

Table 1 - Terpenes that modulate the main symptoms of arthritis in animal models and its major molecular mechanisms.

References	Substance	Arthritis models	Animal (Strain/Sex)	Dose, quantity (route)	In vivo analysis					Mechanism of action
					Behavior/ Body weight	Edema/ swelling /width	Hematological/ biochemical/ immune parameter	Histological/ Morphological/	Molecular/ Immunohistochemistry	
Cascão et al. (2012)	Celastrol (triterpenoid)	AIA	Rats (Wistar/F)	1 and 2 µg/g (I.P)	-	ankle diameter	-	Paw	-	Decreased inflammatory infiltrate
Chen et al. (2015)	Geniposide (iridoid glycoside)	Adjuvant induce arthritis	Rats (Sprague–Dawley/M)	30, 60, or 120 mg/kg (i.g.)	-	Paw volume	-	Ankle joints	↓ IL-1, IL-6, TNF- $\alpha$ , and ↑ IL-10; ↓ (p)-MKK-3/6, p38, MAPKAP2	Attenuated immune and inflammatory response
Chen et al., (2013)	Emodinol, (oleane triterpene)	Crystal-induced ankle arthritis	Mice (BALB/c/M)	20, 40 or 80 mg/kg (g.f.)	thermal hyperalgesia	ankle swelling	-	ankle joints	↓ TNF- $\alpha$ , IL-1 $\beta$ , and IL-6	Attenuated immune and inflammatory response
Endale et al. (2013)	Torilin (sesquiterpene)	CIA	Mice (DBA/1J/M)	30 and 90 mg/kg (o.g.)	Body weight gains	-	Differential white blood cell counts and red blood cell	Hind paws	↓IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IFN- $\gamma$ , IL-17 and ↑ IL-10	Attenuated immune and inflammatory response
Fukumitsu et al. (2016)	Maslinic acid (pentacyclic triterpene)	CAIA	Mice (DBA/1J / M)	100 mg/kg (p.o)	-	paw swelling	-	Knee joints	TNF- $\beta$ , ↓ IL-1 $\beta$ , and ↓ IFN- $\gamma$	Attenuated immune and inflammatory response
Kang et al. (2008)	Ursolic acid (pentacyclic triterpenoic acid)	AIA	Rats (Sprague–Dawley/M)	50 mg kg <sup>-1</sup> ()	Mechanical hyperalgesia (Randall-Selitto test) thermal hyperalgesia (Hargreaves's method)	paw volume	-	Hind limb	↓ PGE <sub>2</sub> and Fos	Attenuated immune and inflammatory response and modulates Fos expression due to PGE <sub>2</sub> regulation
Lee et al. (2013)	Lemnalol (sesquiterpenoid)	monosodium urate (MSU)	Rats (Wistar/M)	30 mg/kg (i.m.)	Mechanical Allodynia (von Frey filaments)	Knee width and ankle edema	-	knee- and ankle-joint;	↓ iNOS, COX-2 and c-Fos	Attenuated immune and inflammatory response and modulates c-Fos expression
Li et al. (2009)	Madecassoside (triterpenoid)	CIA	Mice (DBA/1J/ M)	3, 10, and 30 mg/kg (i.g.)	-	Hind paw	-	Ankle joints	↓ TNF- $\alpha$ , IL-6, COX-2; PGE <sub>2</sub> ; ↑ IL-10;	Inhibited TNF- $\alpha$ , IL-6, PGE <sub>2</sub> , and expression. Of COX-2 and to up-regulate the expression of IL-10

Li et al. (2017)	Crocin (tetraterpenoid)	FCA	Rats (Sprague–Dawley/M)	6.25, 12,5 and 25 mg/kg (i.g.)	-	toe swelling rate; Thymus and spleen index	-	-	↓ iNOS; IL-1 $\beta$ , IL-6, and TNF- $\alpha$	Inhibited expression of iNOS; IL-1 $\beta$ , IL-6, and TNF- $\alpha$
Liu et al, (2014)	1 $\beta$ -hydroxy alantolactone (sesquiterpene lactone)	CIA	Mice (DBA/1/M)	2 and 10 mg/kg (i.p.)	-	-	-	knee joint	↓ MCP-1, MMP3, and MMP13	Inhibited expression of MCP-1, MMP3, and MMP13
Liu et al. (2015)	Parthenolide (sesquiterpene lactone)	CIA	Rats (Dark Agouti/F)	1 mg/kg (s.c.)	-	paw swelling	-	Toes; Hind paws and femora	-	Attenuated inflammatory response
Lu et al. (2012)	Kireinol (diterpenoid)	CIA	Rats (Wistar/ F)	2 mg/kg (o.g.)	-	-	-	ankle joints	↑ Foxp3, TNF- $\alpha$ , IFN- $\gamma$ , IL-17, IL-6, ↑ IL-10, IL-4 and TGF- $\beta$ 1	Immunosuppressive activity and up-regulation IL- 10, IL-17, IL-4 and TGF- $\beta$ 1
Nanjundaiah et al. (2012)	Celastrol (pentacyclic triterpenoid)	AA	Rats (Lewis /SsNHsd/ M)	1 mg/kg (i.p.)	-	-	-	-	↓MMP-9	Attenuated inflammatory response
Quintão et al. (2014)	$\alpha$ , $\beta$ -amyrenone, glutinol, and $\alpha$ , $\beta$ -amyrin (triterpenoid) isomers	AA	Mice (Swiss/ M/F)	2.35–23.5 $\mu$ mol/kg (p.o)	mechanical hypersensitivity (Von Frey hair);	paw edema	-	-	-	Reduction in neutrophil migration
Sabina et al. (2012)	boswellic acid (pentacyclic triterpene)	MSUC	Mice (Swiss/M)	30 mg/kg (i.p)	-	thickness of the paw	-	-	↓TNF- $\alpha$	anti-inflammatory activity
Salinas-Sánchez et al. (2015)	Acid Hautriwaic (entclerodane diterpene)	KC	Mice (CD-1/F)	5, 10 and 20 mg/kg (p.o)	-	Knee joint edema	-	-	↓ IL-1 $\beta$ , IL-6, TNF- $\alpha$ and ↑ IL-10	immunomodulatory effect and increased IL-1
Saravanan et al. (2014)	Swertiamarin (iridoid glycoside)	AIA	Rats (Spargue Dawrley/F)	2, 5 and 10 mg/kg (p.o.)	body weight	Paw thicknes	C Reative Protein; $\beta$ -D-glucuronidase; N-acetyl-b-Dglucosaminidase ; $\beta$ -D-galactosidase	hind paw	↓ IL-1 $\beta$ , TNF- $\alpha$ , IL-6, MMP-9, iNOS, COX-2, ↓ PGE <sub>2</sub> , PPAR $\gamma$ ; ↑ IL-10 and IL-4;	Attenuated immune and inflammatory response
Tong <i>et al.</i> (Tong et al., 2014)	Pristimerin (triterpenoid quinone methide)	AA	Rats (Lewis SsNHsd/M)	1 mg/Kg (i.p.)	-	-	-	hind paws	-	Attenuated inflammatory response
Venkatesha et al. (2012)	Celastrol (pentacycli c triterpene)	AA	Rats (Lewis /Hsd, RT.11/M)	200 $\mu$ g/rat (i.p)	-	-	-	-	↑ GRO/KC, MCP-1 and ↓ RANTES; ↓ TNF- $\alpha$ ,	

									↓ IL-1 $\beta$	
Wang et al. (2014)	Boswellic acid (pentacyclic triterpene)	DMM	Mice (C57BL/6J /M)	10 mg/kg (p.o) 25 $\mu$ l of m (c.t.) 140 $\mu$ g/ml	-	-	-	Knees	-	attenuated articular cartilage erosion
Wang et al. (2011)	Kirenol (diterpenoid)	CIA	Rats (Wistar/M)	(1, 2, and 4 mg/kg (i.g.))	-	Paw swelling	-	ankle joints	↓IL-1 $\beta$ ; ↓NF- $\kappa$ B; Annexin-1; GR- $\alpha$ ;	Attenuated inflammatory response
Wang et al. (2016b)	Taraxasterol (triterpene)	AA	Rats (Wistar/M)	2, 4 and 8mg/kg (i.g)	Body weight	hind paw	-	Knee joints and hind paws	TNF- $\alpha$ , IL-1 $\beta$ , PGE <sub>2</sub> , ↑OPG and ↓RANKL	Attenuated inflammatory response
Wang et al. (2017)	Geniposide (iridoid glycoside)	CIA	Rats (Wistar/F)	33, 66, and 132 mg/kg (i.g.)	-	hind paw	-	mesenteric lymph nodes	-	Attenuated inflammatory response
Xiong et al. (2014)	Clematichinenside (triterpenoid saponin)	AIA	Rats (Sprague-Dawley/M)	8, 16, 32 mg/kg (i.g.)	-	Paw swelling	-	Rear paw	↑Foxp3 and ↓ROR $\gamma$ ; ↑IL-10 and TGF- $\beta$ <sub>1</sub> ; ↓IL-17, ↓TNF- $\alpha$	Attenuated inflammatory response
Zhang et al. (2017)	Tanshinone IIA (diterpenoid naphthoquinone)	AIA	Mice (C57BL/6/F)	5, 10, 25 $\mu$ M (?)	-	Joint diameter	-	ankle joint	↓MPO, ↓NE	Attenuated inflammatory response