some parts of *A. zerumbet* are also known to have anti-inflammatory properties. The methanol leaf extract elicited an inflammatory response in rats, as evidenced by an increase in paw thickness evaluated hourly for 5 h and 24 h after injection. Rats pretreated with the extract (200 and 400 mg/kg, per oral) 1 h earlier showed a dose-dependent reduction in edema thickness values by 33 and 55% of the control values, respectively. The treatment of the latter dose was stronger than that shown in rats given with the usual anti-inflammatory drug, diclofenac (20 mg/kg, orally), which only reduced edema thickness by 40% compared to control rats. Thirty-seven compounds were characterized in compound profiling using high-performance liquid chromatography in tandem with an electro-spray ionization-double mass spectroscopy/mass spectroscopy (HPLC-ESI-MS/MS). These compounds consist of flavonoids (aglycones and glycosides) and benzoic and cinnamic acid derivatives.[42]

Moreover, essential oils of *A. zerumbet*, collected in Zhenfeng County, Guizhou Province, China, in October 2013, reduced the expression of endothelial intercellular adhesion molecules (ICAM-1 and VCAM-1) produced by endothelial cells, and activated NF-kappa B signaling, making it an effective anti-inflammatory drug. Endothelial cells play an important role in inflammatory responses to infection and other stressors by producing adhesion molecules, which activate and recruit circulating leukocytes to the site of tissue inflammation. NF-kappa B signaling controls endothelial cell activation and inflammation. LPS activated NF-kappa B signaling, as evidenced by enhanced phosphorylation and nuclear translocation of p65. Treatment with essential oils of *A. zerumbet* eliminated these symptoms.[43]

Essential oil of dry and ripe fruit *A. zerumbet* showed the ability to reduce inflammatory cytokines TNF-α, IL-6, and IL-1β serum levels in HFD ApoE−/− mice, as an animal model on atherosclerosis, which is characterized by chronic and progressive inflammation. In the reduction of TNF-α and IL-1β expression, EOFAZ showed a dose-dependent manner, whereas, in the reduction of IL-6 expression, a higher dose of EOFAZ exhibited a stronger effect compared to the positive drug atorvastatin.[34]

Alpinia purpurata

The ethyl acetate extract of *A. purpurata* leaves, collected from Kanyakumari, Tamil Nadu, India, revealed potential anti-inflammation and anti-cancer against N-methyl N-nitrosourea (MNU) and testosterone-induced prostate cancer in rats. The animals were divided into five groups: (1) normal healthy rats; (2) rats in the negative control, that were intraperitoneally injected with testosterone (T) at a daily dose of 100 mg/kg for 3 days to induce prostate cancer; (3) rats in the positive control group, that were treated as group 2 along with finasteride at a dose of 25 mg/kg, supplemented for 2 months; (4) rats at dose 1 of ethyl acetate extract of *A. purpurata*, that were treated as group 2 and simultaneously treated with a daily dose of 200 mg/kg of the extract through oral gavage for 2 months; and (5) rats at dose 2 of ethyl acetate extract of *A. purpurata*, that received a daily dose of 200 mg/kg of the extract through oral gavage for 2 months. Histopathological observation of hepatic tissue in the normal group demonstrated normal morphology of hepatocytes surrounding periportal lobules. Rats in group 2 (prostate cancer-induced) showed periportal inflammatory cell infiltration with sinusoidal congestion and the regeneration of fatty cell changes with hepatic cell necrosis. Rats treated with the standard drug finasteride (group 3) confirmed minimal hemorrhagic necrosis in focal areas of hepatocytes. Rats in group 4 showed minimal congestion in focal areas with minimal inflammatory sites of hepatocytes, thus confirming that treatment with *A. purpurata* could improve the morphological appearances of the hepatic tissue with minimal hemorrhagic necrosis in focal areas of hepatocytes when compared to the negative control group.[51]

Alpinia galanga

The anti-inflammatory activity of the ethanolic extract of *A. galanga* was studied in rats with carrageenan-induced pleurisy. This pleurisy model is considered an excellent acute inflammatory model in which fluid extravasations, leukocyte migration, and the various biochemical parameters involved in inflammatory response can be measured easily in the exudates. The extract of *A. galanga* rhizome reduced the exudation effect in the inflammatory edema in a dose-dependent manner (100–400 mg/kg) and *A. galanga* 200 mg/kg and 400 mg/kg significantly inhibited the total leukocyte influx.[52]

Cytotoxicity Studies of Alpinia

It is known that there are several Alpinia species whose toxicity has been tested both in vitro and in vivo. Cytotoxicity analysis is necessary to identify the safe and bioactive concentrations in mammalian cells for oral and topical curative applications.

Rhizomes of *A. officinarum* purchased from the Kyungdong oriental medicine market, Seoul, Korea, were extracted with 99.8% methanol for 72 h at room temperature. Extracts were rotary-evaporated and the thick extract was dissolved in dimethylsulfoxide. The extract could inhibit MCF-7 cell proliferation in a dose- and time-dependent manner by suppressing the expression levels of S-phase cell cycle regulatory proteins, including E2F1, cyclin-dependent protein kinase 2, and cyclin A.[57]

A. officinarum rhizomes obtained from Korea Plant Extract Bank (KPEB, Daejeon, Korea) were dried, powdered, and extracted with distilled water (1 L for 2.5 h at 100°C). The supernatant was filtered, concentrated, and lyophilized. The water extracts were cytotoxicity tested on UVB-irradiated NIH-3T3 cells, the fibroblast cell lines that were isolated from a mouse NIH/Swiss embryo. The administration of water extracts of *A. officinarum* rhizome up to 100 µg/mL did not show cytotoxicity on NIH-3T3 cells.[48]

A. eremochlamys K. Schum. was collected from Lore Lindu National Park Central Sulawesi, Indonesia, in April 2019. The leaves, pseudostems, and rhizomes were washed, cut, and dried at room temperature with no direct sunlight. Approximately 2.0 kg of each part of the plant was extracted using 5 L of 96% ethanol for 3 × 24 h, filtered, and rotary

evaporated. The thick extracts were dissolved in 100% DMSO. The extracts were screened for toxicity in human T lymphocyte (MT-4) cells. It was confirmed that the rhizome extract showed no toxicity in MT-4 cells.[58]

A. galanga rhizomes, collected from Tawangmangu, Central Java, Indonesia in May 2021, were cleaned, dried, and extracted with 500 mL 98% ethanol for 24 h. *A. galanga* extract was cytotoxicity assayed on Vero cells, which are normal kidney epithelial cells extracted from an African green monkey. The high IC_{50} value of *A. galanga* extract in Vero cells of 1120 µg/mL indicated no cytotoxic effect.[45] Fresh rhizomes of *A. galanga* collected from the medicinal plant garden of Chiang Mai University, Chiang Mai, Thailand in February 2018, were subjected to hydro-distillation for 3 h to obtain the oil. *A. galanga* oil was investigated for its cytotoxicity on human peripheral blood mononuclear cells (PBMCs). The oil exposure to PBMCs resulted in > 80% survival rates for PBMCs throughout all concentration ranges, according to dose–response curve analysis, indicating no cytotoxicity to human cells.[59]

A. malaccensis rhizomes were collected from the medicinal garden of Nature Secret (Pvt) Ltd, Millewa, Horana, Sri Lanka. Different concentrations of *A. malaccensis* hexane extract were cytotoxicity-assayed on A549, HepG2, 3T3, and COS-7 cell lines and revealed that the extract was nontoxic at doses of 2, 1.4, 30, and 1.4 µg/mL for A549, HepG2, 3T3, and COS-7 cells, with no apoptotic/necrotic cell death or DNA damage seen.[60]

A. oxyphylla petroleum ether fractions were determined in human hepatocellular carcinoma (HCC) cell lines (BEL-7402, HepG2, SMMC-7721, Hep3B), and a human liver cell line, HL-7702. The study found that petroleum ether fraction exhibited cytotoxic effects on HL-7702 cells at a concentration of 100 mg/mL which differed considerably from the survival rate of Hep3B cells.[61]

Toxicity Studies of Alpinia

Toxicity studies of several *Alpinia* genus plants in animal models were also reported. *A. galanga* rhizome water extract, purchased from Chemiloids Pvt. Ltd, Vijayawada, A.P, India, was reported safe as proven by the acute toxicity study using Wistar rats of both males and females. The rats were orally administered a dose of 2000 mg/kg BW and monitored individually over the first 4 h continuously, and then infrequently for another 4 h until 24 h after. After 24 and 72 h, the rats were observed for any lethality or death. Since no animals perished, LD_{50} of the test drug can be taken in amounts larger than 2000 mg/kg.[61]

The acute toxicity of the crude n-hexane extract of *A. malaccensis* rhizome was assessed in three-month-old female Wistar rats. The rats were administered a single oral dose of the extract at 300 or 2000 mg/kg BW, following the modified OECD Test Guidelines. The dose of 2000 mg/kg BW resulted in no notable toxicity or fatality. After 14 days of treatment, no changes were found in behavior, BW, hematological and biochemical markers, or histopathological characteristics as compared to the control group (treated with olive oil), thus confirming the safety of oral dose for *A. malaccensis* extract at 2000 mg/kg BW.[60]

An in vivo toxicity investigation of *A. oxyphylla* petroleum ether fraction in mice was reported by Hui et al (2019). *A. oxyphylla* fruits were bought from the Yonggang Decoction Pieces Factory Co., Ltd. (Bozhou, China). The fruits were reflux-extracted with 60 L 95% ethanol for 2 h, and the above steps were repeated 3x. The extracts were concentrated at 60°C in a rotary evaporator to obtain 375 g of crude extract. The extracts were suspended in 2.5 L water and further fractionated with the same amount of petroleum ether. The petroleum ether layer was separated and evaporated. The petroleum ether fraction exhibited no evident hepatotoxicity or nephrotoxicity.[62]

Studies in Humans

A literature search of clinical trials of *Alpinia* genus plants at the time of writing found only seven articles, with five of them studied on *A. galanga* and the rest on *A. zerumbet* and *A. officinarum* (Table 3).

Alpinia galanga

A study was conducted to determine the effect of *A. galanga* proprietary extract on its possible psychostimulant effects in humans. The interventional product (placebo, *A. galanga* proprietary extract coded as E-AG-01, caffeine, and a combination of E-AG-01 with caffeine), was given to 59 participants aged 18–40 years, with body mass index of ≥ 18.5 and < 25.00 kg/m^2, and with moderate caffeine consumption, followed by sequential administration of the remaining

Table 3 Human Studies of Alpinia Genus Plants

Botanical Name	Intervention Product and Dosage Form	Design of Study, Aim of Study, Participant Characters, Inclusion Criteria, and Methods	Standard Drug	Efficacy or Clinical Outcomes	Adverse Effects	Reference
Alpinia galanga	*A. galanga* proprietary extract coded as E-AG-01 The interventional product (placebo, E-AG-01, caffeine, and a combination of E-AG-01 with caffeine).	A randomized, double-dummy, double-blind, placebo-controlled cross-over study was conducted to determine the effect of *A. galanga* on mental alertness and sustained attention in comparison with caffeine and placebo in participants with a habitual caffeine intake. 59 participants, 18–40 years old, BMI of ≥18.5 and <25.00 kg/m^2, with moderate caffeine consumption were enrolled. The participants had a Generalized Anxiety Disorder-7 score of ≤ 7, a Patient Health Questionnaire-9 score of ≤ 14, and a Jin Fan's Attention Network Test alertness score of 50 ± 20 ms. The interventional product (placebo, E-AG-01, caffeine, and a combination of E-AG-01 with caffeine) was administered to the participants, followed by sequential administration of the remaining interventions on consecutive study visits. The effects on mental alertness, sustained attention, and sleep architecture, along with safety and tolerability, were analyzed by validated methods.	Caffeine.	In the E-AG-01 group, the alertness score was increased by 11.65 ± 23.94, 12.50 ± 19.73, and 12.62 ± 0.68 ms from baseline at 1, 3 (p = 0.042), and 5 h, respectively, indicating its efficacy to enhance mental alertness and the increase in alertness score as compared to placebo. In the composite group (E-AG-01 with caffeine), mean response time was significantly reduced, by 15.55 ms (p = 0.026) at 3 h. This finding demonstrates that *A. galanga* promotes mental alertness, and combining *A. galanga* with caffeine reduces the caffeine crash and improves sustained attention after 3 h. Because of these stimulating properties, *A. galanga* may be used as a main ingredient in energy drinks or similar products.	Not described.	[63]

(*Continued*)

Table 3 (Continued).

Botanical Name	Intervention Product and Dosage Form	Design of Study, Aim of Study, Participant Characters, Inclusion Criteria, and Methods	Standard Drug	Efficacy or Clinical Outcomes	Adverse Effects	Reference
Alpinia galanga	*A. galanga* proprietary extract coded as E-AG-01 The interventional product (placebo, E-AG-01, caffeine, and a combination of E-AG-01 with caffeine).	A randomized, double-dummy, double-blind, placebo-controlled cross-over study was conducted to determine the effect of *A. galanga* on mental alertness and sustained attention in comparison with caffeine and placebo in participants with a habitual caffeine intake. Fifty-nine healthy nonsmoking caffeine-habituated males and females, 18–40 years old with at least minimal computer literacy were enrolled in the study. Caffeine-consumption history was recorded to ensure that participants were acquainted with caffeine's stimulant effects and were not caffeine-sensitive. Subjects with body-mass index 18.50–25.0 kg/m^2, resting blood pressure ≤ 140/90 mmHg, and alertness score (ANT version 1.3.0) of 50 ± 20 ms at screening visits and subsequent study visits were considered eligible. Pregnant or breast-feeding females were excluded, and those currently in their menstrual period were included only after the last day of menstrual flow. Females consuming oral contraceptives were included in the study only after switching to barrier contraception and a washout period of 7 days from the last dose of oral contraception. Any concomitant therapy was strictly prohibited during the study.	Caffeine.	The participants received either 300 mg of the extract or a placebo, 30 min after lunch on day 1 followed by cross-over treatments on day 7. *A. galanga* extract supplementation showed significant improvements in alertness, reaction time, correct responses, and reduction in errors at several time points over placebo. Additionally, the *A. galanga* extract intervention demonstrated a significant elevation in the participants' energetic sense and a diminished fatigue intensity over the placebo. The error rate per second in the *A. galanga* extract group declined from 4.48 (0.85%) at baseline to 2.85 (0.36%), exhibiting a decrease of 1.63% at 1 h. The error rate remained low: 1.32% and 0.77% from baseline at 3 and 5 h, respectively. This decrease in error rate was remarkable and consistent for 5 h compared to placebo, which demonstrated almost no change at 1 h and an increase in error rate at 3 (0.14%) and 5 h (0.77%). The caffeine group demonstrated a decrease of 0.37% (1 h) and 0.44% (3 h) and subsequently an increase of 0.2% (5 h), whereas the error rate of subjects in the caffeine + *A. galanga* extract group decreased by 0.24% and 0.26% at 1 and 3 h, respectively, followed by an increase of 0.2% at 5 h.	Not described.	[64]

Alpinia galanga	Fresh rhizomes of *A. galanga* imported from Thailand were purchased and, upon arrival, the rhizomes were split longitudinally, and freeze-dried. Before incorporation in tablets, the dry rhizomes were pulverized. Tablets were produced containing either 191 mg of the above-mentioned dried powder of *A. galanga* or 250 mg of *P. granatum* extract. The daily active treatment consisted of four tablets with extract of *P. granatum* and four tablets with *A. galanga* (Punalpin, Nerthus ApS, Lejre, Denmark), two of each kind taken in the morning, and two of each kind in the evening. The placebo tablets were produced in two variations to visually match the two kinds of active treatment.	The study was a prospective, randomized, placebo-controlled, double-blinded trial. Seventy healthy adult men ≥18 years of age with a semen quality not meeting the standards for commercial application at Nordic Cryobank were recruited. Enrollment was calculated as the average number of motile spermatozoa in two ejaculates. The participants were daily treated with four tablets containing *P. granatum* extract and four tablets containing *A. galanga* extract, two of each kind taken in the morning, and two of each kind in the evening, for 3 months. After 4–8 days, the participants ejaculated once, followed by two more shortly before quitting the tablets. The intervention was completed by 66 participants (34 active treatment and 32 placebo). In addition to the two ejaculates delivered before intervention (baseline was defined as the mean of the two ejaculates), the participants delivered an ejaculate after 4–8 days of tablet intake and two ejaculates at the end of the study. Upon termination of the study, the participants completed a questionnaire to determine the occurrence of any negative or positive side-effects.	Not described.	In this study, it was investigated whether oral consumption of tablets with standardized content of *P. granatum* extract *and A. galanga* powder would increase the total number of motile spermatozoa (TMSC) and sperm morphology, defined by strict criteria, in adult men with reduced semen quality.	Following the intervention, those treated with plant extracts had more motile spermatozoa than the placebo group (p = 0.026). After 3 months of active medication, the average total amount of motile sperm increased by 62% (from 23.4 to 37.8 million), while the placebo group showed a 20% increase. Sperm morphology was unaffected by the therapy.	[65]

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https://doi.org/10.2147/JEP.S499115

Table 3 (Continued).

Botanical Name	Intervention Product and Dosage Form	Design of Study, Aim of Study, Participant Characters, Inclusion Criteria, and Methods	Standard Drug	Efficacy or Clinical Outcomes	Adverse Effects	Reference
Alpinia galanga	The study product *A. galanga* extract weighed 390 mg which included 300 mg of proprietary extract of *A. galanga* (commercially known as enXtra®) and 90 mg of microcrystalline cellulose and the placebo weighed 390 mg of microcrystalline cellulose.	Sixty-two adult healthy male and female participants, aged between 18 and 55 years, were enrolled in the study after signing written informed consent. Inclusion criteria were as follows: BMI 18.5 kg/m^2 to 29.9 kg/m^2, Fatigue Severity Scale score > 4, history of consuming < 3 cups of tea/coffee per day, post-lunch sleepiness as indicated by Epworth sleepiness score ≥ 11 and ≤ 17, agreed to sleep for 8 ± 1 h the night before the visit day, maintain their usual lifestyle, agreed to refrain from consuming caffeine and caffeine-containing products 12 h before visit days, agreed to refrain from vigorous physical activity 12 hours before visit days, and agreed to stay weight stable during the study period. The study was conducted following ICH-GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use–Good Clinical Practice) guidelines, "Declaration of Helsinki" and Indian Council of Medical Research codes. The study was registered on the Clinical Trials Registry-India (CTRI) [Registration No. CTRI/2022/05/042770].	Not described.	On day 1, 62 adults were randomly assigned to receive either 300 mg of *A. galanga* extract or placebo 30 min after lunch, with cross-over treatments on day 7. The primary goal was to analyze the effect of *A. galanga* extract on mental alertness and accuracy as measured by the Symbol Digit Coding Test, Shifting Attention Test, Stroop Test, and CNS Vital Signs Alertness Rating Scale at baseline, 0.5, 1, 2, and 5 h post-dose. As secondary outcomes, exhaustion, and energy levels were examined using the visual analog scale, and daily drowsiness was assessed using the Epworth drowsiness Scale. Adverse incidents were monitored to ensure safety purposes.	At numerous time intervals, the extract supplementation significantly improved alertness, reaction time, accurate responses, and mistake reduction compared to placebo. Furthermore, *A. galanga* extract ingestion resulted in a substantial improvement in the subjective feelings of energy and lower fatigue levels compared to placebo. *A. galanga* extract supplementation enhances alertness, accuracy, reaction time, and error reduction in individuals, and may be a viable alternative to caffeine for those looking for same-day effects to boost alertness and energy levels.	[66]

Alpinia galanga	One group received *Alpinia galanga* extract in the form of a 500-mg tablet, while the other received similar-looking placebo tablets containing Avicel (a starch-like substance).	This triple-blind randomized clinical trial included 60 adult males who were currently using SSRIs. The participants were divided into two groups: 30 received 500 mg of *A. galanga* extract and 30 received a placebo. The population was re-assessed at weeks 2 and 4 of the study using the International Index of Erectile Function (IIEF), Beck Depression Inventory, and the Beck Anxiety Inventory. In all tests, the threshold for significance was used at a *p*-value of 0.05. The inclusion criteria for the study were as follows: male gender, age under 60 and over 18, use of SSRI medication for at least the past 6 consecutive weeks, sexual dysfunction (confirmed by examiner physician's diagnosis), lack of substance abuse, lack of co-existing other mental illnesses (as ruled out by a clinical psychiatrist), lack of physical/somatic illnesses, and lack of using medications other than SSRIs. The exclusion criteria for the study included: symptoms of liver, kidney, or thyroid dysfunction, use of any medication other than SSRIs, age 18–60, substance use disorder, other somatic illnesses, and co-existing mental disorders other than major depression or anxiety. In addition, the participants were routinely checked during the study and those who were found to meet any of the above criteria were removed from the sample population.	Not described.	Both groups were told to consume their medication with a glass of milk on an empty stomach. The participants were assessed on week 2 and week 4 of the study. Additionally, to investigate the possible side-effects, the participants were regularly assessed using a self-report medication side-effect questionnaire, as well as laboratory tests including complete blood count (CBC), blood urea nitrogen (BUN), Creatinine, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and thyroid stimulating hormone (TSH).	At the beginning of the study, the IIEF scores of the placebo group and the intervention group were 10.6 ± 3.8 and 11.2 ± 4.8, respectively, which were not significantly different (p-value = 0.577). By week 4 of the study, the IIEF scores of the control group and the *A. galanga* group had increased to 13.7 ± 4.3 and 17.4 ± 3.7, respectively, which demonstrates a remarkably larger increase in the group receiving *A. galanga* extract in comparison to the placebo group (p-value < 0.001). In this study, the inclusion of *A. galanga* extract in the treatment regimen of male patients using SSRIs showed promise in terms of sexual dysfunction.	[67]
Alpinia zerumbet	The leaves of *A. zerumbet* were collected always in the morning (7 am) in a greenhouse located at the University Tiradentes, Aracaju/SE, Brazil.	Fifteen adults with a mean age of 43 ± 13 years, of both sexes, with clinical diagnosis of stroke and entered the Health Center of the Tiradentes University, presented spasticity in the gastrocnemius muscle (GM), ability to perform plantar flexion, independence for gait even making use of orthosis and ability to remain in the standing posture, parallel to the wall, without signs of imbalance during the test were included in the study.	Not described.	Fifteen adults with unilateral hemiparesis and stiffness caused by stroke were subjected to surface electromyography readings of the gastrocnemius muscle before and after 10 daily administrations (dermal 0.05 mL per muscle belly) of *A. zerumbet* essential oil. Healthy contralateral muscles that were not treated with oil were used as controls.	The investigation found that diseased legs saw substantial decreases in all analyzed variables (root mean square, maximum amplitude, and median power frequency) during muscular contraction (Wilcoxon test, $p < 0.05$). Furthermore, spastic muscles showed distinct responses before and after dermal administration of *A. zerumbet* essential oil. The lateral and medial gastrocnemius showed significant increases in the root mean square and median power frequency, while the medial gastrocnemius had a higher maximum amplitude (Mann–Whitney test, $p < 0.05$). The findings imply that *A. zerumbet* essential oil regulates skeletal spastic muscle contraction by increasing relaxation and improving muscle function.	[68]

(*Continued*)

Table 3 (Continued).

Botanical Name	Intervention Product and Dosage Form	Design of Study, Aim of Study, Participant Characters, Inclusion Criteria, and Methods	Standard Drug	Efficacy or Clinical Outcomes	Adverse Effects	Reference
Alpinia officinarum Hance	Capsules containing dried extract of *A. officinarum* rhizome or placebo.	In a prospective double-blinded randomized clinical trial, 76 participants with idiopathic infertility were included in the intervention (plant treatment: n = 31; placebo: n = 29).	Not described.	Participants were randomized to take capsules containing dried extract of *A. officinarum* rhizome or placebo on a daily (total daily dosage of 300 mg) basis for 3 months. After 12 weeks of intervention, the sperm count and total number of spermatozoa with normal morphology were increased in participants treated with *A. officinarum* extract compared with the placebo group.	Twelve weeks after the intervention, the sperm count and total number of spermatozoa with normal morphology were higher in individuals administered *A. officinarum* extract, than in those administered a placebo. Following the intervention, the mean sperm count increased from $52 \times 10^6 \pm 24 \times 10^6$/mL to $71 \times 10^6 \pm 23 \times 10^6$/mL ($p$ = 0.043). The average proportion of spermatozoa with normal morphology was 14.34 ± 9.16% before the treatment resulting in a substantial rise of 19 ± 14.89% (p < 0.001). These findings demonstrate that *A. officinarum* can be useful in the development of sperm morphology and count in idiopathic infertility without producing unfavorable effects.	[69]

https://doi.org/10.2147/JEP.S499115

interventions on subsequent study visits. The effects on mental alertness, sustained attention, sleep architecture, safety, and tolerability, were assessed using validated methods. The E-AG-01 group enhanced their alertness score by 11.65 ± 23.94, 12.50 ± 19.73, and 12.62 ± 0.68 ms from baseline at 1, 3 ($p = 0.042$), and 5 h, respectively, showing its efficacy in enhancing mental alertness. At 3 h, the composite group (E-AG-01 plus caffeine) had a significantly lower mean response time of 15.55 ms ($p = 0.026$). This finding demonstrates that *A. galanga* promotes mental alertness, and combining *A. galanga* with caffeine reduces the caffeine crash and improves sustained attention after 3 h. Because of these stimulating properties, *A. galanga* may be used as a main ingredient in energy drinks or similar products.[63]

In another study, *A. galanga* extract (the source and extraction procedure were not described) was studied for its effect on mental alertness, accuracy, and fatigue through a randomized, double-blind, placebo-controlled, cross-over clinical study. Of 124 participants screened for the study, 59 meeting the protocol-defined inclusion criteria were enrolled in the study. The participants received either 300 mg of the extract or a placebo, 30 min after lunch on day 1 followed by cross-over treatments on day 7. *A. galanga* extract supplementation showed significant improvements in alertness, reaction time, correct responses, and reduction in errors at several time points over placebo. Additionally, the *A. galanga* extract intervention demonstrated a significant elevation in the participants' energetic sense and a diminished fatigue intensity over the placebo.[64]

A. galanga has also been shown to improve sperm motility. This study was planned as a prospective, randomized, controlled, double-blind trial. Fresh rhizomes of *A. galanga* imported from Thailand were purchased and, upon arrival, the rhizomes were split longitudinally, and freeze-dried. Before incorporation in tablets, the dry rhizomes were pulverized. Tablets were produced containing either 191 mg of the above-mentioned dried powder of *A. galanga* or 250 mg of *P. granatum* extract. Seventy healthy adult men ≥ 18 years of age with a semen quality not meeting the standards for commercial application at Nordic Cryobank were recruited. Enrollment was calculated as the average number of motile spermatozoa in two ejaculates. The participants were daily treated with four tablets containing *P. granatum* extract and four tablets containing *A. galanga* extract, two of each kind taken in the morning, and two of each kind in the evening, for 3 months. After 4–8 days, the participants ejaculated once, followed by two more shortly before quitting the tablets. The intervention was completed by 66 participants (34 active treatment and 32 placebo). Following the intervention, those treated with plant extracts had more motile spermatozoa than the placebo group ($p = 0.026$). After 3 months of active medication, the average total amount of motile sperm increased by 62% (from 23.4 to 37.8 million), while the placebo group showed a 20% increase. Sperm morphology was unaffected by the therapy.[65]

A. galanga extract has been used in clinical studies to improve mental health. A randomized, double-blind, placebo-controlled, cross-over clinical trial involving healthy human participants was conducted to assess the acute effects of *A. galanga* extract on mental alertness, accuracy, and weariness. On day 1, 62 adults were randomly assigned to receive either 300 mg of *A. galanga* extract or placebo 30 min after lunch, with cross-over treatments on day 7. The primary goal was to analyze the effect of *A. galanga* extract on mental alertness and accuracy as measured by the Symbol Digit Coding Test, Shifting Attention Test, Stroop Test, and CNS Vital Signs Alertness Rating Scale at baseline, 0.5, 1, 2, and 5 h post-dose. As secondary outcomes, exhaustion, and energy levels were examined using the visual analog scale, and daily drowsiness was assessed using the Epworth drowsiness Scale. Adverse incidents were monitored to ensure safety purposes. At numerous time intervals, the extract supplementation significantly improved alertness, reaction time, accurate responses, and mistake reduction compared to placebo. Furthermore, *A. galanga* extract ingestion resulted in a substantial improvement in the subjective feelings of energy and lower fatigue levels compared to placebo. *A. galanga* extract supplementation enhances alertness, accuracy, reaction time, and error reduction in individuals, and may be a viable alternative to caffeine for those looking for same-day effects to boost alertness and energy levels.[66]

Another study aimed to determine whether adding *A. galanga* extract to the treatment regimen of adult males with selective serotonin reuptake inhibitors (SSRIs) could improve SSRI-induced erectile dysfunction. This triple-blind randomized clinical trial included 60 adult males who were currently using SSRIs. The participants were divided into two groups: 30 received 500 mg of *A. galanga* extract and 30 received a placebo. The population was re-assessed at weeks 2 and 4 of the study using the International Index of Erectile Function (IIEF), Beck Depression Inventory, and the Beck Anxiety Inventory. In all tests, the threshold for significance was used at a *p*-value of 0.05. The IIEF scores were significantly higher in the group receiving *A. galanga* extract than in the placebo group ($p < 0.001$). In this study, the

inclusion of *A. galanga* extract in the treatment regimen of male patients using SSRIs showed promise in terms of sexual dysfunction. If validated, similar findings can help both patients and therapists to develop and implement better treatment programs with more positive outcomes.[67]

Alpinia zerumbet

A. zerumbet essential oil has myorelaxant and antispasmodic properties for cardiac and smooth muscle. A previous study examines the effect of *A. zerumbet* essential oil on skeletal muscle contractions in patients with post-stroke spasticity. Fifteen adults with unilateral hemiparesis and stiffness caused by stroke were subjected to surface electromyography readings of the gastrocnemius muscle before and after 10 daily administrations (dermal 0.05 mL per muscle belly) of *A. zerumbet* essential oil. Healthy contralateral muscles that were not treated with oil were used as controls. The investigation found that diseased legs saw substantial decreases in all analyzed variables (root mean square, maximum amplitude, and median power frequency) during muscular contraction (Wilcoxon test, $p < 0.05$). Furthermore, spastic muscles showed distinct responses before and after dermal administration of *A. zerumbet* essential oil. The lateral and medial gastrocnemius showed significant increases in the root mean square and median power frequency, while the medial gastrocnemius had a higher maximum amplitude (Mann–Whitney test, $p < 0.05$). The findings imply that *A. zerumbet* essential oil regulates skeletal spastic muscle contraction by increasing relaxation and improving muscle function. Thus, the *A. zerumbet* essential oil may be effective in the clinical management of secondary effects in individuals with cerebral vascular disease.[68]

Alpinia officinarum

This study aimed to determine the effect of *A. officinarum* on semen analysis in men suffering from idiopathic infertility. In this clinical research, 76 people with idiopathic infertility were enrolled in the intervention (plant treatment: 31 and placebo: 29). The participants were randomly assigned to receive capsules containing dried extract of *A. officinarum* rhizome or placebo daily (total daily dosage of 300 mg) for 3 months. Twelve weeks after the intervention, the sperm count and total number of spermatozoa with normal morphology were higher in individuals administered *A. officinarum* extract than in those administered a placebo. Following the intervention, the mean sperm count increased from $52 \times 10^6 \pm 24 \times 10^6$/mL to $71 \times 10^6 \pm 23 \times 10^6$/mL ($p = 0.043$). The average proportion of spermatozoa with normal morphology was 14.34 ± 9.16% before the treatment resulting in a substantial rise of 19 ± 14.89% ($p < 0.001$). These findings demonstrate that *A. officinarum* can be useful in the development of sperm morphology and count in idiopathic infertility without producing unfavorable effects.[69]

Herbal Drug–Drug Interaction

The administration of herbal drugs in combination with therapeutic drugs may raise the potential for pharmacokinetic or pharmacodynamic interactions. Pharmacokinetic herbal–drug interactions occur due to altered absorption, metabolism, distribution, and excretion of the therapeutic drugs.[70] It was described that the oral administration of *A. officinarum* significantly altered the pharmacokinetic parameters of indomethacin by decreasing the systemic exposure of indomethacin and increasing its elimination.[23] Another species, *A. galanga*, was reported for its possible interaction with warfarin by increasing the warfarin effect.[24]

Alpinia plants may increase the release of hydrochloric acid in the stomach, thus decreasing the effectiveness of some medications such as histamine H2 receptor antagonists, including cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid). (https://www.rxlist.com/supplements/alpinia).

Conclusion

Our study unveiled that only *A. galanga*, *A. officinarum*, *A. zerumbet*, and *A. oxyphylla* have been the most reported for their anti-inflammatory activity in numerous in vitro and in vivo studies. *Alpinia* plants have the potential as exogenous antioxidants, can reduce proinflammatory cytokines such as tumor necrosis-alpha and interleukins, inhibit proinflammatory enzymes such as cyclooxygenases and inducible nitric oxide synthase, improve gastric acid and gastrointestinal motility, and promote ulcer healing, by which their diterpenoids, flavonoids, and diarylheptanoids contents may crucially

contribute. These plants did not show toxicity toward numerous normal cells or animal models. During the study period, we found only *A. galanga*, *A. officinarum*, and *A. zerumbet* have been used to treat humans. Of the three plants, *A. galanga* was the most studied for psychostimulant effects, sperm motility, and erectile dysfunction, with the fewest adverse effects. However, the use of supplements containing *Alpinia* extract should be monitored for patients treated with warfarin, NSAIDs, and histamine H2 receptor antagonists, to avert the herbal–drug interactions.

Acknowledgments

The authors thank the Rector of Universitas Padjadjaran, West Java, Indonesia for facilitating the APC of this article. The present study was conducted in the framework of the dissertation project of the first author at the Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, West Java, Indonesia.

Disclosure

The authors state that they have no conflicts of interest in this work.

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