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Review Article

TERPENOIDS AS SOURCE OF ANTI-INFLAMMATORY COMPOUNDS

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ABSTRACT

Terpenoids accounts for the major class of secondary metabolites produced by plants. It shows defense activity against environmental stress and help to heal injuries. Medicinal plants are rich in monoterpenoids, diterpenoids, sesquiterpenes, triterpenes, tetraterpenes, and ceramide. A number of therapeutic applications such as antibacterial, antimicrobial, antitumor, anti-inflammatory activity have been identified. Terpenoids are compounds similar to terpenes derived from 5-carbon monomer isoprene units. The review puts and detail insight on different class of compounds isolated from natural source from 2000 to 2016 showing anti-inflammatory potential of pharmacologically interesting agent and their mechanism of action.

Keywords: Anti-inflammatory, Mechanism of action, Natural source, Plant, Terpenoid, Bioactive compound.

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INTRODUCTION

Inflammatory diseases have become one of the leading causes of health issue throughout the world, having a considerable influence on health-care costs. With the emerging developments in natural product, synthetic and combinatorial chemistry, a notable success has been achieved in discovering natural products and their synthetic structural analogs with anti-inflammatory activity [1]. The first four characteristics of inflammation are redness, heat, swelling, and pain against any harmful stimuli, pathogen or injury. Inflammation originally referred to the combination of heat, redness, swelling and pain in a local area, it has gradually evolved to focus on cellular and humoral processes that occur in tissues when external or internal agents cause damage to them [2]. Nuclear factor-kappa B (NF-κB) plays an important role in the regulation of immune and inflammatory responses. Indeed, deregulated NF-κB expression is a characteristic phenomenon in several inflammatory diseases and NF-κB has become a major target in drug discovery [3]. In the inflammatory response there is an increase of permeability of endothelial lining cells and influxes of blood leukocytes into the interstitium, oxidative burst, and release of cytokines (interleukins [IL] and tumor necrosis factor-α [TNF-α]). At the same time, there is also an induction of the activity of several enzymes (oxygenases, nitric oxide [NO] synthases, and peroxidases) as well as the arachidonic acid metabolism. In the inflammatory process, there is also the expression of cellular adhesion molecules, such as intercellular adhesion molecule and vascular cell adhesion molecule [4]. NO is a gaseous short-lived free radical has been implicated as a mediator of inflammation and modulation of biosynthesis or activity of NO results in amelioration of acute inflammation and experimental arthritis model [5,6]. In plants terpenoids are synthesized basically by two pathways, i.e., mevalonic acid pathway and methylerythritol 4-phosphate (MEP) pathway. In the mevalonate pathway, it has been speculated that isopentenyl diphosphate (IPP) is synthesized from acetyl-CoA and then isomerized to dimethylallyl diphosphate (DMAPP). In contrast, the MEP pathway synthesizes IPP and DMAPP from pyruvate and D-glyceraldehyde 3-phosphate [7]. A wide range of bioactive compounds has been isolated that have shown potential to reduce inflammation by wide mechanisms (Fig. 1).

A wide class of drugs such as nonsteroidal anti-inflammatory drugs and glucocorticoids are present in market but all suffer from adverse toxicity, gastrointestinal tract irritation, and liver dysfunction. Natural counterpart has always remained an area of interest as it has less toxicity as well as it is cost-effective with less immune response. Therefore, screening and development of drug from medicinal plants with potent anti-inflammatory potential is need of hour.

BIOACTIVE METABOLITES FROM PLANTS

A wide aspect of study has been done to find out anti-inflammatory potential of bioactive metabolites derived from natural products. The structures of all compound mentioned in Table 1 is drawn in Fig. 2. Lupeol (1) was isolated from alcohol (70%) extract of the whole plant of *Hygrophila auriculata* and anti-inflammatory activity was assessed. Administration of TF significantly (p-50.005) restored the serum levels of cytokines, lipid peroxide (7.77±0.034 vs. 4.59±0.059 nmole of thiobarbituric acid reactive substances), NO (9.72±0.18 vs. 4.15±0.23 mmol nitrite/mg of wet tissue), and superoxide dismutase (SOD) (4.89±0.036 vs. 7.83±0.033 unit/mg protein) compared with the lipopolysaccharide (LPS)-challenged rats [8]. Andrographolide (2) and neoandrographolide (3) are major bioactive molecules isolated from *Andrographis paniculata.* These molecules exhibited varying degrees of anti-inflammatory activities *in vitro* and *in vivo* [9]. Filifolinone (4) is a semisynthetic terpenoid derivative obtained from *Heliotropium filifolium.* Filifolinone appeared responsible of an important upregulation of interferon (IFN)-a1, IFN-g, IL-4/13A, and IL-17D in the kidney [10]. Umbelliprenin (5) and methyl galbanate (6) was isolated from *Ferula szowitsiana*. Study showed terpenoid coumarins isolated from *F. szowitsiana* on immune cells isolated from naive mice and to elucidate possible underlying mechanisms of action. Compounds reduced remarkably phytohemagglutinin (PHA)-induced splenocyte proliferation and both preferentially induced TH2 IL-4 and suppressed TH1 IFN secretion. Each also significantly suppressed LPS-induced production of NO and prostaglandins E2 apparently and also led to reductions in inducible NO synthase (iNOS) and cyclooxygenase (COX)-expression [11]. Geraniol (GOH) a monoterpenoid, and main ingredient of coriander oil. GOH has been shown to possess anti-inflammatory. Study showed that supplementation with GOH (100 mg/kg b.w) to AD-induced hamsters oxidative stress and inflammation by that it prevents fibrosis through NF-κB switching off [12]. (5R,8S,9S,10R,13R,14S,17R,20R,23S,24S)-21,24-epoxy-23,25-dihydroxy-cyclolanostan-3-one (1), 21,25-epoxy-23α,24β-dihydroxycyclolanostan-3-one (2), (3S,5R,8S,9S,10S,13R)3hydroxy isopimara-15-en-11-one (8), 2-oxokolavenic acid methyl ester (15) (7-10) isolated from leaves twigs of *Dysoxylum gotadhora* exhibited noteworthy inhibition of NO production induced by LPS in RAW 264.7 cells with IC50 values of 25.5,

Table 1: Plants with anti-inflammatory potential

S. No.	Plant name	Plant family	Compound isolated	Mechanism of action	References
1	*Hygrophila auriculata*	Acanthaceae	Lupeol (1)	Significantly (p=50.005) restored the serum levels of cytokines, LPO and SOD	[8]
2	*Andrographis paniculata*	Acanthaceae	Andrographolide and neoandrographolide (2)(3)	C2/TrAP inhibit the activation of SnRK1 in terpenoids pathway and removes the negative regulation of HMGR by SnRK	[9]
3	*Heliotropium filifolium*	Boraginaceae	Filifolinone (4)	Increases the expression level of pro-inflammatory and anti-inflammatory cytokines	[10]
4	*Ferula szowitsiana*	Apiaceae	UMB and MG (5)(6)	Inhibition of both iNOS and COX-2 pathways in inflammatory macrophages	[11]
5	*Coriandrum sativum* L.	Apiaceae	GOH	GOH supplementation greatly prevented the remodeling of tissues by enhancing the free radical scavenging and anti-inflammatory effects	[12]
6	*Dysoxylum gotadhora*	Meliaceae	(5R,8S,9S,10R,13R,14S,17R,20R,23S,24S)-21,24-epoxy 23,25-dihydroxycyclolanostan-3-one (1), 21,25-epoxy-23α,24β-dihydroxycyclolanostan-3-one (2), (3S,5R,8S,9S,10S,13R)-3-hydroxyisopimara-15-en-11-one (8), 2-oxokolavenic acid methyl ester (15) (7-10)	Inhibition of nitric oxide production induced by LPS in RAW 264.7 cells	[13]
7	*Ocimum labiatum*	Lamiaceae	Labdane diterpenoid (11)	Inhibited AP-1 significantly ($p<0.05$) at 50 μM	[14]
8	*Scutellaria agrestis*	Lamiaceae	Free steroids, saponins	Anti-inflammatory activity on the formalin test (30, 100 and 300 mg/kg p.o.)	[15]
9	*Plectranthus hadiensis*	Lamiaceae	Compared with the std. nonsteroidal drug, viz., diclofenac sodium	BSA denaturation inhibition, HRBC membrane stabilization and platelet aggregation inhibition assays	[16]
10	*Macrosiphonia longiflora*	Apocynaceae	Hydroethanolic extract	It effectively inhibited ($p<0.05$) paw edema induced by carrageenan and dextran	[17]
11	*Boswellia ovalifoliolata*	Burseraceae	6R,7R-epoxy-1-oleanen-3-ol (2) 3a-hydroxy-tirucall-8,24-dien-21-oic acid (5) (12,13)	Significantly inhibited the expression of TNF-α in murine neutrophils and also reduced the IL (IL-6 and IL-8) and NO production levels	[18]
12	*Lindera umbellata*	Lauraceae	Linalool	KEO suppressed LPS-induced pro-inflammatory cytokine production such as that of NO, IL-6, and TNF-α	[19]
13	*Linum usitatissimum*	Linaceae	CBD	CBD from *Cannabis sativa* activates the specific peripheral CB2 gene expression	[20]
14	*Vernonia polyanthes*	Asteraceae	Ethanol ext.	The ext. reduced the no. of abdominal contortions by 16.75% and 31.44% at a dose of 200 and 400 mg/kg, resp.	[21]

(Contd...)

Table 1: ***(Continued)***

S. No.	Plant name	Plant family	Compound isolated	Mechanism of action	References
15	*Chloranthus serratus*	Chloranthaceae	A lindenanesesquiterpenoid (14) dimer, shizukaols B and D	Inhibitory effects on LPS-induced nitric oxide production in RAW264.7 cells. Compd. 2 and two known compounds, shizukaols B and D, showed significant anti-inflammatory activities	[22]
16	*Wedelia trilobata*	Asteraceae	Water ext.	Inhibiting the heat induced albumin denaturation and red blood cells membrane stabilization	[23]
17	*Loranthus* sp.	Loranthaceae	Endophytic extracts (Methanol and water exts.)	Inhibiting the heat induced albumin denaturation and red blood cells membrane stabilization	[24]
18	*Sansevieria libericag*er. and labr.	Dracaenaceae	Crude extract	Significantly ($p<0.05$) inhibited the development of paw edema induced by egg albumen in rats	[25]
19	*Tinospora cordifolia*	Menispermaceae	Methanolic extract	Capable of inhibiting LOX and COX-2 isoenzymes	[26]
20	*Fagraea racemosa*	Gentianaceae/ Loganiaceae	Terpene alkaloid	Fagraeoside inhibited the prodn. of PGE2 in 3T3 murine fibroblasts (IC50~5.1 μM), and was not cytotoxic to this cell line or to a P388 murine leukemia cell line	[27]
21	*Myrciaria dubia*	Myrtaceae	3β-hydroxy-lup-20 (29)-en-28-oic acid, betulinic acid (15)	The extract significantly suppressed both the formation of edema in mice by oral administration and the release of nitric oxide from macrophage-derived RAW 264.7 cells *in vitro*	[28]
22	*Rhizophora mucronata*	Rhizophoraceae	Lupeol, quercetin, β- sitosterol, adene-5-en-3-ol and caffeic acid	Inhibiting the prostaglandins synthesis and due their antioxidant action	[29]
23	*Dodonaea polyandra*	Sapindaceae	Hexane and methylene chloride/methanol extracts	Inhibition of inflammation in TPA-induced mouse ear edema	[30]
24	*Albizia chinensis*	Legumes	Chloroform ext.	Reduced in the ulcer index ($p<0.001$) when compared to control and pos. control	[31]
25	*Cannabis sativa* L.	Cannabaceae	Cannabinoids and cannabivarins	Anti-inflammatory activity than those at the C-3 alkyl residue, suggesting the involvement not only of cannabinoid receptors but also of other inflammatory end-points targeted by phytocannabinoids	[32]
26	*Inula racemosa*	Compositae	Etoll: Benzene eluents	Inflammation in hind paw of albino rats significantly affected by *I. racemosa* as well as its active principle	[33]
27	*Acalypha indica* Linn.	Euphorbiaceae	Methanolic extract	Inhibition of carrageenan-induced inflammation of rat paw was observed	[34]

(Contd...)

Table 1: ***(Continued)***

S. No.	Plant name	Plant family	Compound isolated	Mechanism of action	References
28	*Tripterygium wilfordii*	Celastraceae	Tripterygium terpenoid	The tripterygium terpenoid vesicles are preferably used to prep. oral formation or external formulation of gel	[35]
29	*Pergularia daemia* and *Carissa carandas*	(Asclepiadaceae) and (Apocynaceae)	Ethanol and aq. exts	Reduce significantly the formation of edema induced by carrageenan	[36]
30	*Schizophragma integrifolium*	Hydrangeaceae	Essential oil	The essential oil significantly inhibited the inflammation that caused by PMA or xylene	[37]
31	*Abies chensiensis*	Pinaceae	Neoabieslactone E (5), (12R,13R)-8,12-epoxy-14-labden-13-ol (7), and manool (8) (16-18)	Inhibitory activities against LPS induced NO production in RAW 264.7 macrophages	[38]
32	*Hemidesmus indicus*	Asclepiadaceae	Hydroalcoholic extract	Inhibitory effect	[39]
33	*Croton cajucara Benth*	Euphorbiaceae	CTN and the triterpene AAA (19,20)	The oral administration inhibited the acetic acid-induced writhing in mice. The AE, CTN and AAA had shown significant inhibition of carrageenin-induced edema in rats	[40]
34	*Boswellia serrata*	Burseraceae	AKBA (21)	Mechanism is poorly understood, abolishes osteoclastogenesis by suppressing NF-κB and NF-κB-regulated gene expression	[41]
35	*Protium heptaphyllum*	Burseraceae	Alpha- and beta-amyrin (22,23)	Diminution in oxidative stress and toxic metabolite formation as likely mechanisms involved in its hepatoprotection	[15]
36	*Auxemmaoncocalyx*	Boraginaceae	Oncocalyxone A (1) (24)	QF (10 and 30 mg/kg body wt., i.p.) significantly inhibited paw edema induced by carrageenan at the 2nd, 3rd, and 4th hrs. The effect was dose-dependent	[42]
37	*Garcinia subelliptica*	Clusiaceae	Garcinielliptones F (I), garcinielliptones G (IV) (25,26)	Potent concentration - dependent inhibitory effect on superoxide anion generation in rat neutrophils stimulated with fMLP/CB with an IC50 value of 17.0±0.9 μM	[43]
38	*Scrophularia auriculata*	Scrophulariaceae	Verbascosaponin A, verbascosaponin, scropolioside A and scrovalentinoside (28-31)	Significantly reduced the inflammatory lesion and suppressed the cellular infiltration	[44]
39	Many plants	Not mentioned	1,8-cineole (27)	Significant reduction in paw edema induced by carrageenan by 26%, 26%, and 46%, respectively	[45]
40	*Macleaya cordata* or *M. microcarpa*	Papaveraceae	Heletrine bisulfate and sanguinarine bisulfate	Anti-inflammatory activity contain compound of heletrine bisulfate and sanguinarine bisulfate as active compounds found	[46]

(Contd...)

Table 1: ***(Continued)***

S. No.	Plant name	Plant family	Compound isolated	Mechanism of action	References
41	*Mortonia greggii*	Celastraceae	Exts. of the leaves, stems and roots; acetonic leaf exts.	Diminished the edema, leukocyte migration and acetic acid-induced writhing	[47]
42	*Alchornea cordifolia*	Euphorbiaceae	Crude ME	Significant ($p<0.05$) edema inhibition (68.25%) at 3 hr	[48]
43	*Gynandropsis gynandra*	Cleomaceae	Methanolic extract	Inhibition of increased paw edema (38.66±1.5) at a dose of 400 mg/kg	[49]
44	*Centella asiatica*	Apiaceae	Extract	Reduction of acute radiation reaction in rats	[50]

LPO: Lipid peroxide, SOD: Superoxide dismutase, SnRK1: SNF-1 related protein kinase 1, HMGR: 3-hydroxy-3-methylglutaryl-CoA reductase, UMB: Umbelliprenin, MG: Methyl galbanate, iNOS: Inducible NO synthase, COX: Cyclooxygenase, HRBC: Human red blood cell, BSA: Bovine serum albumin, TNF-α: Tumor necrosis factor-α, IL: Interleukin, LPS: Lipopolysaccharide, NO: Nitric oxide, CBD: Cannabidiol, CB2: Cannabinoid receptor 2, PGE2: Prostaglandin E2, CTN: 19-nor-clerodane trans-crotonin, AAA: Acetyl aleuritolic acid, AKBA: Acetyl-11-keto-beta-boswellic acid, NF-κB: Nuclear factor-κB, ME: Methanolic extract, GOH: Geraniol

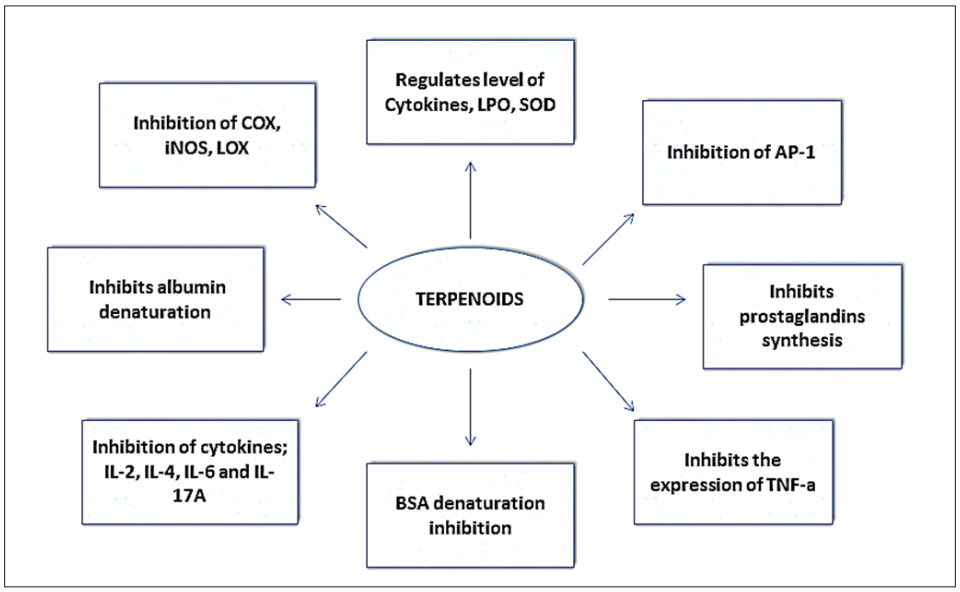
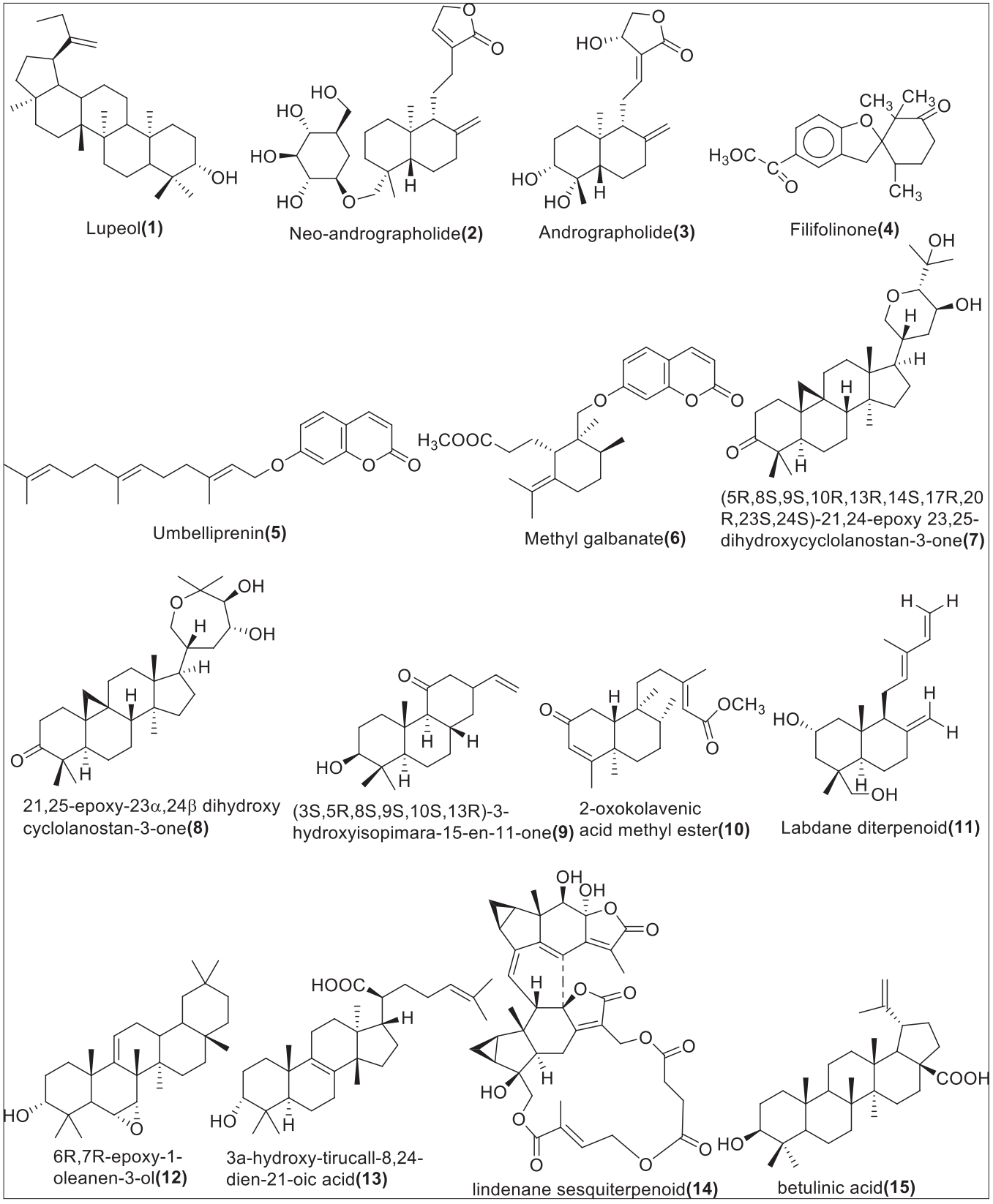


Fig. 1: Role of terpenoids in anti-inflammation

41.5, 27.4, 14.5, and 45.2 μM, respectively [13]. Anti-inflammatory effect of *Ocimum labiatum* ethanolic extract and an isolated diterpenoid was determined using a cytometric bead array technique. 25 μg/mL noncytotoxic concentration of *O. labiatum* extract significantly ($p<0.05$) inhibited the production of pro-inflammatory cytokines; IL-2, IL-4, IL-6, and IL-17A [14]. Free steroids, saponin contents of crude extract from leaves of *Scutellaria agrestis* showed significant analgesic effect and the anti-inflammatory doses of 30, 100, and 300 mg/kg of the formalin test [15]. Terpenoid fraction obtained from shoot of *Plectranthus hadiensis in vitro* anti-inflammatory assays included bovine serum albumin (BSA) denaturation inhibition, human red blood cell membrane stabilization, and platelet aggregation inhibition assays. The fraction showed IC50 values of 56.18±0.766, 57.17±0.890, and 54.26±0.744 μg/mL for BSA denaturation inhibition [16]. Hydroethanolic extract of *Macrosiphonia longiflora* effectively inhibited (p-0.05) paw edema induced by carrageenan dextran [17].

6R,7R-epoxy-1-oleanen-3-ol (2) 3a-hydroxy-tirucall-8,24-dien-21-oic acid (5) (12,13) isolated from *Boswellia ovalifoliolata* were found to considerably reduce levels of IL (IL-6 and IL-8) and NO production, which suggests they have anti-inflammatory potential [18]. Linalool a naturally occurring small terpenoid was isolated from *Lindera umbellata.* Essential oil suppressed LPS-induced pro-inflammatory cytokine production such as that of NO, IL-6, and TNF-α in a dose-dependent manner. In addition, iNOS and cyclooxygenase-2 mRNA expression and protein levels were suppressed by treatment with KEO cells [19]. Cannabidiol (CBD) was isolated from flax fabric extract. The mRNA level increase for the SOCS-1 gene, and decrease in MCP-1 and IL6 genes on human and mouse fibroblast treatment with fabric preparations indicate the biological activity of the CBD-like molecules [20]. Ethanol extract from *Vernonia polyanthes* leaves at doses of 200 and 400 mg/kg, administered 4 h before the carrageenan injection, significantly reduced the exudate volume (29.25% and 45.74%, respectively) and leukocyte migration (18.19% and 27.95%, respectively) [21]. Lindenanesesquiterpenoid (14) dimer, shizukaols B and D were isolated from the whole plant of *Chloranthus serratus.* The compound showed significant anti-inflammatory activities with IC50 values of 0.22, 0.15, and 7.22 μM, respectively [22]. Water extract obtained from *Wedelia trilobata* showed anti-inflammatory activity. It showed inhibition of albumin denaturation. Maximum inhibition 89.61±0.06 was observed from fresh leaf extract followed by flower (86.81±0.06) and stem (51.14±0.08). Water extract also showed inhibiting the heat induced hemolysis. The maximum inhibition was recorded 78.82±0.06 from leaf extract followed by flower (76.65±0.05) and stem (52.31±0.06) from fresh parts extracts [23]. Methanol fractions isolated from endophytes of *Loranthus* sp. showed *in vitro* anti-inflammatory activity by inhibiting the heat induced albumin denaturation (87.88, 88.89, 87.03 g/ml) and red blood cells membrane stabilization with 78.42, 77.61, 77.98 g/ml, respectively [24]. Methanolic extracts of leaves of *Sansevieria libericager.* and *labr.*


Lupeol(1)
Neo-andrographolide(2)
Andrographolide(3)
Filifolinone(4)
Umbelliprenin(5)
Methyl galbanate(6)
(5R,8S,9S,10R,13R,14S,17R,20R,23S,24S)-21,24-epoxy 23,25-dihydroxycyclolanostan-3-one(7)
21,25-epoxy-23α,24β dihydroxy cyclolanostan-3-one(8)
(3S,5R,8S,9S,10S,13R)-3-hydroxyisopimara-15-en-11-one(9)
2-oxokolavenic acid methyl ester(10)
Labdane diterpenoid(11)
6R,7R-epoxy-1-oleanen-3-ol(12)
3a-hydroxy-tirucall-8,24-dien-21-oic acid(13)
lindenane sesquiterpenoid(14)
betulinic acid(15)

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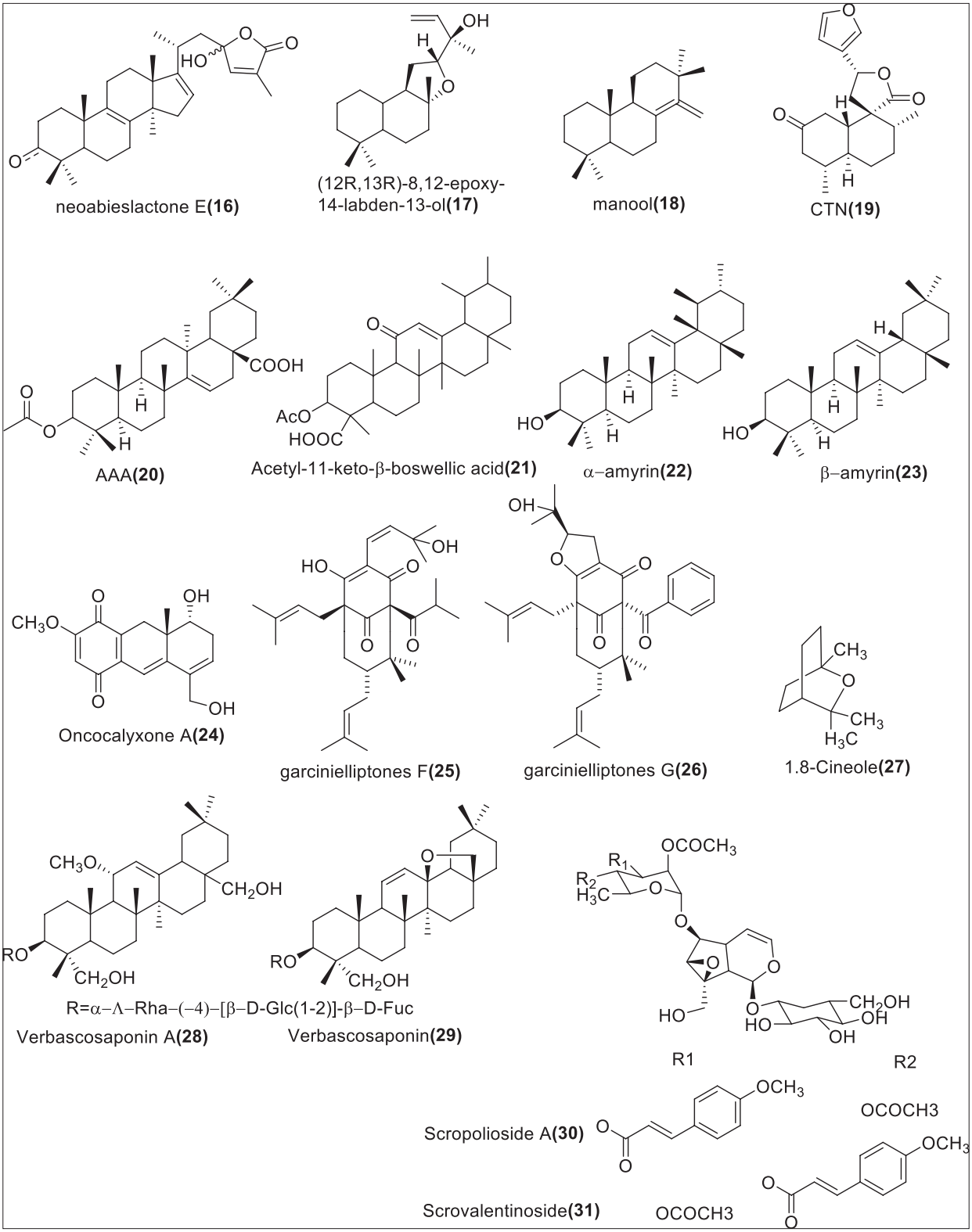

Fig. 2: Structures of compounds having anti-inflammatory potential

significantly inhibited the development of paw edema induced by egg albumen in rats [25]. Methanolic extracts prepared from stem of *Tinospora cordifolia* has identified the presence of bioactive molecules in the methanolic extract capable of inhibiting LOX and COX-2 isoenzymes [26]. Terpene alkaloid from *Fagraea racemosa* inhibited the production of prostaglandin E2 in 3T3 murine fibroblasts (IC50~5.1 μM) and was not cytotoxic to this cell line or to a P388 murine leukemia cell line [27].

3β-hydroxy-lup-20(29)-en-28-oic acid, betulinic acid (15) isolated from fruit of *Myrciaria dubia* showed anti-inflammatory activity in carrageenan-induced paw edema model mice. The crude extract suppresses the formation of paw edema by inhibiting localized NO production in carrageenan-treated mice [28]. Bark extract from *Rhizophora mucronata* showed the anti-inflammatory potential extracts led to the isolation of active phytoconstituent/s (1-6) such as lupeol, a new terpenoid adeneneol, quercetin, and caffeic acid, all of

which were subjected to carrageen induced paw edema and castor oil induced diarrheal method to assess the activity, it was observed that decrease in percentage of paw volume as caffeic acid <adeneol<lupeol< β-sitosterol, quercetin at 10 mg/kg with respect to control and quercetin and caffeic acid reduced the number of wet feces during the 4 hr study [29]. Several extracts from leaves of *Dodonaea polyandra* showed significant anti-inflammatory potential using the mouse ear edema model of acute inflammation induced by croton oil and TPA-12-o-tetradecanoylphorbol-13-acetate PMA- phorbol 12-myristate 13-acetate (TPA). The significant inhibitory effects of the extracts tested suggest that the prostaglandin pathway of the inflammation process may be a potential target of the active component [30]. Chloroform extract obtained from *Albizia chinensis* has shown reduction in the ulcer index ($p<0.001$) when compared to control and positive control [31]. Dried plant material (inflorescences, 404 g) was powdered and then heated in a ventilated oven at 120°C for 4 hr to decarboxylate pre-cannabinoids to cannabinoids. The compounds show outstanding potency in *in vivo* assays of inhibition of inflammatory responses [32]. Etoll: Benzene eluents obtained from *Inula racemosa* significantly affected inflammation in hind paw of albino rats by *I. racemosa* as well as its active principle [33]. Methanolic extract of *Azadirachta indica* L. showed statistically significant ($p<0.001$) analgesic activity in mice in a dose-dependent manner. A sustained and significant ($p<0.001$) inhibition of carrageenan-induced inflammation of rat paw was observed with 125 and 250 mg/kg body weight [34]. Active constituents have been extracted from *Tripterygium wilfordii*. Among the active constituents, celastrol, pristimerin, triptolide, tripchlorolide, and triptonide possess various pharmacological effects on inflammatory and immune response [35]. The ethanol and aqueous extracts from roots of *Pergularia daemia* and *Carissa carandas* exhibited significant ($p<0.01$) analgesic, anti-inflammatory and antipyretic activities at the doses of 100 and 200 mg/kg body wt. The ethanol and aqueous extracts of *P. daemia* and *C. carandas* were found to reduce significantly the formation of edema induced by carrageenan after 2 hr [36]. The essential oil isolated from *Schizophragma integrifolium* significantly inhibited the inflammation that caused by TPA- 12-o-tetradecanoylphorbol-13-acetate PMA-phorbol 12-myristate 13-acetate (PMA) or xylene. The essential oil from *S. integrifolium* mainly consisted of terpenoid and aromatic hydrocarbon with good anti-inflammatory effects [37].

Neoabieslactone E (5), (12R,13R)-8,12-epoxy-14-labden-13-ol (7), and manool (8) (16-18) was isolated from aerial parts of *Abies chensiensis* with anti-inflammatory potential. In a bioassay against LPS-induced NO production in RAW264.7 macrophages, three compounds, neoabieslactone E (5), (12R,13R)-8,12-epoxy-14-labden-13-ol (7), and manool (8), exhibited IC50 values of 9.1, 1.9, and 9.6 µg/mL, respectively [38]. Hydroalcoholic extract and its ethyl acetate fraction of *Hemidesmus indicus* showed significantly higher antiarthritic activity than chloroform and residual fraction. Histopathological analysis demonstrated that both of hydroalcoholic extract and its ethyl acetate fraction had comparable antiarthritic activity with methotrexates [39]. The 19-nor-clerodane trans-crotonin (CTN) (19) and the triterpene acetyl aleuritolic acid (AAA) (20) isolated from the stem bark of *Croton cajucara* Benth. Compound showed exhibited significant inhibition in the dextran-induced edema 90 minutes after the stimulus: 31.9% for CTN and 28.5% for AAA. In the histamine-induced edema, the inhibition showed by CTN and AAA were 43.2% and 40.5%, respectively [40]. Acetyl-11-keto--boswellic acid (AKBA) (21), a component of an Ayurvedic therapeutic plant *Boswellia serrata*, is a pentacyclic terpenoid active against a large number of inflammatory diseases AKBA inhibited the NF-B-dependent reporter gene expression activated by TNFR type 1, TNFR-associated death domain protein, TNFR-associated factor 2, NF-B-inducing kinase, and IKK [41].

α- and β-amyrin, (22,23) a triterpene mixture isolated from the trunk wood resin of folk medicinal plant, *Protium heptaphyllum* offers hepatoprotection against acetaminophen-induced hepatotoxicity. It results in diminution of oxidative stress and to the inhibition of cytochrome-P450 [15]. Oncocalyxone A (24) was isolated form quinone fraction (10 and 30 mg/kg body wt., i.p.) significantly inhibited paw edema induced by carrageenan at the 2nd, 3rd, and 4th hrs. The effect was dose-dependent and long lasting, and QF was less effective orally [42]. Three novel phloroglucinol derivatives, garcinielliptones F (25), and I (26), have been isolated from the seeds of *Garcinia subelliptica.* Compound 4 showed a potent inhibitory effect on NO production in culture media of N9 cells in response to LPS/IFN-gamma in a concentration-dependent manner with an IC50 value of 7.4±0.2 mm [43]. Two saponins, verbascosaponin A (28) and verbascosaponin (29), and two iridoids, scropolioside A (30) and scrovalentinoside (31), isolated from *Scrophularia auriculata* ssp. *Pseudoauriculata.* Verbascosaponin A showed potency twice as high as that of indomethacin in the acute TPA model. Both iridoids were active on the delayed type hypersensitivity reaction. They significantly reduced the inflammatory lesion and suppressed the cellular infiltration [44].

CONCLUSION

Plants have always been considered rich source of terpenoid. Recently discovered compounds like have shown significant advances in field of ant inflammation compounds. Terpenoids significantly inhibit the development of chronic joint swelling. Terpenoids may affect diverse mechanism relevant to inflammation arising in response to varied etiological factor because comprehensive studies of the action mechanisms of terpenoid have shown therapeutic effect on inflammation. Such approaches will likely show the diversity of the physiological effects and underlying action mechanisms of functional phytochemicals develop anti-inflammatory with additional safety. Hence, considering benefits of natural source all such herbal medicines should be screened for pharmacological activities, isolation of single entity responsible for anti-inflammatory activity, and development of suitable drug which would be beneficial against inflammatory ailments.

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