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Review Article

Sesquiterpenoids from the sunflower family as potential anti-inflammatory candidates: a review

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ABSTRACT

Inflammation is an essential part of the immune response to injury and infection. Emerging evidence indicates that long-term low-grade inflammation is positively correlated with many diseases, such as cancer, metabolic disorders, and cardiovascular diseases. Due to common anti-inflammatory drugs are suitable for treating acute inflammation and cause severe adverse effects, new safe and effective drug candidates are urgently needed for treating chronic inflammation. Plants of the Asteraceae family have been widely used in traditional medicines for relieving fever symptoms and killing pathogens. The anti-inflammatory properties of sesquiterpenoids from plants in the Asteraceae family have attracted increasing attention in recent decades because of their structural complexity and potent bioactivities. Herein, we provide a comprehensive and up-to-date summary of sesquiterpenoids from the Asteraceae family with anti-inflammatory properties, including their drug likeness and druggability, as analyzed with the SwissADME and ADMETlab online tools. In the future, some sesquiterpenoids might serve as therapeutic agents to treat inflammation-associated diseases.

Keywords: Asteraceae, sesquiterpenoids, anti-inflammation, drug-likeness, SwissADME, ADMETlab

1. INTRODUCTION

Inflammation is a key response of the immune system [1, 2]. Long-term low-grade inflammation is considered a culprit of cancer, metabolic disorders, and cardiovascular diseases [3-5]. During chronic inflammation, the profiles of pro-inflammatory and anti-inflammatory mediators greatly vary [6, 7]. Macrophages are present in most organs and tissues, and play important roles in tissue development, inflammation, and defense against pathogens [8-10]. M0 type macrophages can differentiate into either pro-inflammatory M1 type or anti-inflammatory M2 type macrophages [8-11]. The nuclear factor-κB (NF-κB) pathway and mitogen-activated protein kinase (MAPK) pathway are the main regulators of inflammatory responses. In the unstimulated state, the p50/p65 heterodimer is retained by the inhibitory protein IκB in the cytoplasm. Under external stimuli, IκB kinase (IKK) is activated and subsequently phosphorylates serine in the IκB subunit, resulting in IκB release and ubiquitination. The liberated NF-κB dimer then translocates to the nucleus and initiates downstream transcription [12]. Increased MAPK activity, particularly p38, c-Jun N-terminal kinases (JNKs), and extracellular signal-regulated kinases (ERKs), and their involvement in the regulation of the synthesis of inflammation mediators, make them potential targets for anti-inflammatory therapeutics [13].

Current clinically applied anti-inflammatory drugs include glucocorticoids and non-steroidal anti-inflammatory drugs, all of which can cause serious adverse reactions [14-16]. Thus, safe and effective anti-inflammatory drugs must urgently be developed. Natural products have become a promising alternative to identify drug leads, owing to their efficiency and safety. Growing evidence indicates the great potential

of natural medicines in treating inflammation-associated diseases [17, 18]. Drug-likeness is determined from structural or physicochemical inspection of a molecule, and used to qualitatively evaluate its bioavailability, and enable its use as an oral drug. Drug-likeness can be applied in the prediction of drug absorption, distribution, metabolism, and excretion (ADME) properties [19]. Drug-likeness and ADME properties of hits can be predicted in early stages of drug discovery, and compounds with ideal properties can be selected for experimental validation, thus decreasing costs and increasing the success rate of lead compound discovery.

Asteraceae is a very large family of flowering plants comprising more than 1,620 genera and 23,600 accepted species. Plants in the Asteraceae family are widely distributed worldwide except in Antarctica, and are particularly abundant in North America, the Andes in South America, eastern Brazil, the Mediterranean, Central Asia, and southwestern China [20, 21]. Many Asteraceae plants possess substantial therapeutic value in traditional medicines, such as *Artemisia annua* and dandelion [22, 23]. In China, many Asteraceae plants are used for treating inflammatory responses occurring after pathogens invade the human body. For example, chrysanthemum is widely used to treat throat inflammation, fever, headache, and oral ulcers [24], and dandelion is used to treat upper respiratory tract infections, lung infections, and purulent diseases [25]. Modern pharmacological studies have indicated that Asteraceae plants possess anti-cancer, cardiovascular-protective, hepatoprotective, anti-diabetic, anti-bacterial, and anti-viral properties [26-31]. Chemical investigations have been widely performed on Asteraceae plants to identify terpenoids, flavonoids, lignans, polyacetylenes, and polyphenols. Among these compounds, sesquiterpenoids are notable for their great structural complexity and diverse bioactivities [32]. Sesquiterpenoids consist of three isoprene units, which can be linear, monocyclic, bicyclic, or tricyclic. Most sesquiterpenoids exist in the form of volatile oils, as oxygen-containing derivatives, such as alcohols, ketones, lactones, etc. Several sesquiterpenes have been successfully developed as medicines, such as artemisinin for the treatment of malignant malaria [33].

Interestingly, many sesquiterpenoids from plants in the Asteraceae family have been reported with anti-inflammatory properties in *in vitro* or *in vivo* models [34, 35]. Herein, we provide a comprehensive and up-to-date summary of these sesquiterpenoids. We further analyzed their drug likeness by using the SwissADME and ADMETlab online tools, to aid in their development as candidates to treat inflammation-associated diseases.

2. SESQUITERPENOIDS FROM ASTERACEAE PLANTS WITH ANTI-INFLAMMATORY PROPERTIES

We searched the Google Scholar, Web of Science, Scopus, and PubMed databases with the keywords sesquiterpenoids, Asteraceae, and inflammation. A total of 88 sesquiterpenoids from Asteraceae plants with anti-inflammatory properties were identified (**Figures 1–4**). According to their carbon skeletons, these compounds can be classified into guaiane-type sesquiterpenoids (**1–65**, **Figures 1–3**), oplopane-type sesquiterpenoids (**66–75**), bisabolane-type sesquiterpenoids (**76–80**), eudesmanolide-type sesquiterpenoids (**81–83**), cadinane-type sesquiterpenoids (**84–87**), and a caryophyllane-type sesquiterpenoid (**88**) (**Figure 4**). The anti-inflammatory activities of these sesquiterpenoids are summarized in **Table 1**.

Lipopolysaccharides (LPS) are composed of lipids and polysaccharides, consisting of O-antigens, an outer nucleus and an inner nucleus linked by covalent bonds; they are present in the outer membranes of Gram-negative bacteria [69, 70]. LPS bind Toll-like receptor 4 (TLR4) or CD14, and consequently induce inflammatory responses in macrophages. LPS have been widely applied to identify anti-inflammatory agents and investigate their underlying mechanisms. Compounds **1–28**, **32**, **33**, **52**, **54–56**, and **61–80** exhibit anti-inflammatory activities in LPS-stimulated RAW264.7 macrophages [36-40, 42, 52, 53, 56, 58, 59, 61, 62, 71, 72]. Among them, compounds **1–28**, **32**, **33**, and **63–80** exhibit inhibitory effects against nitric oxide (NO) production, and compounds **66** and **70** down regulate heme oxygenase expression [57]. Compound **56** was found to suppress the mRNA expression of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, inducible NO synthase (iNOS), and cyclooxygenase-2 (COX-2) [53]. Compounds **52**, **54**, **55**, **61**, and **62** decrease the production of inflammatory factors through inhibiting the NF-κB pathway. Notably, compound **52** blocks NF-κB signaling through directly interacting with cysteine 46 of IKKα/β, according to activity-based protein profiling [35]. In LPS- and ATP-induced THP-1 macrophages, compounds **29–31** and **53** suppress inflammatory responses; among them, compounds **29** and **53** inhibit the activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasomes, thus decreasing the secretion of IL-1β [34, 41]. Interestingly, compound **53**, a structural analogue of compound **52** isolated from the same plant (*Ainsliaea macrocephala*), activates the deacetylase Sirtuin1, and consequently decreases the acetylation of NLRP3 and inhibits the activation of NLRP3 inflammasomes [34]. Furthermore, compound **53** decreases adipose tissue inflammation in C57BL/6J mice stimulated with LPS plus ATP [34]. LPS-induced BV-2 cells are often used as a model of neuroinflammation. In this model, compounds **34–47** were found to effectively inhibit NO production, suggesting their potential in the treatment of neuroinflammation [44, 45]. In addition, compounds **57–60** were found to inhibit NO production in LPS-induced 293T cells [55]. Ameliorating inflammation in macrophages is critical for a variety of human inflammatory disorders, such as sepsis-associated multiple organ dysfunction, acute brain/lung/hepatic/renal injuries, microbial infection, tumorigenesis, neurodegenerative

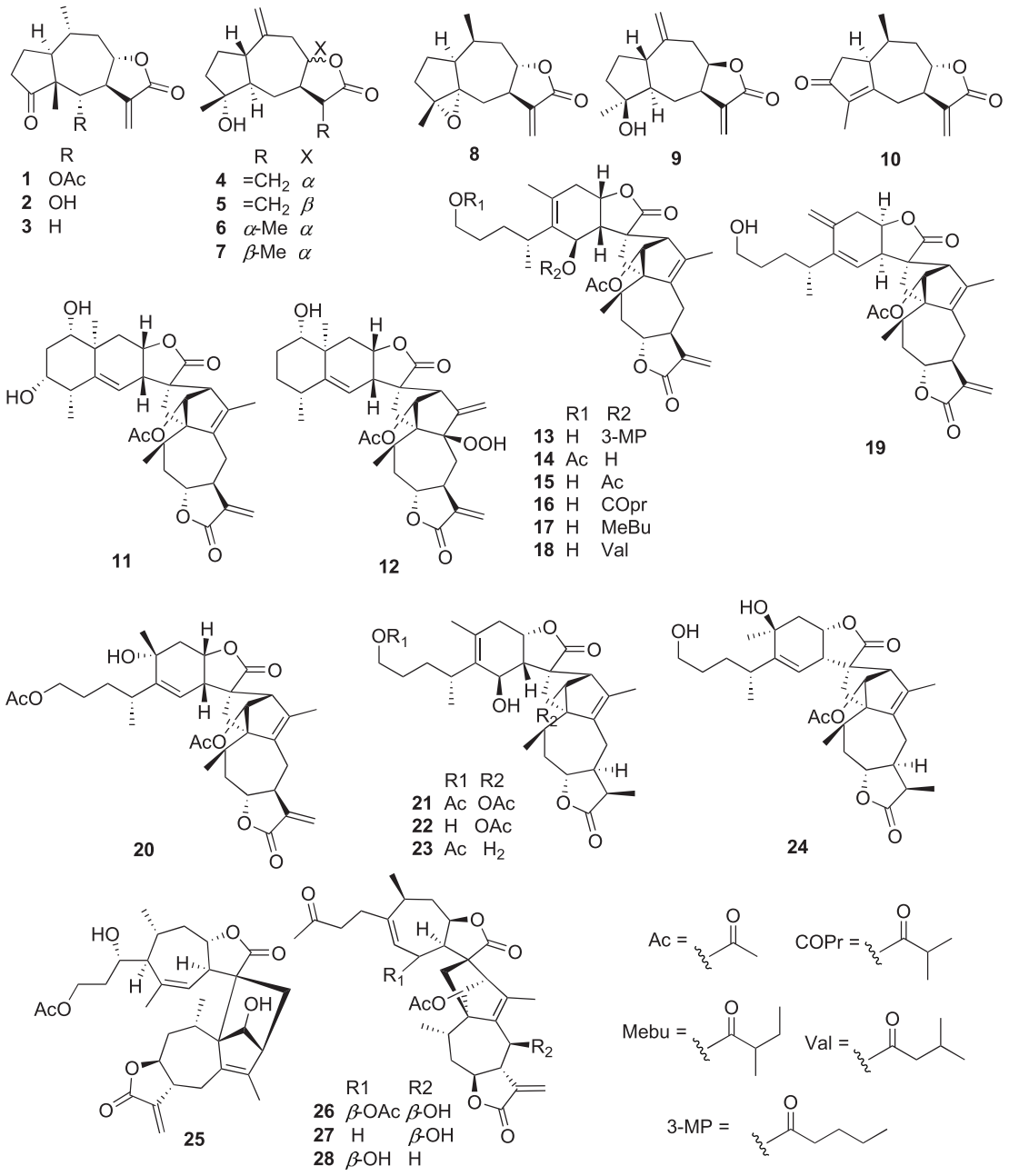

Figure 1 | Structures of guaiane-type sesquiterpenoids from plants of the genus *Inula* with anti-inflammatory activity.

disorders, cardiovascular and metabolic diseases, and autoimmune diseases. Thus, these compounds possess great potential to be further developed to treat a variety of inflammatory diseases.

TNF-α is a key pro-inflammatory cytokine [73]. Compound **48** was found to decrease TNF-α-induced inflammation in Jurkat cells through inhibiting the NF-κB pathway [46, 74]. In particular, compound **48** directly alkylates the p65 subunit of NF-κB at Cys38 and Cys120 [46], and might be used to treat acute T cell leukemia. COX-2 is an enzyme responsible for inflammation and pain [75]. In human colon HT29 cells, compounds **49** and **51** were found to suppress COX-2 levels, thereby alleviating inflammation [47-49]. Compounds **81–83**, were found to reduce inflammatory pain in a rat model of carrageenan-induced foot swelling [63]. Compound 12-*O*-tetradecanoylphorbol 13-acetate (TPA) induces skin inflammation through promoting the production of TNF-α and the formation of leukotriene B4 (LTB4) [66, 76]. Prolonged TPA exposure results in ear

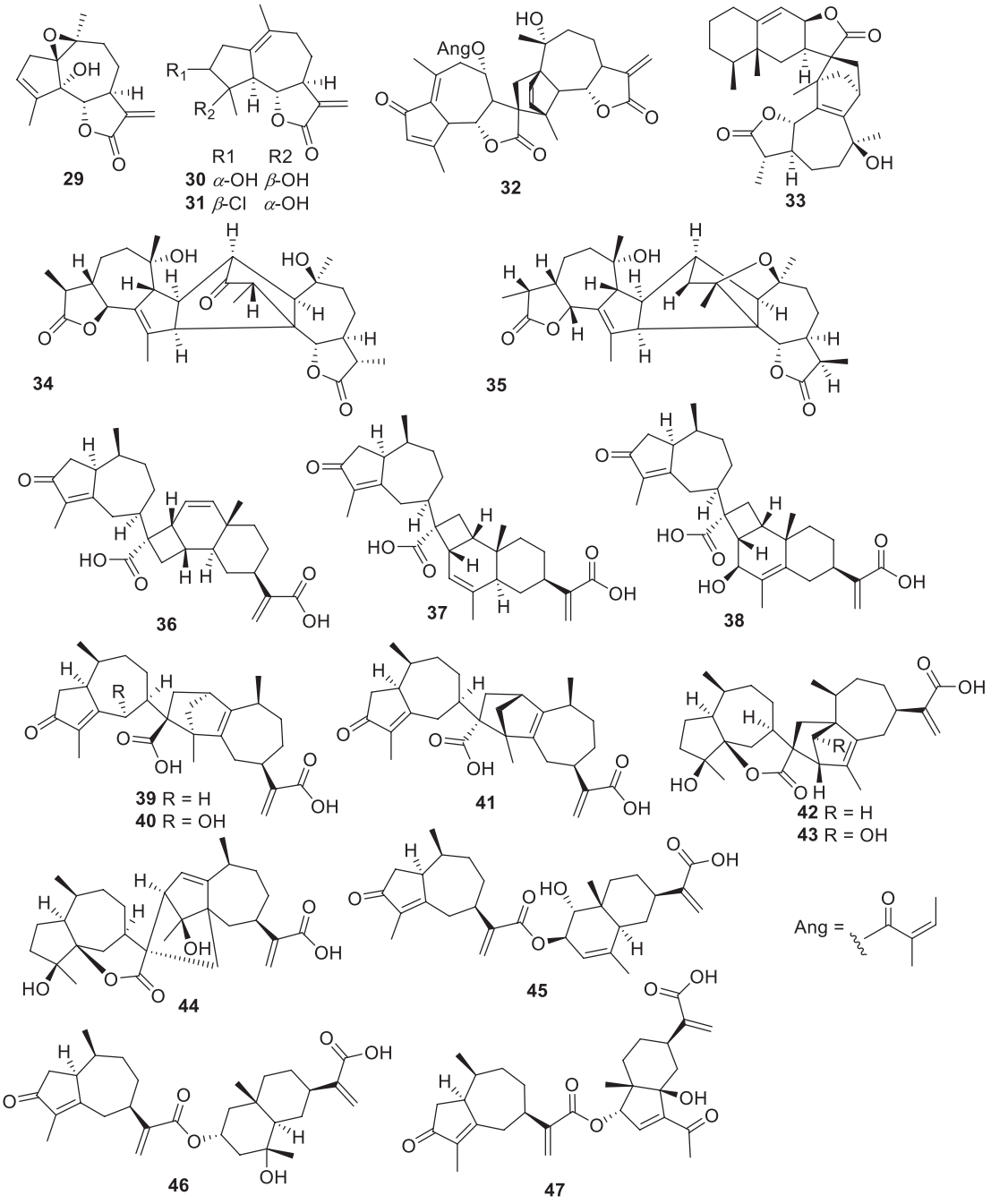

Figure 2 | Structures of guaiane-type sesquiterpenoids from plants of the genus *Artemisia* with anti-inflammatory activity.

swelling, inflammatory cell infiltration, and epidermal hyperplasia in mice [77]. In TPA-induced ear swelling mice, compounds **84–86** and **87** effectively alleviate ear inflammation [64-66, 76, 78]. These compounds could be developed to alleviate swelling and pain.

Acute lung injury (ALI) is a respiratory failure disease whose main pathological changes include excessive recruitment of pro-inflammatory mediators and activation of neutrophils. Compound **50** was found to decrease inflammatory cell infiltration and pro-inflammatory cytokine levels in an LPS-induced mouse model of ALI [50, 51]. Furthermore, compound **50** treatment suppresses phosphorylation of key regulators of the NF-κB signaling pathway in lung epithelial BEAS-2B cells and alveolar macrophage MH-S cells. In a murine model of colitis induced by dextran sulfate sodium, compound **88** attenuates inflammatory responses through suppressing NF-κB activity [67], and activating the endogenous

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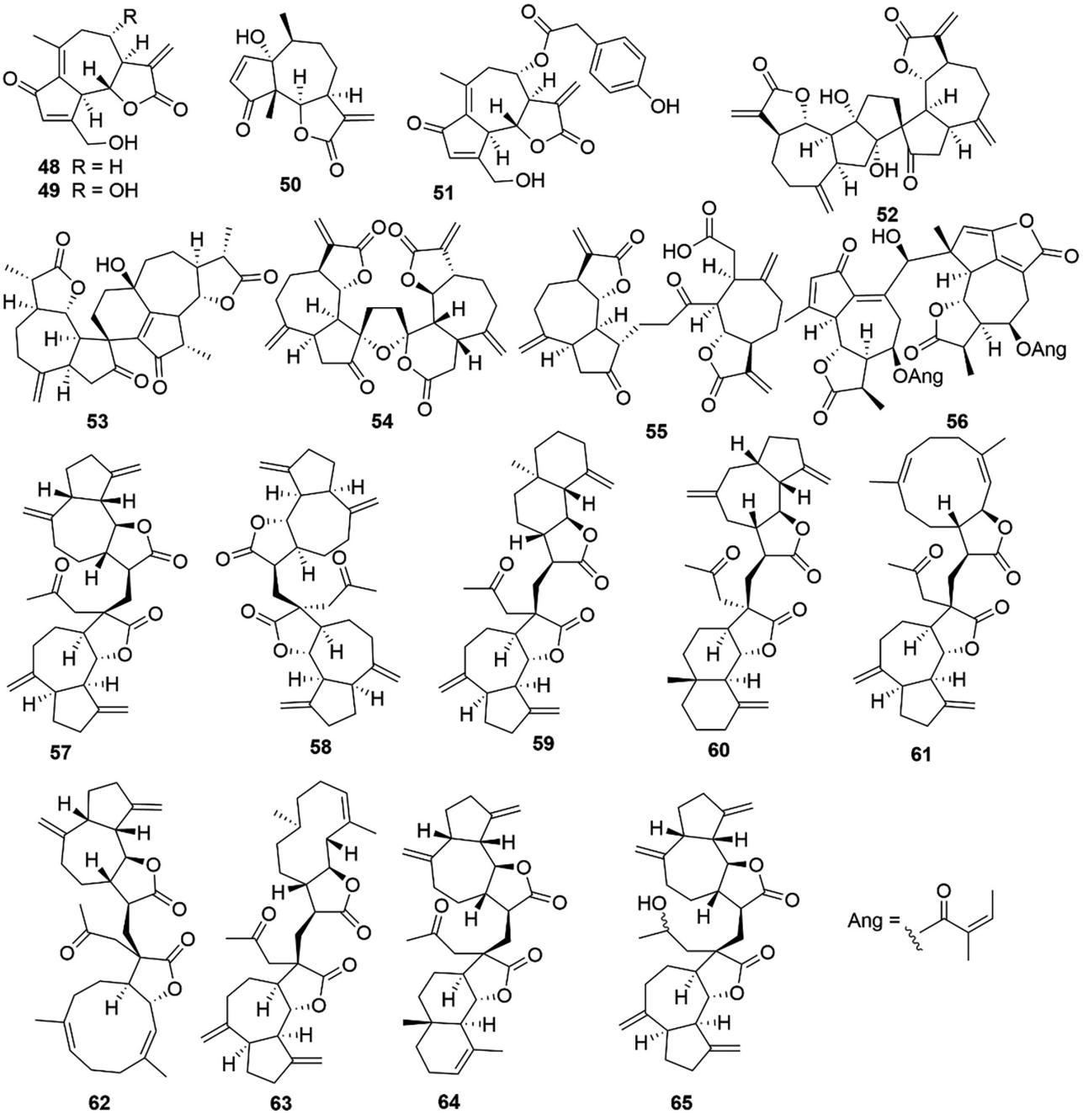

Figure 3 | Structures of guaiane-type sesquiterpenoids from other Asteraceae plants with anti-inflammatory activity.

cannabinoid 2 receptor and peroxisome proliferator-activated receptor-γ (PPARγ) pathway [68].

3. COMPARISON OF THE DRUG-LIKENESS OF ANTI-INFLAMMATORY SESQUITERPENOIDS FROM ASTERACEAE PLANTS WITH RESPECT TO MARKETED DRUGS

We used SwissADME, an online tool developed by the Swiss Institute of Bioinformatics [79], to predict the molecular descriptors of the anti-inflammatory sesquiterpenoids from Asteraceae plants. The simplified molecular input line entry system (SMILES) files of the compounds were uploaded to the website, and descriptors were predicted, including molecular weight (MW), number of chiral centers, numbers of hydrogen bond acceptors (HBA) and donors (HBD), number of rotatable bonds (RBs), number of rings, fraction of sp^3 carbons (Fsp^3, the ratio of sp^3 hybridized carbons to the total number of carbons), and the fraction of aromatic

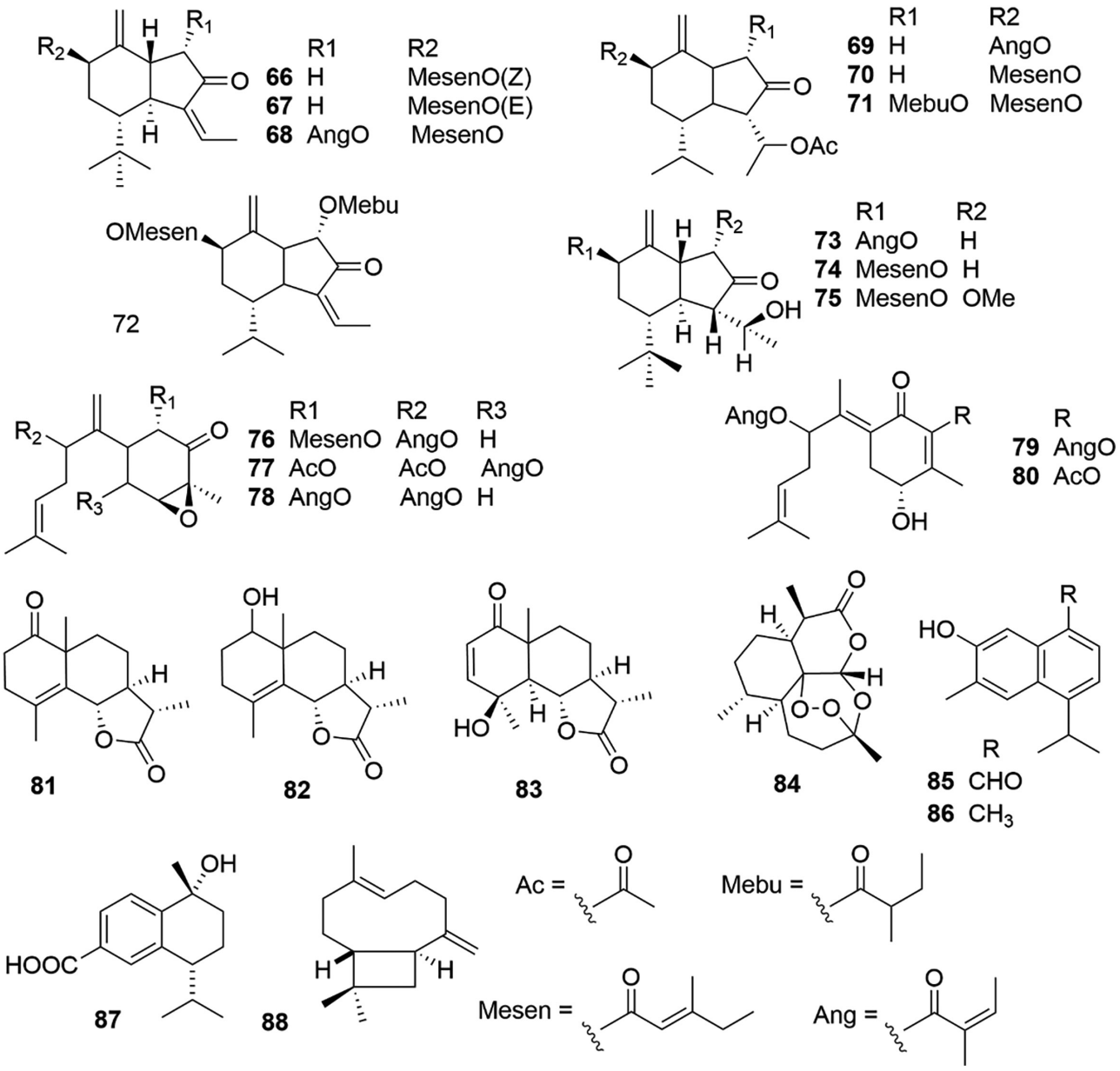

Figure 4 | Structures of oplopane-type sesquiterpenoids (66–75), bisabolane-type sesquiterpenoids (76–80), eudesmanolide-type sesquiterpenoids (81–83), cadinane-type sesquiterpenoids (84–87), and a caryophyllane-type sesquiterpenoid (88) from Asteraceae plants with anti-inflammatory activity.

heavy carbon atoms (Far, the number of heavy aromatic atoms divided by the total number of heavy atoms) [80]. In addition, the database supports simultaneous prediction and comparison of pharmacokinetic properties of multiple compounds. Seven molecular descriptors for each compound, including the mean and median values, were shown in **Supplementary Information Table S1**. ADME, drug-likeness, and medicinal chemistry friendliness are important factors in drug development [81]. The physicochemical properties, pharmacokinetics, polar surface area (PSA), logS, logP, and bioavailability properties of these sesquiterpenoids were documented in **Supplementary Information Table S2**. In addition, multiple algorithmic procedures were used to determine the values of logP and logS [82, 83].

We classified marketed drugs into synthetic compounds, assumed synthetic compounds, natural-product-type macrocycles, polycyclic compounds, natural products, and natural-product derivatives. Their molecular descriptors, including MW, HBA, HBD, logP, PSA, RBs, and number of chiral centers, were obtained from previous publications (**Supplementary Information**

Table 1 | Sesquiterpenoids from Asteraceae plants with anti-inflammatory activity.

Skeleton	Source	No	name	Model	Dose	Outcomes	References
Guaiane-type	*Inula falconeri*	**1**	Ergolide	LPS-induced RAW264.7 macrophages	0.07 μM*	Inhibition of NO production	[36]
		2	Carpesiolin		2.18 μM*		
		3	2,3-Dihydroaromaticin		0.40 μM*		
		4	Inuviscolide		9.64 μM*		
		5	8-Epiinuvisolide		3.94 μM*		
		6	11β,13-Dihydroinuviscolide		41.20 μM*		
		7	11α,13-Dihydroinuviscolide		19.53 μM*		
		8	4α,5α-Epoxy-10α,14H-1-***epi***-inuviscolide		0.11 μM*		
		9	4,8-Bis-***epi***-inuviscolide		7.30 μM*		
		10	Xerantholide		12.86 μM*		
	Inula japonica	**11**	Japonicone R	LPS-induced RAW264.7 macrophages	8.90 μM*	Inhibition of NO production	[37]
		12	Japonicone T		4.30 μM*		
		13	Japonicone Q		8.50 μM*		
		14	Inulanolide A		4.20 μM*		
		15	Japonicone M		12.0 μg/ml		[38]
		16	Japonicone N		-		
		17	Japonicone O		-		
		18	Japonicone P		-		
		19	Inulanolide C		4.90 μM*		[37]
		20	Japonicone S		4.30 μM*		
		21	Dibritannilactone B		43.77 μM*		[39]
		22	Dibritannilactone C		49.44 μM*		
		23	Dibritannilactone D		25.08 μM*		
		24	Dibritannilactone E		29.18 μM*		
	Inula linearііfolia	**25**	Linearііfolianoid I	LPS-induced RAW264.7 macrophages	1.02 μM*	Inhibition of NO production	[40]
		26	Linearііfolianoid J		1.79 μM*		
		27	Linearііfolianoid K		10.02 μM*		
		28	Linearііfolianoid L		10.16 μM*		

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Table 1 | Continued

Skeleton	Source	No	name	Model	Dose	Outcomes	References
	Artemisia codonocephala	**29**	Lavandolide D	LPS- plus ATP-induced THP-1 cells	3.31 μM*	Inactivation of NLRP3 inflammasomes	[41]
		30	3α,4β-Dihydroxy-5,7α,6β(H)-guai-1(10),11(13)-dien-12,6-olide		3.68 μM*	Inhibition of NO production	
		31	3β-Chloro-4α-hydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide		0.51 μM*		
	Artemisia argyi	**32**	Dsf-27	LPS-induced RAW264.7 macrophages	10 μM	Inhibition of NO production	[42]
	Artemisia freyniana	**33**	Artefreynisin A		38.30 μM*		[43]
	Artemisia absinthium	**34**	Absinthin C	LPS-induced BV-2 cells	1.52 μM*	Inhibition of NO production	[44]
		35	Isoanabsinthin		1.98 μM*		
	Artemisia rupestris	**36**	Artepestrin A	LPS-induced BV-2 cells	27.30 μM*	Inhibition of NO production	[45]
		37	Artepestrin B		39.80 μM*		
		38	Artepestrin C		29.80 μM*		
		39	Artepestrin D		32.70 μM*		
		40	6α-Hydroxyartepestrin D		23.00 μM*		
		41	Artepestrin E		38.60 μM*		
		42	Artepestrin F		17.00 μM*		
		43	2′α-Hydroxyartepestrin F		71.80 μM*		
		44	Artepestrin G		43.60 μM*		
		45	Rupestrinate A		33.00 μM*		
		46	Rupestrinate B		40.60 μM*		
		47	Rupestrinate C		30.10 μM*		
	Cichorium intybus	**48**	8-Deoxylactucin	TNF-α-induced Jurkat T-cells	50 μM#	Alkylation of Cys38 and Cys120 of the p65 subunit of NF-κB, and inhibition of NF-κB activation	[46, 47]
		49	Lactucin	Human colon HT29 cells	16 μg/ml	Inhibition of COX-2	[48, 49]
	Tanacetum vulgare	**50**	(3as,6S,6as,9as,9br)-6a-Hydroxy-6,9a-dimethyl-3-methylene-4,5,6,9b-tetrahydro-3ah-azuleno[8,7-b]furan-2,9-dione	Lung epithelial BEAS-2B cells and alveolar macrophage MH-S cells	20 μM	Inhibition of NF-κB pathway, decreased airway permeability and production of pro-inflammatory cytokines	[50, 51]
				LPS-induced ALI mice	10 mg/Kg		

Table 1 | Continued

Skeleton	Source	No	name	Model	Dose	Outcomes	References
	Cichorium intybus	**51**	Lactucopicrin	Human colon HT29 cells	-	Inhibition of COX-2	[48, 49]
	Ainsliaea macrocephala	**52**	Ainsliadimer A	LPS-induced RAW264.7 macrophages	8 μM	Targeting of Cys46 in IKKα/β to block NF-κB signaling	[35, 52]
		53	Ainsliadimer C	LPS- plus ATP-induced THP-1 cells/LPS plus ATP induced C57BL/6J mice	80 μM	Inactivation of NLRP3 inflammasomes	[34, 52]
		54	Macrocephadiolide A	LPS-induced RAW264.7 macrophages	0.99 μM*	Inhibition of NF-κB pathway	[52]
		55	Macrocephadiolide B		6.13 μM*		
	Eupatorium perfoliatum	**56**	Diguaiaperfolin	LPS-induced RAW264.7 macrophages	16.5 μM*	Suppression of mRNA expression of TNF-α, IL-1β, IL-6, iNOS, and COX-2	[53, 54]
	Vladimiria souliei	**57**	Vlasouliolide A	LPS-induced 293T cells	1.14 μM*		[55]
		58	Vlasouliolide B		2.53 μM*		
		59	Vlasouliolide C		1.57 μM*		
		60	Vlasouliolide D		3.19 μM*		
		61	Vlasouliolide E	LPS-induced RAW264.7 macrophages	1.88 μM*	Inhibition of NF-κB pathway	[56]
		62	Vlasouliolide F		4.89 μM*		
		63	Vlasouliolide G		-	Inhibition of NO production	
		64	Vlasouliolide H		7.24 μM*		
		65	Vlasouliolide I		2.46 μM*		
Oplopane-type	*Tussilago farfara*	**66**	Tussilagonone	LPS-induced RAW264.7 macrophages	11.86 μM*	Inhibition of NO production by regulation of heme oxygenase	[57, 58]
		67	7β-(4-Methylsenecioyloxy)-oplopa-3(14) E,8(10)-dien-2-one	LPS-induced RAW264.7 macrophages	10.80 μM*	Inhibition of NO production	[58]
		68	1α-Angeloyloxy-7β-(4-methylsenecioyloxy)-oplopa-3(14)Z,8(10)-dien-2-one		13.87 μM*		
		69	Tussilagone		71.57 μM*		[58, 59]
		70	14-Acetoxy-7β-angeloyloxy-notonipetranone	LPS-induced RAW264.7 macrophages	5.60 μM*	Inhibition of NO production by regulation of heme oxygenase	[59, 60]

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Table 1 | Continued

Skeleton	Source	No	name	Model	Dose	Outcomes	References
		71	14-Acetoxy-7β-(3-ethyl cis-crotonoyloxy)-1α-(2-methylbutyryloxy)-notonipetranone	LPS-induced RAW264.7 macrophages	3.50 μM*	Inhibition of NO production	[59]
		72	7β-(3-Ethyl cis-crotonoloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro-Z-notonipetranone		4.60 μM*		
		73	7β-Angeloyloxy-14-hydroxy-notonipetranone	LPS-induced RAW264.7 macrophages	60.29 μM*	Inhibition of NO production	[58]
		74	7β-(3′-Ethyl-cis-crotonoyloxy)-14-hydroxy-notonipetranone		32.87 μM*		
		75	7β-(3′-Ethyl-cis-crotonoyloxy)-14-hydroxy-1α-(2′-methylbutyryloxy)-notonipetranone		15.64 μM*		
Bisabolene-type	*Tussilago farfara*	**76**	1α-(3″-Ethyl-cis-crotonoyloxy)-8-angeloyloxy-3β,4β-epoxy-bisabola-7(14),10-diene	LPS-induced RAW264.7 macrophages	20.86 μM*	Inhibition of NO production	[58]
		77	1α,5α-Bisacetoxy-8-angeloyloxy-3β,4β-epoxy-bisabola-7(14),10-dien-2-one	LPS-induced RAW264.7 macrophages	5.51 μM	Inhibition of NO production	[61]
		78	1β,8-Bisangeloyloxy-3α,4α-epoxybisabola-7(14),10-dien-2-one	LPS-induced RAW264.7 macrophages	-	Inhibition of NO production	[62]
		79	Tussfararin F		13.60 μM*		
		80	(4R,6E)-2-Acetoxy-8-angeloyloxy-4-hydroxybisabola-2,6,10-trien-1-one		17.70 μM*		
Eudesmanolide-type	*Artemisia barrelieri*	**81**	Barrelierin	Carrageenan-induced foot swelling in rats	90 mg/Kg	-	[63]
		82	Artemalin		90 mg/Kg		
		83	Barrelin		15 mg/Kg		
Cadinane-type	*Artemisia annua*	**84**	Artemisinin	TPA-induced ear swelling in mice	200 μM	Inhibition of NF-κB pathway	[64]
	Heterotheca inuloides	**85**	7-Hydroxy-14-cadalenal		> 228 μg/ear		[65]
		86	7-Hydroxycadalene		>0.5 mg/ear	-	[66]
		87	1α-Hydroxy-4αh-1,2,3,4-tetrahydrocadalen-15-oic acid		>0.5 mg/ear	-	
Caryophyllane-type	*Heterotheca inuloides*	**88**	B-caryophyllene	Dextran sulfate sodium-induced colitis in mice	300 mg/Kg	Suppression of NF-κB activity, and activation of the endogenous CB2 receptor and PPARγ pathway	[67, 68]

*IC_{50}, #IC_{100}, maximum dosage for those without asterisk or pound marker.

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Table S3) [84]. We summarized the biophysiochemical properties of 88 sesquiterpenoids with anti-inflammatory properties from Asteraceae plants and compared with those of marketed drugs (Figure 5).

3.1 Size: molecular weight

Lipinski's rules have been widely used to evaluate drug candidates. These rules include no more than five HBD, no more than ten HBA, an MW <500 Daltons, and an octanol-water partition coefficient (logP) ≤5 [85]. The MWs of approved drugs showed an increasing trend from 300–360 Daltons (in 1959–1964) to 360–440 Daltons (in 2005–2009); in 2017, the MWs of 64% Food and Drug Administration (FDA)-approved drugs exceeded 440 Daltons [86]. The mean MW for anti-inflammatory sesquiterpenoids from Asteraceae plants is 436.00 Daltons, thus meeting Lipinski's rules (Figure 5a). Among these compounds, 60% of sesquiterpenoids had an MW <500 Daltons.

3.2 Chirality: number of chiral centers

A total of 56% of FDA-approved drugs contain one or more chiral centers, of which 88% exist in the form of a racemate [87]. Chirality is highly important for the interaction between a molecule and its protein target. The mean number of chiral centers of anti-inflammatory sesquiterpenoids from Asteraceae plants is 7.86, a number exceeding those of synthetic compounds, assumed synthetic compounds, polycyclic compounds, natural products, and natural-product derivatives, and less than those of natural-product-type macrocycles, owing to the structural complexity of sesquiterpenoids, particularly sesquiterpenoid dimers (Figure 5b). In general, total synthesis of a molecules containing multiple chiral centers is difficult [88, 89]. Thus, total synthesis of these sesquiterpenoids poses major challenges.

3.3 Polarity: PSA and HBD/HBA

PSA, defined as the molecular surface area of oxygen or nitrogen atoms plus hydrogen atoms connected to nitrogen or oxygen atoms, reflects the transportability of a molecule in the gastrointestinal (GI) tract. Topological PSA is often used in actual drug prediction [90]. Most molecules with more than five HBD and/or more than ten HBA are glycosylated compounds or amino acids, which cannot easily cross the blood-brain barrier (BBB) or any cellular membrane. Shultzs dataset analysis has indicated that 90% of drugs contain four or fewer HBD. The number of HBA increases significantly with increasing MW. The numbers of HBA and HBD affect the lattice energy and melting point, and thus are associated with solubility. In macromolecules, intramolecular hydrogen bonds are associated with permeability [91]. Owing to hydrogen bonding, PSA is highly correlated with the quantity of HBA but is less correlated with the quantity of HBD [89]. The mean PSA values are 84.36 $Å^2$ for anti-inflammatory sesquiterpenoids from Asteraceae plants, 86.9 $Å^2$ for new polycyclic drugs, and 105.3 $Å^2$ for natural products. The mean numbers of HBA and HBD for these sesquiterpenoids are 5.64 and 1.01. Similarly, HBA, HBD, and PSA values increase with increasing MW (Figures 5c-e and 6). Most anti-inflammatory sesquiterpenoids from Asteraceae plants meet Lipinski's rules and thus might exhibit good oral bioavailability.

3.4 Molecular flexibility: RBs and aromatic character

RBs, bonds with free rotation, are single bonds that are not adjacent to triple bonds, do not connect hydrogen or halogen atoms, and are not included in rings containing fewer than five single bonds [92]. Aromatic compounds, particularly hetero-aromatic compounds, have made substantial contributions to drug discovery. However, the amide C-N bond is excluded from RBs because of its high rotational energy barrier. Aromaticity and RBs, but not MW, greatly affect solubility. Low molecular flexibility, as measured by the number of RBs, and low PSA or total HB, are important predictors of good oral bioavailability [93]. A higher RB number decreases the permeation rate, and the permeation rate is a prerequisite for oral bioavailability. The data of 164 FDA-approved small molecules in the past 5 years indicated a high proportion of N-heterocycles (88%) and aromatic skeletons (87%), followed by chiral molecules (63%) [94].

The mean number of RBs in the anti-inflammatory sesquiterpenoids from Asteraceae plants is 4.06, and the mean number of aromatic heavy atoms is 0.36. The mean values of RBs for polycyclic compounds, natural products, natural-product derivatives, and synthetic drugs are 7.4, 9.4, 7.4, and 5.4, respectively. The RBs for most of these sesquiterpenoids are below those of polycyclic natural products, thus indicating a good permeation rate (Figure 5f).

Fsp^3 is the ratio of sp^3 hybridized carbons to the total number of carbons [95]. Fsp^3 is used to characterize the carbon saturation, aliphatic degree, and complexity of the spatial structures of molecules: a higher Fsp^3 value indicates less aromatic character [95, 96]. The complexity of the spatial structure of molecules is highly correlated with target affinity and specificity. Molecules with more complex 3D shapes commonly possess higher druggability, whereas molecules with high aromaticity show planar features, which are not conducive to target binding. Compared with synthetic compounds (mean Fsp^3 of 0.27) and natural products (mean Fsp^3 of 0.55), the anti-inflammatory sesquiterpenoids exhibit a mean Fsp^3 of 0.68, indicating complex spatial characteristics, less aromatic character, and higher druggability [97].

3.5 Lipophilicity: logP

The parameter logP, also termed hydrophobicity, is important in drug discovery and design [98]. The logP is closely associated with water solubility, membrane permeability, bioactive potency, and target selectivity and heterogeneity, and it affects the pharmacokinetic and pharmacodynamic properties of compounds. Proper lipid solubility, low MW, and PSA are the main

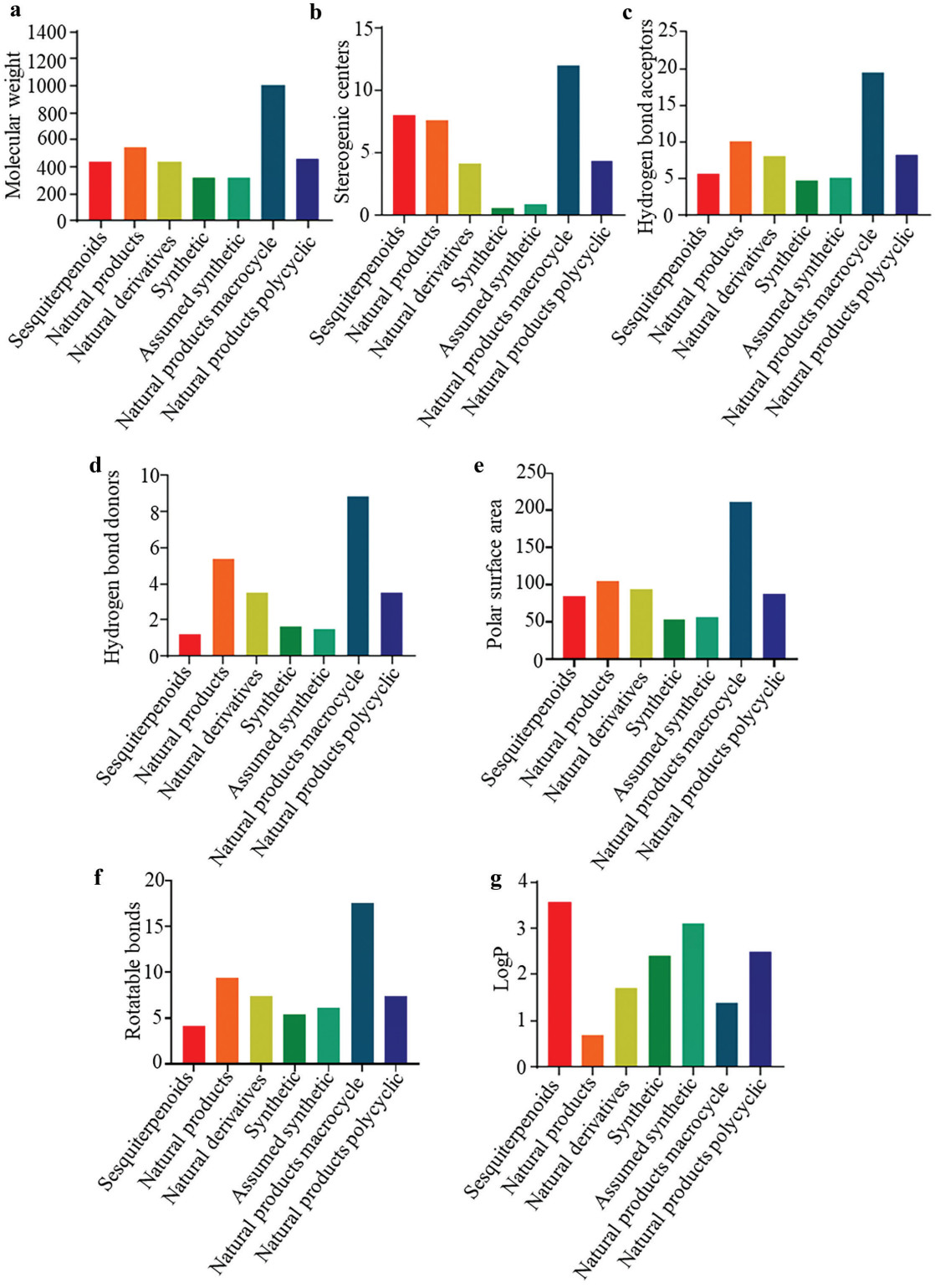

Figure 5 | Mean values of MW (a), stereogenic centers (b), HBA (c), HBD (d), PSA (e), RBs (f), and logP (g), for anti-inflammatory sesquiterpenoids from Asteraceae plants (red), natural products (orange), natural derivatives (yellowish brown), synthetic compounds (dark green), assumed synthetic compounds (aquamarine), macrocycle natural products (indigo), and polycyclic natural products (royal blue).

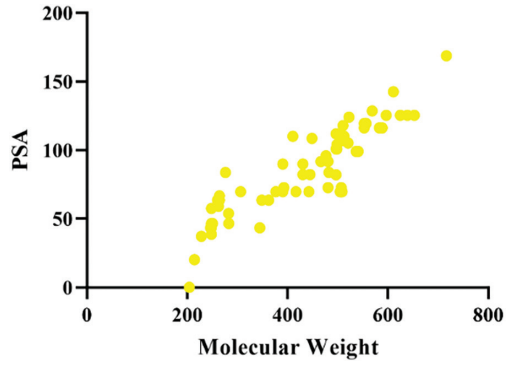

Figure 6 | PSA values of the anti-inflammatory sesquiterpenoids from Asteraceae plants vs MW.

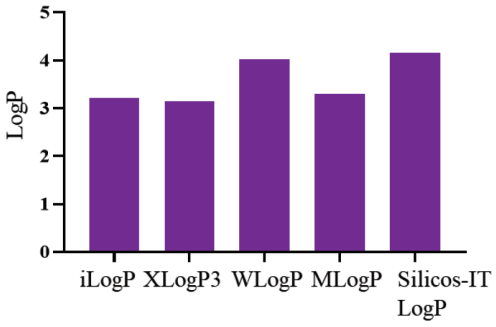

Figure 7 | Mean logP values of the anti-inflammatory sesquiterpenoids from Asteraceae plants, calculated with different methods.

forces driving good oral absorption of a compound. Lipophilicity is the ratio between the equilibrium concentrations of a molecule in 1-octanol and water, commonly described as logD, which represents the ratio for all species (unionized + ionized) of the molecule at a given pH value. D is therefore pH dependent for ionizable drugs. The distribution coefficient (D) is replaced with a partition coefficient (P) at any given pH if only one species (typically neutral) is present. The logP value of an ideal drug is generally between 1 and 5 [99].

The logP values of anti-inflammatory sesquiterpenoids from Asteraceae plants substantially vary depending on the predictive method in SwissADME. SwissADME supplies five available predictive models: 1) ilogP, an in-house physics-based method relying on free energies of solvation in n-octanol and water, calculated by the generalized Born and solvent-accessible surface area (GB/SA) model [98]; 2) XlogP3, an atomistic knowledge-based method [100]; 3) WlogP, a purely atomistic method based on the fragmental system [101]; 4) MlogP, an archetypal topological method relying on a linear relationship with 13 molecular descriptors [102]; and 5) Silicos-IT logP, a hybrid method relying on 27 fragments and seven topological descriptors [79]. The calculated logP values are averages of all five predictions. The logP value of anti-inflammatory sesquiterpenoids (3.56) satisfies the criteria for good oral bioavailability (**Figure 5g**). For each sesquiterpenoid, we compared the logP values obtained from the above five methods with the average logP value. The greatest differences (maximum discreteness) of ilogP, XlogP3, WlogP, MlogP, and Silicos-IT log P were 18, 30, 7, 16, and 17, respectively. Thus, XlogP3 is the most discrepant method among all logP indexes (**Figure 7** and **Supplementary Information Table S2**).

3.6 Solubility: logS

To be absorbed into the body, drugs must be dissolved in water and be able to penetrate biofilms. The solubility of a compound is expressed in logS (mol/L). The commonly used water solubility prediction methods include the free energy calculation method based on quantum mechanics and molecular mechanics, and the quantitative structure-activity relationship method, which has relatively high computational complexity [103]. The development of poorly water-soluble compounds would be risky and time-consuming. A compound with a solubility of at least 100 μg/mL can be considered to have good water solubility. logS values greater than -4 are acceptable for drugs. In fact, only 39% of anti-inflammatory sesquiterpenoids from Asteraceae plants meet this requirement, indicating that most compounds would face solubility challenges (**Figure 8**).

4. COMPLIANCE OF ANTI-INFLAMMATORY SESQUITERPENOIDS FROM ASTERACEAE PLANTS WITH DRUG-LIKENESS RULES

Drugs can be effectively assessed according to Lipinski's rules, as described above. Candidates with poor oral bioavailability can be quickly excluded. Most anti-inflammatory sesquiterpenoids from Asteraceae plants show good drug-likeness, according to the results of SwissADME global assessment (**Supplementary Information Tables S1-S4**). However, FDA-approved drugs with high MW and high logP account for only 1%. Only a few oral active drugs violate two or more Lipinski's rule parameters. Recently, GlaxoSmithKline has considered additional physicochemical data for small drug molecules and discussed behavioral patterns, refinements, and implications of these five rules, providing new insights and principles for drug discovery [91]. According to ADMETlab 2.0 [104] prediction results, only 22% of these compounds simultaneously meet the Lipinski, Pfizer, GlaxoSmithKline, and Golden Triangle rules (**Figure 9** and **Supplementary Information Table S5**).

5. TRENDS IN THE PHARMACOKINETIC BEHAVIOR OF ANTI-INFLAMMATORY SESQUITERPENOIDS FROM PLANTS OF THE ASTERACEAE FAMILY

Beyond efficacy and toxicity, a great number of failures in drug development are attributable to poor

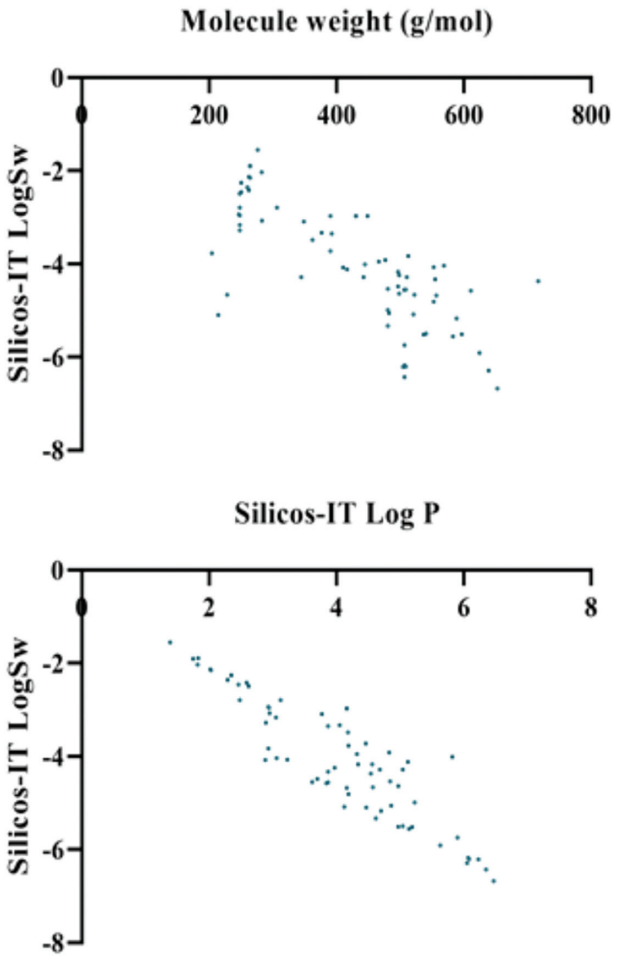

Figure 8 | logS (SILICON-IT) of anti-inflammatory sesquiterpenoids from Asteraceae plants vs MW and logP (SILICON-IT).

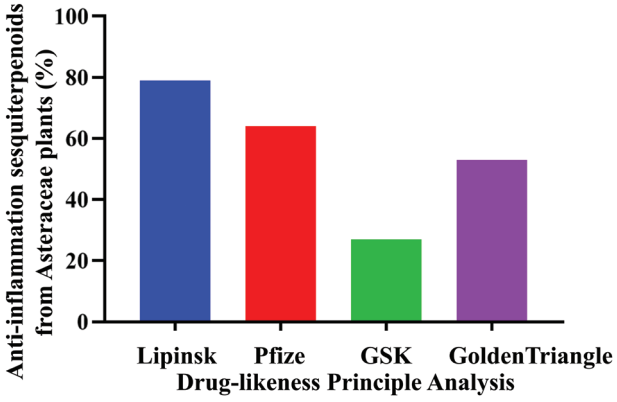

Figure 9 | Drug-likeness principle analysis of the sesquiterpenoids from Asteraceae plants.

pharmacokinetics and bioavailability. GI absorption and the BBB are critical considerations in various stages of the drug discovery process. BOILED-Egg was proposed as an accurate predictive model that calculates the lipophilicity and polarity of small molecules [105]. The evaluation and optimization of active chemicals from the perspective of drug metabolism and pharmacokinetics, the selection of clinical candidates, and applications for new investigational drugs provide indispensable knowledge for scientific and management personnel involved in research and development of new drugs. These methods can be applied in a variety of settings, from chemical library filtering in the early stages of drug discovery to evaluation [106].

Approximately 82% of the anti-inflammatory sesquiterpenoids from Asteraceae plants exhibit a high probability of being absorbed in the GI (**Figure 10a** and **Supplementary Information Figure S1**). Approximately 72 sesquiterpenoids exhibit high GI absorption, possibly because of their relatively low MW. In addition, 51 sesquiterpenoids show a high probability of being a substrate for P-gp (**Figure 10b**). The BBB, formed by the brain capillary endothelium, is the most important barrier in the human body, and excludes 100% of macromolecular drugs and more than 98% of small-molecule drugs [107]. Most anti-inflammatory sesquiterpenoids possess a low probability of being able to cross the BBB (**Figure 10c**), suggesting the possibility of their development as neuroinflammatory drugs.

The pharmacokinetic properties of drugs are substantially determined by their physical and chemical properties. However, metabolic enzymes and transporters in the human body greatly affect the pharmacokinetic properties of drugs. Metabolic enzymes can metabolize drugs into more water-soluble metabolites, thus accelerating drug excretion from the body, whereas membrane transporters regulate the drug distribution in the body through the selective transport of some drugs. SwissADME indicates the potential ability of these sesquiterpenoids to act as P-gp substrates, thus inhibiting one of five major isoforms of cytochrome p450 (CYP450, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) [80, 108]. CYP450 is widely involved in drug metabolism. The predicted results were shown in **Supplementary Information Table S4**. The anti-inflammatory sesquiterpenoids from Asteraceae plants provide substantial opportunities to serve as CYP450 enzyme inhibitors, particularly for CYP2C9 (**Figure 11**). If a drug metabolized by CYP450 is used in combination with its inducer or inhibitor, the effectiveness and safety of drug interaction should be noted. If necessary, the dosage should be adjusted, or other drugs should be chosen.

6. TOXICITY

With ADMETlab 2.0, the toxicity of these sesquiterpenoids was predicted and analyzed (**Supplementary Information Table S6**). We selected three representative toxicity evaluation indicators: carcinogenicity, human Ether-a-go-go-associated Gene (hERG) toxicity,

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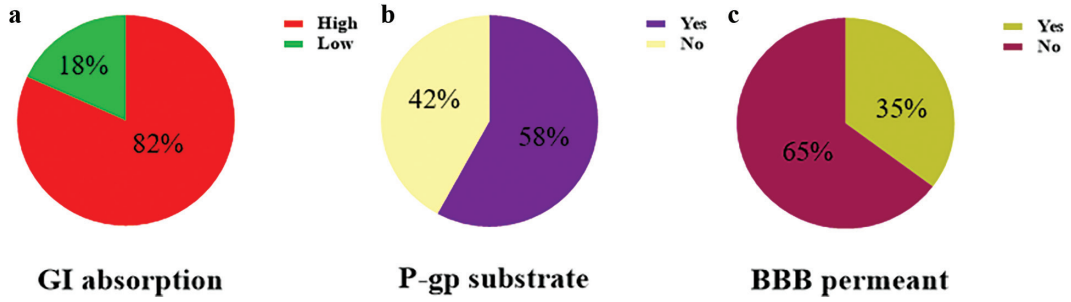

Figure 10 | (a) GI absorption of sesquiterpenoids from Asteraceae plants. (b) Classification of P-gp substrates for compounds with high GI absorption. (c) BBB permeability of sesquiterpenoids from Asteraceae plants.

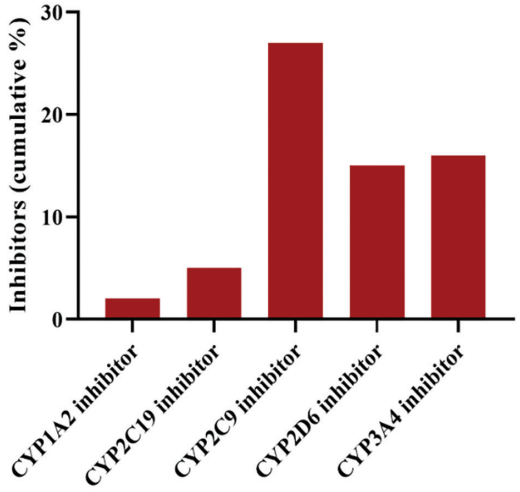

Figure 11 | Numbers of CYP450 enzyme inhibitors from the sesquiterpenoids from Asteraceae plants.

and drug-induced liver injury (DILI). Carcinogenicity is an important indicator in drug safety evaluation [109]. Carcinogenic compounds increase the incidence of tumors, thus severely threatening human health. The predictive models of the carcinogenicity of compounds can be classified into local models and global models. Local models focus on N-nitroso compounds, aromatic amines, and polycyclic aromatic hydrocarbon equivalents. hERG is a human delayed rectifier potassium channel gene. The potassium channel encoded by this gene plays an important role in repolarization of the action potential. Many drugs increase the cardiac QT interval through their action on hERG potassium channels, resulting in serious adverse effects and potentially sudden death [110]. Several marketed drugs show a tendency to inhibit hERG, leading to a risk of adverse drug reactions associated with sudden death, such as terfenadine and cisapride. DILI is a common adverse drug reaction [111] and a serious threat to human health which is a major reason for failures in drug research and development, restriction of use, and withdrawal from the market. Because the molecular mechanism of drug-induced hepatotoxicity is complex, predicting DILI is very difficult. Bioinformatics and computational models based on drug molecular structure are widely used to predict drug-induced hepatotoxicity, such as the Bayesian method, deep learning, and the substructure pattern-recognition method. These models have yielded useful results in practical applications for predicting hepatotoxicity.

Approximately 44% of these sesquiterpenoids might exhibit carcinogenicity (**Figure 12a**), 9% sesquiterpenoids might possess hERG toxicity (**Figure 12b**), and, more importantly, 74% may cause hepatotoxicity. Critical attention should be paid to the toxicity of these compounds in pre-clinical research.

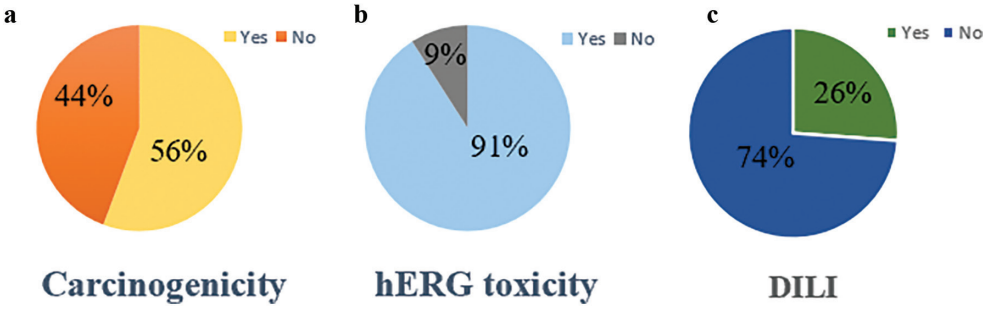

Figure 12 | Toxicity analysis of the sesquiterpenoids from Asteraceae plants.

7. CLINICAL RESEARCH

By searching the ClinicalTrials.gov website, we identified four relevant clinical studies (compounds **50**, **51**, **84**, and **88**). Parthenolide (**50**) is to be developed in an allergic contact dermatitis detection panel. As part of the appetite suppressor in dietary supplement, the effects of lactucopicrin (**51**) in regulating incretin (GIP and GLP-1) and peptide hormones in human plasma have been evaluated. A total of 233 relevant clinical studies have investigated artemisinin (**84**), many of which have focused on its application in the treatment of malaria. Its effect on schizophrenia induced by *Toxoplasma gondii* infection was studied. Notably, artemisinin has been evaluated in the treatment of hospitalized patients with severe Coronavirus Disease 2019. The National Center for Complementary and Integrative Health at the University of Washington investigated whether β-caryophyllene (**88**) inhalation has positive feedback effects on the stress-reducing effects of forest bathing.

8. CONCLUSIONS AND PERSPECTIVES

Drug discovery is a complex interdisciplinary process. On average, only one of every 80,000–100,000 compounds is approved for marketing. Plants in the Asteraceae family are widely distributed and have been traditionally used for the treatment of inflammation-associated diseases. In this review, 88 anti-inflammatory sesquiterpenoids from plants in the Asteraceae family were summarized according to their carbon skeletons, origins, and pharmacological activities. Although many *in vitro* and *in vivo* studies have demonstrated these sesquiterpenoids with anti-inflammatory activities, practical applications of these compounds remain less. More clinical trials are necessary for development of these compounds as anti-inflammatory drugs.

In new drug research and development, most candidates fail during clinical trials, owing to low efficacy and selectivity, adverse pharmacokinetic properties, or unexpected adverse effects. Among these factors, pharmacokinetics and toxicity issues account for around 50% of failures in drug development. ADME determines the bioavailability, duration of action, and required dosage of a drug *in vivo*. In addition, toxicity is closely associated with pharmacokinetics, which is usually considered in combination with ADME, termed ADME/T. Owing to the poor consistency in findings between animal models and *in vitro* cellular models in evaluating the potential toxicity of candidate drugs, and the inability to simulate the complex environment in human body, the accuracy of ADME/T is low. With the development of combinatorial chemistry and high-throughput screening technology, extensive data have been generated, thus enabling progress in artificial intelligence and learning algorithms. Artificial intelligence and machine learning tools are increasingly being applied to predict drug pharmacokinetics properties and drug-induced toxicity. With the large amount of *in vitro* toxicity data generated by high-throughput experiments, as well as the development of neural networks and learning algorithms, artificial intelligence may become a powerful tool for mining hidden information in big data, and play major roles in predicting the pharmacokinetics and toxicity of drug candidates.

Herein, the anti-inflammatory sesquiterpenoids were virtually predicted with SwissADME to obtain their ADME and drug-likeness properties. Many sesquiterpenoids show potential to become drug candidates for treating inflammatory diseases. More phytochemical, structural modification, and pharmaceutics studies are needed to enhance potency and selectivity, improve bioavailability, and decrease toxicity. SwissADME is a powerful tool to predict the druggability of a molecule, and may decrease the likelihood of failure in clinical research.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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