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► To cite this version:

Corinne Vanucci-Bacqué, Florence Bedos-Belval. Anti-inflammatory Activity of Naturally Occuring Diarylheptanoids - A Review. Bioorganic and Medicinal Chemistry, 2021, 31, pp.115971. <10.1016/j.bmc.2020.115971>. <hal-03102451>

HAL Id: hal-03102451

<https://hal.science/hal-03102451v1>

Submitted on 22 Jan 2021

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Anti-inflammatory Activity of Naturally Occurring Diarylheptanoids - A Review

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Abstract:

Inflammation involving the innate and adaptive immune systems is a normal response to infection. However, if it becomes uncontrolled, inflammation may result in autoimmune or auto inflammatory disorders, neurodegenerative diseases or cancers. The currently available anti-inflammatory drug therapy is often not successful or induces severe side effects. Thus, the search of new therapeutic options for the treatment of inflammation is highly required. Medicinal plants have been an interesting source for obtaining new active compounds. Diarylheptanoids characterized by a 1, 7-diphenylheptane structural skeleton, are a class of secondary plant metabolites that have gained increasing interest over the last few decades due to a wide variety of biological activities. This review covers 182 natural linear or macrocyclic diarylheptanoids described in the period of 1982 to 2020 with anti-inflammatory activities evaluated using quantified *in vitro* and/or *in vivo* assays. All of these data highlight the pharmacological potential of these natural compounds to act as anti-inflammatory drugs.

Keywords: anti-inflammatory activity, natural diarylheptanoids, inflammatory mediator, macrocycles.

Abbreviations : AA: ascorbic acid ; ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid ; Akt: Protein kinase B ; Api : β -D-apiofuranosyl ; BMDC: bone marrow derived cell ; COX: cyclooxygenase ; DPPH : 2,2-diphenyl-1-picrylhydrazyl ; EGFR: epidermal growth factor receptor ; ERK: extracellular signal-regulated kinase ; Glc : β -D-glucopyranosyl ; 5-HETE : 5-Hydroxyeicosatetraenoic acid ; HO-1: heme oxygenase 1 ; HUVEC: human umbilical vein endothelial cell ; IC₅₀: half maximal inhibitory concentration ; ID₅₀ : half maximal inhibitory concentration dose; ICAM-1: intercellular adhesion molecule 1 ; IL: interleukin ; INF- γ : interferon γ ; iNOS: inducible nitric oxide synthase ; L-NMMA : N-monomethyl-L-arginine ; LPS : lipopolysaccharide ; MAPK: mitogen-activated protein kinase ; mRNA: messenger ribonucleic acid ; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide ; NBT: nitro-blue tetrazolium ; NF- κ B: nuclear factor kappa light chain enhancer of activated B cells ; NO: nitric oxide ; NSAID: non-steroid anti-inflammatory drug ; PG: prostaglandin ; PPAR : peroxisome proliferator-activated receptor; ROS: reactive oxygen species ; TBARS: Thiobarbituric acid reactive substances ; STAT: signal transducers and activators of transcription ; TNF- α : tumor necrosis factor α ; TPA: 12-O-tetradecanoylphorbol- 13-acetate ; VCAM-1: vascular cell adhesion protein 1 ; Xyl: β -D-xylopyranosyl

1. Introduction

Inflammation is a combination of reactions generated by the body due to an aggression which can be external, such as an injury, infection or trauma, or internal, such as those observed in autoimmune diseases.¹ The inflammation process is complex and divided mainly into acute and chronic inflammation. Acute inflammation is the immediate response to an aggressive agent and is essential to maintain the organism integrity. To the opposite, chronic inflammation does not heal spontaneously, persists over several months or even years and sustains many pathologies such as rheumatoid arthritis,² inflammatory bowel disease,³ atherosclerosis,⁴ diabetes,⁵ cancers⁶ and Alzheimer's disease.⁷ These inflammatory diseases are self-induced by excessive secretion of numerous pro-inflammatory mediators such as cytokines, reactive oxygen species (ROS) and nitric oxide (NO) radicals.

The therapy of inflammation mainly focuses on steroid and non-steroid anti-inflammatory drugs (NSAIDs). Corticosteroid is one of the most commonly used medications and can regulate the fat and protein metabolisms. However, corticosteroid therapy has side-effects such as sepsis and gastrointestinal hemorrhage, making their long-term consumption controversial and representing an important limitation to the use of these drugs. NSAIDs, a group of different chemical classes without any steroidal structure, display also diverse adverse-effects (mainly digestive, renal and cutaneous) making their long-term use inappropriate.⁸ Although continuous efforts have been made to discover molecules with anti-inflammatory therapeutic value in organic and medicinal chemistry, finding potentially non-toxic and effective substances for inhibiting inflammation is always urgently required.

Toward this aim, diarylheptanoids, a class of secondary plant metabolites with a wide range of biological activities including anti-inflammatory [see ref cited in this review], pro-apoptotic,⁹ anti-influenza,¹⁰ anti-emetic¹¹ and anti-cancer activities¹² have been attracting growing interest over the last few decades. Diarylheptanoids consist of a 1,7-diphenylheptane skeleton. They can be subdivided into linear and macrocyclic compounds (**Fig. 1**). The latter can be further distributed into biaryl and diarylether structures, depending whether the aromatic rings are connected to form [7.0]-*meta,meta*- or [7.1]-*meta,para*-cyclophanes respectively. The aromatic rings of diarylheptanoids are often hydroxylated or methoxylated. The C7-chain essentially incorporates ketone, alkene and alcohol functionalities, but also 1,5- or 3,6-oxy bridges (pyran or furan ring), flavonoid (e.g. chalcone, flavanone) and glycosyl moieties. Historically, the yellow pigment curcumin has been characterized as the first diarylheptanoid and the extensive research on naturally occurring analogues is still ongoing. Approaching 500 diarylheptanoids have been isolated and characterized so far.¹³

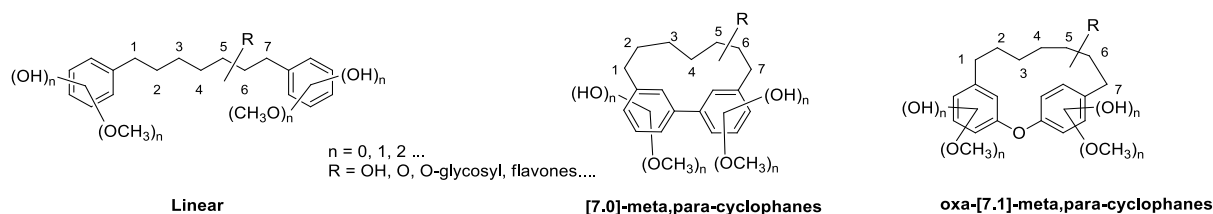


Fig. 1. Representative diarylheptanoid skeletons

This review provides a comprehensive overview of 182 naturally occurring diarylheptanoids displaying anti-inflammatory activity. Most of them have been isolated from plant genus including *Curcuma*, *Zingiber*, *Alpinia* (Zingiberaceae), *Alnus*, *Corylus*, *Betula*, *Carpinus* (Betulaceae), *Myrica* (Myricaceae),

Acer (Aceraceae) and *Juglans* (Juglandaceae), which roots, leaves and barks are often used in traditional Asian medicine. Figure 2 illustrates the distribution of the 182 diarylheptanoids between the different genus.

Fig. 2. Sources of anti-inflammatory diarylheptanoids

2. Materials and methods

2.1. Sources, search and selection modes

This review compiled extensive literature (from 1982 to June 2020) of the anti-inflammatory activity of natural diarylheptanoids evidenced by *in vitro* and *in vivo* studies with quantified data. All articles without any mention of anti-inflammatory assay were excluded. All values in the present review are rounding values. Positive control values are mentioned as reference point whenever they were cited in the referenced article. Most of positive references used in this review are acid ascorbic (AA), indomethacin, N-monomethyl-L-arginine (L-NMMA). AA acts as anti-inflammatory drugs through its strong antioxidant properties.¹⁴ Indomethacin is a non-steroid anti-inflammatory drug (NSAID) acting as non-selective inhibitor of the isoenzymes cyclooxygenases 1/2 (COX-1/COX-2).¹⁵ L-NMMA is an inhibitor of inducible nitric oxide synthase (iNOS).¹⁶

Curcumin and its better known derivatives demethoxycurcumin and bis-demethoxycurcumin, major constituents of *Curcuma longa* rhizomes, have been deliberately excluded from this review. Curcumin is low-soluble, unstable in aqueous media, poorly bioavailable, non-selective¹⁷ and has already been widely reviewed for its pleiotropic activity.^{18,19}

Only accessible online articles in English available via classic databases such as Pubmed and Scifinder were considered. Patents, proceedings, conferences abstracts and theses were rejected.

2.2. Studies descriptions

In the pathological inflammatory process, immune cells such as macrophages are first activated, then recruited to the injury site, resulting in the generation of ROS that damage macromolecules including DNA. At the same time, these inflammatory cells produce also large amounts of inflammatory mediators which further activate multiple signal transduction cascades and transcription factors associated with inflammation. The nuclear factor kappa-B (NF- κ B), mitogen-activated protein kinase (MAPK), and janus kinase (JAK), signal transducers and activators of transcription (STAT) signaling pathways are involved in the development of the classical pathway of inflammation. Thus, the NF- κ B transactivation will increase the production of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6), and the activity of important pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenases-2 (COX-2) and their derived production NO and prostaglandin E2 (PGE₂), respectively.²⁰ The anti-inflammatory activity of a compound is thus usually highlighted by evaluating its potency to inhibit the pro-inflammatory cytokines/mediators production and the inflammatory protein and enzyme expression. Among the mentioned articles in this review, 182 diarylheptanoids were selected for their reported anti-inflammatory activity. Their toxicity was evaluated by measuring cell viability with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and their antioxidant potency was

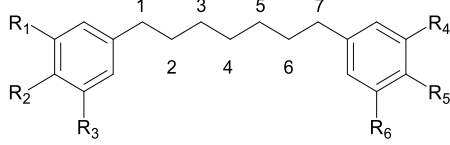
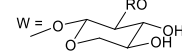
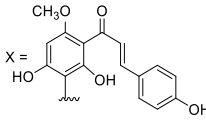
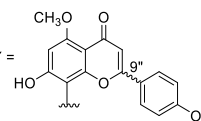
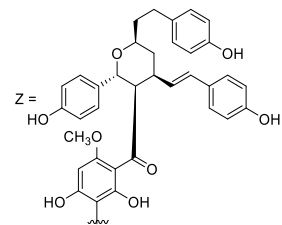
essentially estimated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, nitro-blue tetrazolium (NBT) superoxide or 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging assays. Their *in vitro* and/or *in vivo* anti-inflammatory activities were measured through different assays. Among the examined methods for *in vitro* evaluation, cell stimulation (mostly by lipopolysaccharides (LPS)) to induce inflammation followed by quantification of production/inhibition and RNA expression of inflammatory mediators such as NO, TNF- α , IL-1 β , IL-6 or PGE₂, of transcription factor such as NF- κ B, or inflammatory enzymes such as iNOS or COX-2, were applied in the majority of the studies. Most of the assays were conducted using RAW 264.7 or J774.1 murine macrophage cell lines, mouse peritoneal macrophages, HepG2 cells, N-11 or BV-2 microglia cells and activated bone marrow derived (BMD) macrophages. *In vivo* studies were performed essentially using the carrageenan-induced hind paw edema test in rats and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear inflammatory edema assay in mice. All these assays are relevant for inflammation studies.

The reported data will be subdivided into two structure types, including linear (Tables 1 and 2) and macrocyclic diarylheptanoids (Tables 3 and 4).

3. Linear natural diarylheptanoids

The structures of the selected linear diarylheptanoids are compiled in Table 1 (compounds **1-133**) for compounds with a linear heptanoid chain and in Table 2 (compounds **134-150**) for derivatives including 1,5-oxo bridge in the seven-carbon chain skeleton. Compound **151** with a 3,6-oxo bridge in the C7-chain is depicted in Fig.3. Stereochemistry is reported as mentioned in the original articles.

Table 1. Structures and sources of natural anti-inflammatory linear 1,7-diarylheptanoids.

		 <p>W₁ : R = p-coumaroyl W₂ : R = benzoyl W₃ : R = 2-methylbutanoyl W₄ : R = cinnamoyl</p>													
Diarylheptanoids	Sources of evaluated diarylheptanoids	1	2	3	4	5	6	7	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	
Muricarpone B (1)	<i>Alnus sibirica</i> ²³⁻²⁵ <i>Nidus vepae</i> ²⁶	–	–	O	–	–	–	–	OH	OH	–	OH	OH	H	
Hirsutenone (2)	<i>Alnus sibirica</i> ²³⁻²⁵ <i>Alnus formosana</i> ²⁷ <i>Alnus japonica</i> ^{28, 30-32, 33} <i>Alnus hirsuta</i> ²⁹ <i>Alnus tinctoria</i> ³⁴	–	–	O	Δ ⁴ (E)	–	–	OH	OH	–	OH	OH	H		
Hirsutanonol (3)	<i>Alnus sibirica</i> ^{23, 25} <i>Alnus formosana</i> ²⁷ <i>Alnus japonica</i> ²⁸ <i>Alnus hirsuta</i> ^{29, 35, 36}	–	–	O	–	(S)-OH	–	OH	OH	H	OH	OH	H		
5-O-Methyl hirsutanonol (4)	<i>Alnus sibirica</i> ²³ <i>Alnus japonica</i> ^{37, 38}	–	–	O	–	(S)-OMe	–	OH	OH	H	OH	OH	H		
5	<i>Alnus formosana</i> ²⁷ <i>Alnus japonica</i> ²⁸ <i>Alnus nepalensis</i> ³⁹	–	–	O	–	(S)-O-GLc	–	OH	OH	H	OH	OH	H		
Oregonin (6)	<i>Alnus sibirica</i> ²³ <i>Alnus formosana</i> ^{27, 41, 42} <i>Alnus japonica</i> ^{28, 37, 41, 45} <i>Alnus hirsuta</i> ^{35, 36, 43} <i>Alnus nepalensis</i> ³⁹ <i>Alnus tinctoria</i> ³⁴ <i>Alnus incana</i> ⁴⁴	–	–	O	–	(S)-O-Xyl	–	OH	OH	H	OH	OH	H		

Rubranol (7)	<i>Alnus sibirica</i> ^{23, 25} <i>Alnus formosana</i> ²⁷ <i>Alnus japonica</i> ²⁸	–	–	(R)-OH	–	–	–	–	OH	OH	–	OH	OH	H
Rubranoside A (8)	<i>Alnus sibirica</i> ²³ <i>Alnus formosana</i> ²⁷ <i>Alnus japonica</i> ²⁸	–	–	(R)-O-Glc	–	–	–	–	OH	OH	H	OH	OH	H
Rubranoside B (9)	<i>Alnus sibirica</i> ²³ <i>Alnus formosana</i> ²⁷ <i>Alnus hirsuta</i> ⁴³	–	–	(R)-O-Xyl	–	–	–	–	OH	OH	H	OH	OH	H
10	<i>Alnus japonica</i> ²⁸	–	–	(R)-O-Xyl(3→1)-Glc	–	–	–	–	OH	OH	H	OH	OH	H
11	<i>Alnus japonica</i> ²⁸	–	–	(R)-O-Glc(6→1)-Api	–	–	–	–	OH	OH	H	OH	OH	H
Platypylloside (12)	<i>Alnus japonica</i> ²⁸ <i>Alnus nepalensis</i> ³⁹	–	–	O	–	(S)-O-Glc	–	–	H	OH	H	H	OH	H
Alluside A (13)	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-O-Xyl	–	–	OH	OH	H	H	OH	H
Alluside B (14)	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-O-Xyl	–	–	H	OH	H	OH	OH	H
15	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-OMe	–	–	H	OH	H	H	OH	H
16	<i>Alnus formosana</i> ²⁷	$\Delta^1(E)$		O	–	–	$\Delta^6(E)$		OH	OH	H	OH	OH	H
17	<i>Alnus formosana</i> ²⁷	–	–	(R)-OH	–	–	–	–	H	OH	H	OH	OH	H
18	<i>Alnus formosana</i> ²⁷	–	–	(R)-O-Xyl	–	–	–	–	H	OH	H	H	OH	H
19	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-W ₁	–	–	OH	OH	H	OH	OH	H
20	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-W ₂	–	–	OH	OH	H	OH	OH	H
21	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-W ₃	–	–	OH	OH	H	OH	OH	H
22	<i>Alnus formosana</i> ²⁷	–	–	O	–	(S)-W ₄	–	–	OH	OH	H	OH	OH	H
Platyphyllenone (23)	<i>Alnus formosana</i> ²⁷ <i>Alnus sibirica</i> ²³	–	–	O		$\Delta^4(E)$	–	–	H	OH	–	H	OH	H
24	<i>Alnus formosana</i> ²⁷	–	–	(R)-O-Glc	–	–	–	–	H	OH	H	OH	OH	H
25	<i>Alnus formosana</i> ²⁷	–	–	(R)-O-Glc	–	–	–	–	OH	OH	H	H	OH	H
Aceroside VII (26)	<i>Alnus formosana</i> ²⁷ <i>Acer nikoense</i> ⁴⁶	–	–	(R)-O-Glc	–	–	–	–	H	OH	H	H	OH	H

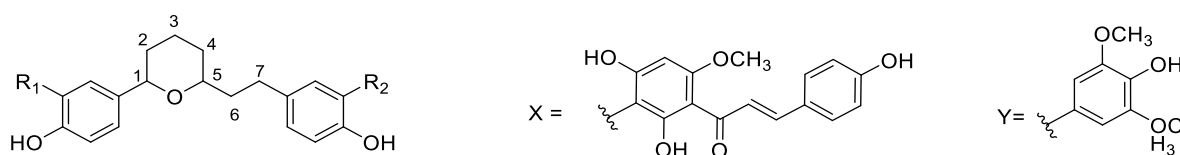
(-)-Centrololol (27)	<i>Alnus sibirica</i> ²³ <i>Acer nikoense</i> ⁴⁷	–	–	(R)-OH	–	–	–	–	H	OH	H	H	OH	H
(+)-Centrololol (28)	<i>Nidus vespa</i> ²⁶	–	–	(S)-OH	–	–	–	–	H	OH	H	H	OH	H
29	<i>Nidus vespa</i> ²⁶	–	–	(S)-OH	–	–	–	–	H	OH	H	OH	OH	H
30	<i>Nidus vespa</i> ²⁶	–	–	O	–	–	–	–	OH	OH	H	H	OH	H
Tsaokoarylone (31)	<i>Dioscorea nipponica</i> ⁴⁸	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		H	OH	H	OCH ₃	OH	H
32	<i>Dioscorea nipponica</i> ⁴⁸	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		H	OH	H	OH	OH	H
33	<i>Dioscorea nipponica</i> ⁴⁸ <i>Alnus formosana</i> ²⁷	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		OH	OH	H	OH	OH	H
34	<i>Dioscorea nipponica</i> ⁴⁸	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		H	OH	H	H	OCH ₃	H
35	<i>Dioscorea nipponica</i> ⁴⁸		$\Delta^1(E)$	O	–	(R)-OH	–	–	H	OH	H	H	OH	H
Yakuchinone A (36)	<i>Alpinia oxyphylla</i> ⁵⁰⁻⁵²	–	–	O	–	–	–	–	OCH ₃	OH	H	H	H	H
Yakuchinone B (37)	<i>Alpinia oxyphylla</i> ⁵⁰⁻⁵³		$\Delta^1(E)$	O	–	–	–	–	OCH ₃	OH	H	H	H	H
38	<i>Alpinia officinarum</i> ^{55, 56}	–	–	O	$\Delta^4(E)$		–	–	H	H	H	H	OH	H
39	<i>Alpinia officinarum</i> ^{50, 55, 57-60}	–	–	O	$\Delta^4(E)$		–	–	H	H	H	OCH ₃	OH	H
40	<i>Alpinia officinarum</i> ⁵⁰	–	–	O	–	O	–	–	H	H	H	OCH ₃	OH	H
41	<i>Alpinia officinarum</i> ^{50, 55, 58-63}	–	–	O	–	OH	–	–	H	H	H	OCH ₃	OH	H
42	<i>Alpinia officinarum</i> ^{50, 55}	–	–	O	–	(R)-OMe	–	–	H	H	H	OCH ₃	OH	H
43	<i>Alpinia officinarum</i> ⁵⁸	–	–	O	–	OH	–	–	OCH ₃	OH	H	OCH ₃	OH	H
44	<i>Alpinia officinarum</i> ⁵⁸	–	–	OH	–	OH	–	–	OCH ₃	OH	H	H	H	H
45	<i>Alpinia officinarum</i> ⁵⁸	–	–	OH	–	OH	–	–	OCH ₃	OH	H	OH	OH	H
46	<i>Alpinia officinarum</i> ⁶⁴	–	–	O	$\Delta^4(E)$		OH	–	H	H	H	H	H	H
47	<i>Alpinia officinarum</i> ^{55, 64}	–	–	O	–	(S)-OCH ₃	–	–	H	H	H	H	H	H
48	<i>Alpinia officinarum</i> ^{55, 60, 61, 64}	–	–	O	$\Delta^4(E)$		–	–	H	H	H	H	H	H
49	<i>Alpinia officinarum</i> ^{50, 55, 61}	–	–	O	–	(R)-OH	–	–	H	H	H	H	H	H
50	<i>Alpinia officinarum</i> ⁶⁰	–	–	O	–	(S)-OH	–	–	H	H	H	H	H	H
51	<i>Alpinia officinarum</i> ⁶⁰	–	–	O	–	(R)-OH	$\Delta^6(E)$		H	H	H	H	H	H
52	<i>Alpinia blepharocalyx</i> ⁶⁵	–	–	O	–	O	$\Delta^6(E)$		OCH ₃	OH	H	OCH ₃	OH	H

Calyxin A (53)	<i>Alpinia blepharocalyx</i> ⁶⁵	–	–	(S)-OOH	–	(R)-X	$\Delta^6(E)$	H	OH	H	H	OH	H
Calyxin B (54)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(S)-X	H	OH	H	H	OH	H
Epicalyxin B (55)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(R)-X	H	OH	H	H	OH	H
Calyxin C (56)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(R)-Y	H	OH	H	H	OH	H
EpicalyxinC (57)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(R)-Y	H	OH	H	H	OH	H
Calyxin D (58)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(S)-Y	H	OH	H	H	OH	H
Epicalyxin D (59)	<i>Alpinia blepharocalyx</i> ^{65, 66}	–	–	(S)-OH	–	$\Delta^5(E)$	(S)-Y	H	OH	H	H	OH	H
Calyxin E (60)	<i>Alpinia blepharocalyx</i> ⁶⁵	–	–	(S)-OH	–	Y	$\Delta^6(E)$	H	OH	H	H	OH	H
Blepharocalyxin A (61)	<i>Alpinia blepharocalyx</i> ⁶⁵	–	–	(S)-OH	–	$\Delta^5(E)$	(S)-Z	H	OH	H	H	OH	H
Blepharocalyxin B (62)	<i>Alpinia blepharocalyx</i> ⁶⁵	–	–	(S)-OH	–	$\Delta^5(E)$	(R)-Z	H	OH	H	H	OH	H
Alnustone (63)	<i>Curcuma xanthorrhiza</i> ^{68, 69}	–	–	O		$\Delta^4(E)$	$\Delta^6(E)$	H	H	H	H	H	H
64	<i>Curcuma xanthorrhiza</i> ^{68, 69}	–	–	OH	–	–	$\Delta^6(E)$	H	H	H	H	H	H
65	<i>Curcuma xanthorrhiza</i> ^{68, 69} <i>Curcuma comosa</i> ⁷⁰	–	–	OH		$\Delta^4(E)$	$\Delta^6(E)$	H	H	H	H	H	H
66	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	O		$\Delta^4(E)$	– –	OCH ₃	OH	H	H	OH	H
67	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	O	–	–	$\Delta^6(E)$	H	OH	H	H	H	H
68	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	O	–	–	$\Delta^6(E)$	H	OH	H	H	OH	H
69	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OH	–	–	$\Delta^6(E)$	H	OH	H	H	OH	H
70	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OH	–	–	$\Delta^6(E)$	H	OH	H	H	OH	H
71	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OH	–	–	$\Delta^6(E)$	OH	OH	H	H	OH	H
72	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OH	–	–	$\Delta^6(E)$	OH	OH	H	H	OH	H
73	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OH	–	–	$\Delta^6(E)$	OH	OH	H	H	H	H
74	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OH	–	–	$\Delta^6(E)$	OH	OH	H	H	H	H
75	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OH	–	–	– –	OH	OH	H	H	OH	H
76	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OH	–	–	– –	OH	OH	H	H	OH	H
77	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OAc	–	–	– –	OH	OH	H	H	OH	H
78	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OAc	–	–	– –	OH	OH	H	H	OH	H
79	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(S)-OAc	–	–	$\Delta^6(E)$	OH	OH	H	H	OH	H
80	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	(R)-OAc	–	–	$\Delta^6(E)$	OH	OH	H	H	OH	H

81	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	O	–	–	–	–	OCH ₃	OH	H	H	OH	H
3-Platyphyllone (82)	<i>Curcuma kwangsiensis</i> ⁷¹	–	–	O	–	–	–	–	H	OH	H	H	OH	H
	<i>Alnus sibirica</i> ²³	–	–											
83	<i>Curcuma kwangsiensis</i> ^{71, 72}	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		H	OH	H	H	OH	H
84	<i>Curcuma kwangsiensis</i> ^{73, 74}	–	–	(R)-OH	–	(S)-OH	–	–	OH	OH	H	H	OH	H
85	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OH	–	(S)-OH	–	–	OCH ₃	OH	H	H	OH	H
86	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OH	–	(S)-OH	–	–	OCH ₃	OH	OH	H	OH	H
87	<i>Curcuma kwangsiensis</i> ⁷³	–	–	O	–	(S)-OH	–	–	H	OH	H	H	H	H
88	<i>Curcuma kwangsiensis</i> ⁷³	–	–	O	–	(S)-OH	–	–	H	OH	H	OH	OH	H
89	<i>Curcuma kwangsiensis</i> ⁷³	–	–	O	–	(S)-OH	–	–	OCH ₃	OH	H	H	OH	H
90	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OAc	–	(R)-OH	–	–	H	OH	H	H	OH	H
91	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OAc	–	(R)-OH	–	–	OH	OH	H	OH	OH	H
92	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OAc	–	(R)-OAc	–	–	OH	OH	H	OH	OH	H
93	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(S)-OAc	–	(S)-OH	–	–	OH	OH	H	H	OH	H
94	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OAc	–	(R)-OH	–	–	OH	OH	H	H	OH	H
95	<i>Curcuma kwangsiensis</i> ⁷³	–	–	O	–	(S)-OH	–	–	OCH ₃	OH	H	OH	OH	H
96	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OH	–	(R)-OH	–	–	OH	OH	H	H	OH	H
97	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OAc	–	(R)-OAc	–	–	OH	OH	H	H	OH	H
98	<i>Curcuma kwangsiensis</i> ⁷³ <i>Dioscorea nipponica</i> ⁴⁸	–	–	(R)-OH	–	(R)-OH	–	–	OCH ₃	OH	H	OH	OH	H
Hanokinin (99)	<i>Curcuma kwangsiensis</i> ⁷³	–	–											
	<i>Alnus sibirica</i> ²³ <i>Amomum tsao-ko</i> ⁷⁵	–	–	O	–	(S)-OH	–	–	H	OH	H	H	OH	H
meso-Hannokinol (100)	<i>Curcuma kwangsiensis</i> ⁷³	–	–	(R)-OH	–	(S)-OH	–	–	H	OH	H	H	OH	H
	<i>Amomum tsao-ko</i> ⁷⁵	–	–											
(+)-Hanokinol (101)	<i>Curcuma kwangsiensis</i> ⁷³ <i>Amomum tsao-ko</i> ⁷⁵	–	–	(R)-OH	–	(R)-OH	–	–	H	OH	H	H	OH	H
102	<i>Amomum tsao-ko</i> ⁷⁵	–	–	O	$\Delta^4(E)$		$\Delta^6(E)$		OCH ₃	OH	H	OCH ₃	OH	H
103	<i>Curcuma comosa</i> ⁷⁶	–	–	OH	$\Delta^4(E)$		$\Delta^6(E)$		H	OH	H	H	H	H
104	<i>Curcuma comosa</i> ⁷⁶⁻⁷⁸	–	–	(S)-OH	–	–	$\Delta^6(E)$		OH	OH	H	H	H	H

105	<i>Curcuma comosa</i> ^{76, 79}	–	–	OH	–	–	$\Delta^6(E)$	H	OH	H	H	H	H
106	<i>Curcuma comosa</i> ^{76, 79}	–	–	OH	–	–	$\Delta^6(E)$	OH	OH	H	H	H	H
107	<i>Curcuma zedoaroides</i> ⁸⁰	(<i>R</i>)-OH	(<i>S</i>)-OH	(<i>S</i>)-OH	–	(<i>R</i>)-OH	–	OCH ₃	OH	H	H	OH	H
108	<i>Curcuma phaeocaulis</i> ⁸¹	–	–	(<i>R</i>)-OH	–	(<i>R</i>)-OH	–	OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	H
109	<i>Curcuma phaeocaulis</i> ⁸¹	$\Delta^1(E)$		(<i>R</i>)-OH	–	(<i>S</i>)-OH	–	OCH ₃	OCH ₃	OCH ₃	OCH ₃	OCH ₃	H
110	<i>Curcuma phaeocaulis</i> ⁸¹	$\Delta^1(E)$		(<i>R</i>)-OH	–	(<i>S</i>)-OH	–	OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	H
111	<i>Curcuma phaeocaulis</i> ⁸¹	$\Delta^1(E)$		(<i>R</i>)-OCH ₃	–	(<i>S</i>)-OH	–	OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	H
112	<i>Curcuma phaeocaulis</i> ⁸¹	$\Delta^1(E)$		OCH ₃	–	(<i>R</i>)-OH	–	OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	H
113	<i>Curcuma phaeocaulis</i> ⁸¹	$\Delta^1(E)$		O	$\Delta^4(E)$		$\Delta^6(E)$	H	OH	H	H	OH	H
114	<i>Curcuma phaeocaulis</i> ⁸¹	OH		O	–	O	$\Delta^6(E)$	OCH ₃	OH	H	OCH ₃	OH	H
Plantegineoside A (115)	<i>Tacca plantaginea</i> ⁸²	–	–	O	–	–	–	OH	O-GLc	H	OH	O-GLc	H
Plantegineoside B (116)	<i>Tacca plantaginea</i> ⁸²	–	–	(<i>R</i>)-OH	–	–	–	OH	O-GLc	H	OH	O-GLc	H
117	<i>Tacca plantaginea</i> ⁸²	–	–	(<i>R</i>)-O-GLc	–	(<i>R</i>)-OH	–	H	OH	H	H	OH	H
118	<i>Tacca plantaginea</i> ⁸²	–	–	(<i>R</i>)-O-GLc	–	(<i>R</i>)-OH	–	OH	OH	H	H	OH	H
119	<i>Tacca plantaginea</i> ⁸²	–	–	(<i>R</i>)-O-GLc	–	(<i>R</i>)-OH	–	OH	OH	H	OH	OH	H
120	<i>Juglans mandshurica</i> ⁸³	–	(<i>S</i>)-OH	(<i>S</i>)-OH	–	(<i>S</i>)-OH	–	H	OH	H	OCH ₃	OH	H
121	<i>Juglans mandshurica</i> ⁸³	–	(<i>S</i>)-OH	(<i>S</i>)-OH	–	(<i>S</i>)-O-Xyl	–	H	OH	H	OCH ₃	OH	H
122	<i>Juglans mandshurica</i> ⁸³	–	(<i>S</i>)-OH	(<i>S</i>)-OH	–	(<i>S</i>)-OH	–	OCH ₃	OH	H	OCH ₃	OH	H
123	<i>Viscum album</i> ⁸⁴	–	–	(<i>S</i>)-OH	–	(<i>R</i>)-OMe	$\Delta^6(E)$	H	OH	H	H	OH	H
124	<i>Viscum album</i> ⁸⁴	–	–	(<i>S</i>)-OH	–	(<i>S</i>)-OMe	$\Delta^6(E)$	H	OH	H	H	OH	H
125	<i>Viscum album</i> ⁸⁴	$\Delta^1(E)$		O	–	(<i>S</i>)-OH	–	H	OH	H	H	OH	H
126	<i>Aframomum melegueta</i> ⁸⁶	–	–	(<i>S</i>)-OAc	–	–	–	OCH ₃	OH	OCH ₃	OH	OH	OH
127	<i>Aframomum melegueta</i> ⁸⁶	–	–	O	–	–	–	OCH ₃	OH	H	OH	OH	H
128	<i>Kaempferia galanga</i> ⁷⁴	OH	OH	OH	–	OH	OH	OCH ₃	OH	H	H	OH	H
Gingerenone A (129)	<i>Ginger</i> ⁸⁷	–	–	O	$\Delta^4(E)$		–	OCH ₃	OH	H	OCH ₃	OH	H
130	<i>Pleuranthodium racemigerum</i> ⁸⁸	–		$\Delta^2(E)$	–	–	–	H	OCH ₃	H	H	OH	H
131	<i>Pleuranthodium racemigerum</i> ⁸⁸	–		$\Delta^2(E)$	–	–	–	H	OCH ₃	H	OH	OH	H
132	<i>Pleuranthodium racemigerum</i> ⁸⁸	–		$\Delta^2(E)$	–	–	–	H	OCH ₃	H	OCH ₃	OCH ₃	H
133	<i>Pleuranthodium racemigerum</i> ⁸⁸	–		$\Delta^2(E)$	–	–	–	H	OCH ₃	H	OCH ₃	H	H

Table 2. Structures and sources of natural anti-inflammatory 1,7-diarylheptanoids embedding a 1,5-oxo bridge in the 7-carbon chain.



Diarylheptanoids	Sources of evaluated diarylheptanoids	1	2	3	4	5	6	7	R ₁	R ₂
Diosniponol A (134)	<i>Dioscorea nipponica</i> ⁴⁸	(S)	–	(R)-OH	–	(S)	–	–	OCH ₃	OCH ₃
Diosniponol B (135)	<i>Dioscorea nipponica</i> ⁴⁸	(S)	–	(S)-OH	–	(S)	–	–	OCH ₃	OCH ₃
136	<i>Dioscorea nipponica</i> ⁴⁸	(S)	–	(R)-OH	–	(S)	–	–	H	H
137	<i>Dioscorea nipponica</i> ⁴⁸	(S)	–	(S)-OH	–	(S)	–	–	H	H
138	<i>Dioscorea nipponica</i> ⁴⁸	(S)	–	(S)-OH	–	(R)	Δ ⁶ (E)	–	H	H
Calyxin F (139)	<i>Alpinia blepharocalyx</i> ⁶⁶	(R)	–	(R)-X	–	(S)	–	–	H	H
6-Hydroxycalyxin F (140)	<i>Alpinia blepharocalyx</i> ⁶⁶	(S)	(S)-OH	(R)-X	–	(S)	–	–	H	H
Plantagineoside C (141)	<i>Tacca plantaginea</i> ⁸¹	(R)	–	(S)-O-Glc	–	(R)	–	–	OH	OH
Rhoiptelol B (142)	<i>Juglans mandshurica</i> ⁸³ <i>Alnus hirsuta</i> ²⁹	(R)	–	(S)-OH	–	(S)	(S)-OH	–	OCH ₃	H
143	<i>Kampferia galanga</i> ⁷⁴	(R)	–	(R)-OH	–	(R)	–	–	OH	H
144	<i>Kampferia galanga</i> ⁷⁴	(R)	–	(R)-O-Glc	–	(R)	–	–	OH	H
145	<i>Kampferia galanga</i> ⁷⁴	(S)	–	(R)-OH	–	(S)	–	–	OH	H
146	<i>Kampferia galanga</i> ⁷⁴	(S)	(S)-OH	(R)-OH	–	(S)	(S)-OH	–	OCH ₃	H
Kravanol D (147)	<i>Amomum kravanh</i> ⁸⁹	(R)	(R)-Y	(R)-OH	–	(S)	(R)-OH	–	OCH ₃	OCH ₃
Kravanol G (148)	<i>Amomum kravanh</i> ⁸⁹	(R)	(R)-OH	(S)-OH	–	(S)	–	–	OCH ₃	OCH ₃
Kravanol H (149)	<i>Amomum kravanh</i> ⁸⁹	(R)	–	(R)-OH	–	(S)	–	O	OCH ₃	OCH ₃
Kravanol B (150)	<i>Amomum kravanh</i> ⁸⁹	(R)	–	–	–	(S)	(S)-OH	–	OCH ₃	OCH ₃

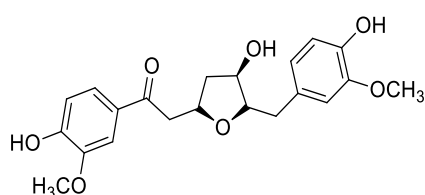


Fig.3. Structure of renealtin A (**151**)^{88, 89}

Diarylheptanoids are the dominant constituents within the genus *Alnus* plants which are well known for their traditional uses in the treatment of various diseases like cancer, hepatitis, inflammation etc... Some of these diarylheptanoids exhibiting potent antioxidant and anti-inflammatory effects are discussed in the review.²¹ In particular, a series of tetraphenolic linear compounds have attracted much interest and been subjected of numerous biological evaluations.

Among them, muricarpon B (**1**), initially characterized in 2006 from *Amomum muricarpum* (Zingiberaceae),²² was isolated by Korean Min-Won Lee's team from fermented barks of *Alnus sibirica* (Betulaceae) and reported intensive biological studies to evaluate its anti-inflammatory activity.

According to the various reported studies, it showed potent antioxidant activities in DPPH radical scavenging assays with IC₅₀ values of 20.1 μ M,²³ 24.1 μ M²⁴ and 38.7 μ M²⁵ (compared to AA: IC₅₀ = 46.0,²³ 24.8²⁴ and 44.7²⁵ μ M respectively), NBT superoxide radical scavenging effect with IC₅₀ values of 30.1 μ M²⁴ and 12.7 μ M²⁵ (compared to allopurinol as positive control, IC₅₀ = 8²⁴ and 3.9²⁵ μ M respectively) and strong NO production inhibitory activity with IC₅₀ values of 6.6 μ M,²³ 22.7 μ M²⁴ and 2.6 μ M²⁵ in LPS-stimulated RAW 264.7 macrophages (compared to N-monomethyl-L-arginine (L-NMMA) : IC₅₀ = 41.9,²³ 37.1²⁴ and 33.9²⁵ μ M respectively). No cytotoxicity activities on RAW264.7 cells was displayed up to 100 μ M.

Muricarpone B (**1**) was also isolated from the unusual source *Nidus vespa* (nest of the paper wasp *Polistes*) and showed to inhibit NO production with IC₅₀ value of 16.8 μ M (compared to proteasome inhibitor MG132 (carbobenzoxymethyl-Leu-Leu-leucinal) as positive control : IC₅₀ = 0.1 μ M) in LPS-stimulated RAW 264.7 macrophages.²⁶

M-W Lee's team equally isolated and similarly biologically evaluated hirsutenone (**2**), displaying an additional conjugated double bond compared to muricarpon B. In a similar way, according to the reported studies, it showed antioxidant activities in DPPH radical scavenging assays with IC₅₀ values of 29 μ M,²³ 14.1 μ M²⁴ and 13.4 μ M²⁵ (compared to AA), NBT superoxide radical scavenging effect with IC₅₀ values of 17.6 μ M²⁴ and 16.8 μ M²⁵ (compared to allopurinol) and NO production inhibitory activity with IC₅₀ values of 5.8 μ M,²³ 14.1 μ M²⁴ and 0.8 μ M²⁵ in LPS-stimulated RAW 264.7 macrophages (compared to L-NMMA). These results are in agreement with those previously obtained on LPS-stimulated NO production inhibitory activity of hirsutenone (**2**) isolated from *Alnus formosana* (Betulaceae) a species of alder endemic to Taiwan, with IC₅₀ value of 5 μ M in RAW 264.7 macrophages. A slight cytotoxicity was mentioned (IC₅₀ value of 39.0 μ M with MTT assay on RAW 264.7 macrophages) which could be explained by non-specific Michael addition reactions.²⁷ Hirsutenone (**2**) was also widely evaluated against cytokines production and proteins expression. Isolated from the barks of *Alnus japonica* (Betulaceae), it was evaluated for its inhibitory activities on NO and prostaglandin E2 production via COX-2 inhibition in interferon- γ (INF- γ)- and LPS-activated RAW 264.7 cells. It dose-dependently inhibited NO production with an IC₅₀ value of 27.2 μ g/mL (compared to L-NMMA: IC₅₀ = 22.8 μ g /mL) and reduced the COX-2 level with an IC₅₀ value of 25.0 μ g/mL (compared to indomethacin : IC₅₀ = 26.2 μ g /mL).²⁸

Alnus hirsuta (Betulaceae) also provided hirsutenone (**2**) which was further evaluated for its inhibitory activity against LPS-induced NO and TNF- α production and NF- κ B activation in RAW 264.7 cells. However, it showed very weak activity with IC₅₀ values above 100 μ M.²⁹ A comprehensive study was conducted by Chung Soo Lee et al.³⁰ to evaluate the anti-inflammatory activity of hirsutenone on TNF- α -stimulated human keratinocytes (HEK001). It revealed that this diarylheptanoid attenuated the TNF- α -elicited formation of IL-8, PGE₂ and chemokine CCL27 in a dose-dependent manner and the TNF- α -induced production of NO, with inhibitory rates of 33%, 46%, 43% and 37% respectively at 7.5 μ M. Hirsutenone decreased inflammatory mediators' production in keratinocytes by inhibiting the activation of nuclear factor NF- κ B.

The same authors³¹ completed this study by evaluating the activity on LPS-stimulated human keratinocytes. IL-1 β , IL-8 and CCL17 release were inhibited with 39 %, 40% and 51% rates respectively

at 7.5 μM in HEK001 keratinocytes. In primary foreskin keratinocytes, IL-1 β and CCL17 inhibition rates were 39% and 49% at 7.5 μM . Moreover, at this concentration, hirsutenone was shown to inhibit NF- κB DNA binding (29.5%) and LPS-induced extracellular signal-regulated kinase (ERK) expression (37%) which suggested that it could prevent LPS-induced inflammatory skin diseases by inhibition of ERK pathway-mediated by NF- κB activation. *In vivo* assays were then conducted by Chung Soo Lee collaborators³² to evaluate the hirsutenone efficacy on atopic dermatitis-like skin lesions in NC/Nga mice. Intraperitoneal injection of 0.1% of hirsutenone resulted in 51 and 37% inhibition of the IL-4 and IL-5 cytokines levels production respectively. These values increased up to 60 and 74%, after injection of 1% of the active compound. COX-2 and iNOS expressions were equally reduced by 57 and 61 % at a dose of 0.1%, and rise up to 62 and 73% at a dose of 1%. Topical application of hirsutenone at 1% also evaluated was equally effective.

In another study, Sung Hee Lee and co-workers³³ investigated the protective effect of hirsutenone against disruption of the intestinal barrier *in vitro* and in a mouse model of colitis. Hirsutenone significantly suppressed mRNA expression of TNF- α , IL-1 β and IL-6, and decreased oxidative stress-induced intestinal epithelial barrier dysfunction by activating both the EGFR/Akt and ERK1/2 pathways, which are involved in the regulation of heme oxygenase 1 (HO-1) expression. Moreover, administration of hirsutenone significantly improved 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced experimental colitis in mice. Hirsutenone stemming from *Alnus tinctoria* Sarg. (Betulaceae) exhibited IL-1 β secretion inhibition in a concentration dependent manner with a reduction rate of 73.4 % at 5 μM in LPS-activated bone marrow derived (BMD) macrophages.³⁴

As shown in this different studies, hirsutenone, demonstrated interesting and applicable anti-inflammatory activities for various pathologies where chronic inflammation plays a major role.

Hirsutanonol (**3**), the hydration product of hirsutenone, was isolated from leaves of *Alnus hirsuta*, and found by M-W Lee et al.³⁵ to inhibit NO production in IFN- γ and LPS-activated RAW 264.7 cells in a dose dependent manner with an IC₅₀ value of 3.8 μM and to suppress the expression of iNOS mRNA. Moreover, the same researcher showed that hirsutanonol dose-dependently inhibited the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of COX-2 protein in immortalized human mammary epithelial MCF-10A cells with inhibitory rates of 27 to 70% in the range 12.5-100 μM .³⁶ They isolated diarylheptanoid **3** from the barks of *Alnus japonica* and reported moderate NO production inhibition with an IC₅₀ value of 44.3 $\mu\text{g/mL}$ (compared to L-NMMA : IC₅₀ = 22.8 $\mu\text{g/mL}$) and potent COX-2 level reduction in a dose dependent manner with an IC₅₀ of 25.7 $\mu\text{g/mL}$ (compared to indomethacin: IC₅₀ = 26.2 $\mu\text{g/mL}$) in INF- γ and LPS-activated RAW 264.7 cells.²⁸ Hirsutanonol (**3**) was further evaluated for its potent inhibitory activity against LPS-induced NO and TNF- α production and NF- κB activation in RAW 264.7 macrophages with IC₅₀ values of 19.3, 23.7 and 9.9 μM respectively (compared to the IC₅₀ values of parthenolide as positive control: 2.4, 2.6 and 3.4 μM respectively).²⁹ *Alnus formosana* and *Alnus sibirica* were also hirsutanonol sources. According to the reported studies, the evaluation of its NO production inhibitory activity led to IC₅₀ values of 30 μM ,²⁷ 21.3 μM ²³ and 17.8 μM ²⁵ in LPS-stimulated RAW 264.7 macrophages. It also demonstrated potent antioxidant activity in DPPH and NBT superoxide scavenging radicals assays with IC₅₀ values of 26.0 and 19.0 μM respectively (compared to AA IC₅₀(DPPH) = 44.7 μM and allopurinol IC₅₀ (NBT) = 3.92 μM as positive controls).²⁵

Hirsutanonol is always extracted from the *Alnus* genus sources and its anti-inflammatory effects are well documented. However, assays conditions are always different, making comparisons difficult.

Nevertheless, it appears that hirsutanonol is a diarylheptanoid with antioxidant properties and capable of inhibiting the production of various mediators and proteins involved in inflammation.

5-O-Methylhirsutanonol (**4**), isolated from *Alnus japonica* leaves, was comprehensively investigated by Jeong et al.³⁷ for its anti-inflammatory and related anti-atherosclerotic activities. In particular, diarylheptanoid **4** was efficient against TNF- α induced vascular cell adhesion protein 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression with 77 and 21 % inhibition rates respectively at 20 μ M in human umbilical vein endothelial cells (HUVEC) making it potentially useful in the prevention and treatment of atherosclerosis. Moreover, 5-O-Methylhirsutanonol inhibited ROS production with 37 to 87 % rates in the range 5-50 μ M, NO release in a dose-dependent manner with IC₅₀ value of 14.5 μ M, LPS-induced iNOS protein expression at 50 μ M, TNF- α mRNA level with 60 % rates at 50 μ M and NF- κ B expression in LPS-activated RAW 264.7 macrophages. In addition, pretreatment with **4** (at 20 and 50 μ M) suppressed the induced mRNA expressions of COX-2 and IL-1 β but not IL-6. By comparing these results with anti-inflammatory activity of two others diarylheptanoids such as oregonin (mentioned later in this review) and curcumin, the authors considered that diarylheptanoids displaying a ketone and an alcohol function or a 5-O-substituted group as well as diarylheptanoids with two ketones functions on their C7-chain were the most effective in reducing the activation of NF- κ B.³⁸ In 2017, M-W Lee et al.²³ supported the interest of **4** as anti-inflammatory agent by reporting potent antioxidant activity in DPPH assay (IC₅₀ = 28.3 μ M compared to AA: IC₅₀ = 46.0 μ M) and NO production inhibition with IC₅₀ value of 11.4 μ M in LPS-stimulated RAW 264.7 macrophages (compared to L-NMMA: IC₅₀ = 42 μ M).

Hirsutanonol 5-O- β -D-glucopyranoside (**5**), was isolated from the barks of *Alnus japonica*²⁸ and stems of *Alnus formosana*²⁷ and *Alnus nepalensis*.³⁹ It displayed moderate NO production inhibition and COX-2 level reduction with an IC₅₀ values of 29.4 μ g/mL and 33.7 μ g /mL respectively (compared to L-NMMA: IC₅₀ (NO) = 22.8 μ g /mL and indomethacin: IC₅₀ (COX-2) = 26.2 μ g /mL) in INF- γ and LPS-activated RAW 264.7 cells.²⁸ Likewise, LPS-induced NO production was inhibited with IC₅₀ value of 10 μ M in RAW 264.7 macrophages.²⁷ Moreover, **5** was able to reduce the production of cytokines TNF- α and IL-6 with 51 and 75 % inhibition rates respectively at 10 μ g/mL by inhibiting the expression of NF- κ B protein in LPS-activated mouse peritoneal macrophages J774A.1.³⁹

Hirsutanonol 5-O- β -D-xylopyranoside called oregonin (**6**), initially isolated in 1974 from *Alnus rubra*,⁴⁰ and found in many *Alnus* genus sources such as *japonica*, *sibirica*, *hisuta*, *formosana* and *nepalensis*, has been widely documented for its biological activities including antioxidant and anti-inflammatory ones. In particular M-W Lee et al.³⁵ showed in 2000 that oregonin inhibited NO production in a dose-dependent manner with an IC₅₀ value of 14.3 μ M in INF- γ and LPS-activated RAW 2647.7 cells and suppressed the iNOS mRNA expression. The same team further highlighted that diarylheptanoid **6** dose-dependently inhibited the TPA-induced expression of COX-2 protein in MCF-10A cells with inhibitory rates of 31.5 to 58 % in the range 12.5-100 μ M.³⁶ Five years later, they confirmed its activity against LPS, INF- γ -induced production of NO and COX-2 in a dose-dependent manner with IC₅₀ values of 16.7 and 20.7 μ g/mL respectively in RAW 264.1 macrophages (compared to L-NMMA: IC₅₀(NO) = 22.8 μ g /mL and indomethacin: IC₅₀ (COX-2) = 26.2 μ g /mL).²⁸ In 2017, they reported that oregonin displayed DPPH radical scavenging activity with an IC₅₀ values of 32.1 μ M and NO production inhibition capacity with an IC₅₀ value of 9.7 μ M against in LPS-activated RAW 264.1 macrophages (compared to

AA : IC₅₀(DPPH) = 46 μ M and L-NMMA: IC₅₀(NO) = 42 μ M).²³ In a devoted study to oregonin, the same Korean team showed that this compound significantly inhibited the production of NO and cytokines (IL-12p 70, TNF- α), the formation of ROS and the change of intracellular Ca²⁺ levels in LPS or IL-1 β stimulated bone marrow dendritic cells in a dose dependent manner.⁴¹ In 2012, they furthermore evaluated the NO inhibitory activity of oregonin with an IC₅₀ value of 21.1 μ M in LPS-activated RAW 264.1 macrophages.²⁷ In a study conducted by Jeong et al. in 2007 already mentioned about 5-O-methylhirsutanonol (**4**),³⁷ oregonin was shown to efficiently reduce in a similar way the expression of VCAM-1 and ICAM-1 with 76.6 and 20.8 % inhibition rates respectively at 20 μ M in TNF- α stimulated HUVECs.

In a complete study, Lin et al.⁴² demonstrated that oregonin dose-dependently (from 10 to 100 μ M) reduced LPS-stimulated NO production (48 to 95% inhibition rates in RAW 264.7 cells, vs 19 to 81% inhibition rates in BV-2 microglia). Oregonin further inhibited the LPS-induced iNOS protein production in RAW264.7 macrophages (48 to 95% inhibition rates from 10 to 100 μ M) and BV-2 microglial cells (22 to 79% inhibition rates from 10 to 100 μ M) notably by acting on HO-1 induction. Oregonin also displayed dose-dependent inhibition (from 10 to 100 μ M) of LPS-mediated NF- κ B promoter activity (35 to 84% inhibition rates in RAW 264.7 cells, vs 26 to 72% inhibition rates in BV-2 microglia) and DNA-binding ability, as well as p65 nuclear translocation and phosphorylation. Oregonin attenuated activator protein (AP)-1 transactivation (which participates in the upregulation of iNOS gene transcription) via p38 MAPK inhibition.

The antioxidant and anti-inflammatory efficiency of oregonin was further reported by Hu and Wang⁴³ with an IC₅₀ value of 8.4 μ M in DPPH assay and inhibition rates of NO production from 31.2 to 77.3 %, inhibition of intracellular ROS formation from 6.7 to 71.6 %, reduction of iNOS expression from 16.7 to 75 % and reduction of COX-2 expression from 7.7 to 71.8% in the range 10-100 μ M in LPS activated RAW 264.7 macrophages.

In a comprehensive study on inflammatory factors promoting atherosclerosis, a Sweden team⁴⁴ demonstrated that oregonin decreased cellular lipid accumulation, ROS production and pro-inflammatory cytokines secretion, with 48.6, 18.9, 31.4, 37.9, 33.3, 75 and 40.6 % inhibition rates against TNF- α , IL-1 β , IL-2, IL-6, IL-10, IFN γ and IL-8 respectively at 50 μ M in LPS-stimulated primary human macrophages. The same year, a IL-1 β secretion inhibition rate of 42% at 5 μ M in LPS-activated BMD macrophages was moreover reported by Choi and co-workers.³⁴ In 2016, Bawankule et al.³⁹ further reported that oregonin acted on TNF- α and IL-6 secretion with 43 and 76 % inhibition rates at 10 μ g/mL in LPS-activated peritoneal macrophages (J774A.1) by inhibiting of the expression of NF- κ B protein. In 2018, SH Lee's team⁴⁵ carried out a comprehensive study on the oregonin effects on intestinal inflammation as well as they did on hirsutenone (**2**) in 2014.³³ Oregonin did not affect the viability of HT-29 cells even at 100 μ M and suppressed the expression of COX-2, ICAM-1, IL-8 and IL-1 β mRNA, inhibited the activation of NF- κ B and increased HO-1 expression in TNF- α stimulated intestinal epithelial HT-29 cells used as cellular model. Moreover, oregonin attenuated *tert*-butyl hydroperoxide-induced intestinal epithelial barrier dysfunction by induction of HO-1 expression. The authors concluded that oregonin can be a potential candidate to prevent mucosal inflammation and barrier disruption

As shown here, oregonin (**6**) was extensively studied as a part of the efforts against chronic inflammation. Although the results of the different studies are difficult to compare because of the disparity of the experimental conditions, taken together, all these results clearly highlight its anti-inflammatory actions.

Another hirsutanonol derivative, the deoxohirsutanonol or rubranol (**7**) isolated from different *Alnus* sources was evaluated for its antioxidant activity through DPPH scavenging assay with IC₅₀ values of 34.9 μ M (compared to AA : IC₅₀ = 46.1 μ M)²³ or 23.3 μ M (compared to AA : IC₅₀ = 44.7 μ M)²⁵ and NBT superoxide scavenging assay with IC₅₀ value of 11.6 μ M (compared to allopurinol : IC₅₀ = 3.9 μ M).²⁵ According to the assays, rubranol showed a potent NO production inhibitory activity in LPS-activated RAW 264.7 macrophages with IC₅₀ values of 28.4 μ g/mL (compared to L-NMMA : 22.8 μ g/mL),²⁸ 20.0 μ M²⁷ (no reported reference) , 10.2 μ M (compared to L-NMMA : 41.9 μ M)²³ and 5.2 μ M (compared to L-NMMA : 33.9 μ M).²⁵ Moreover, a moderate inhibitory activity of COX-2 expression with an IC₅₀ value of 45.3 μ g/mL (compared to indomethacin: IC₅₀ = 26.2 μ g/mL) in LPS-activated RAW 264.7 macrophages was reported.²⁸

It should be noted that the same authors (M-W Lee et al.) published different IC₅₀ values for the same DPPH assay in 2017²³ and 2019²⁵ and for NO production inhibition assay (in 2005²⁸ and 2017²³) illustrating that the comparison between different series of tests is very tricky even when they were conducted by the same team. Nevertheless, a trend emerges to conclude to the real interest of hirsutanonol derivatives as anti-inflammatory agent.

Rubranosides A (**8**) (rubranol 5- β -O-D-glucoside), isolated along with rubranol from *Alnus japonica*,²⁸ *Alnus formosana*²⁷ and fermentation of *Alnus sibirica*,²³ displayed antioxidant activity with IC₅₀ values of 45.1 μ M (compared to AA : IC₅₀ = 46.1 μ M) in DPPH assay,²³ NO release inhibitory activity with IC₅₀ values 32.5 μ g/mL (compared to L-NMMA : IC₅₀ = 22.8 μ g/mL)²⁸ or 81.9 μ M (compared to L-NMMA : IC₅₀ = 41.9 μ M)²³ and COX-2 expression inhibition with IC₅₀ value of 32.2 μ g/mL (compared to indomethacin : IC₅₀ = 26.2 μ g/mL)²⁸ in LPS-activated RAW 264.7 macrophages.

The antioxidant and anti-inflammatory activities of the 5- β -O-D-xylopyranoside rubranoside B (**9**), the xyloside analogue of rubranoside A were tested in 2011 by assessing its DPPH scavenging activity (IC₅₀ = 8.7 μ M (compared to gallic acid : IC₅₀ = 10.4 μ M)⁴³ or IC₅₀ = 31.1 μ M (compared to AA : IC₅₀ = 3.1 μ M)²³) and its efficiency against NO production with 20.8 to 83.3 % inhibition rates, intracellular ROS production with 4.2 to 71 % inhibition rates, iNOS expression with 12.5 to 29.1 % inhibition rates and COX-2 expression with 7.7 to 25.6 % inhibition rates in the range 10-100 μ M in LPS-activated RAW 264.7 macrophages.⁴³ It was latter reported to inhibited NO production in 28 % rate at 30 μ M²⁷ or with an IC₅₀ value of 38.9 μ M (compared to L-NMMA : IC₅₀ = 41.9 μ M)²³ in LPS-activated RAW 264.1 macrophages. No cell toxicity was observed up to 100 μ M.

Barks of *Alnus japonica* also provided others rubranol glycosides **10**, **11**, and platyphylloside **12** which proved a moderate efficiency compared to the control assays against NO production (IC₅₀ values of 48.6, 49.4 and 53.1 μ g/mL respectively compared to 22.8 μ g/mL for L-NMMA) and COX-2 expression (IC₅₀ values of 45.2, 34.2 and 32.7 μ g/mL respectively compared to 26.2 μ g/mL for indomethacin) in LPS-activated RAW 264.7 macrophages.²⁸ In 2016, platyphylloside **12** was further tested after isolation from *Alnus nepalensis* for its activity against TNF- α and IL-6 expression with 52 and 80 % inhibition at 10 μ g/mL in LPS-activated peritoneal macrophages.³⁹

Among tetraphenolic linear diarylheptanoids **8-11**, the presence of any glycoside moiety in 5-position on the heptanoid chain does not seem to significantly improve the desired activity, compared to rubranol (**7**).

In 2012, SS Lee et al. performed a comprehensive study on a series of 28 diarylheptanoids isolated from leaves of *Alnus formosana* to assess the IC₅₀ values of NO production inhibition in LPS-stimulated RAW macrophages 264.7.²⁷ Along with derivatives **2**, **3**, **5-9** already mentioned, alluside A (**13**) (IC₅₀ = 8.1 μM), alluside B (**14**) (IC₅₀ = 15.2 μM), **15** (IC₅₀ = 15.2 μM), **17** (IC₅₀ = 22.1 μM), **18** (IC₅₀ = 30 μM), **19** (IC₅₀ = 22 μM), **20** (IC₅₀ = 15.4 μM), **21** (IC₅₀ = 30 μM), **22** (IC₅₀ = 10.5 μM) were found efficient. Conjugated diarylheptanoids **16** (IC₅₀ = 2.9 μM), platyphyllenone (**23**) (IC₅₀ = 6.9 μM) and **33** (IC₅₀ = 8.6 μM) were found the most potent but the most cytotoxic from the MTT assay with IC₅₀ values of 9, 30.7 and 36.4 μM respectively.²⁷ The authors concluded that compounds **13-16** and **20** were more effective than oregonin without consideration of their significant toxicity. Diarylheptanoids **24** (11% inhibition rate at 30 μM), **25** (37% inhibition rate at 30 μM), aceroside VII (**26**) (24% inhibition rate at 30 μM) and (-)-centrolol (**27**) (29% inhibition rate at 30 μM) were found less active as NO production inhibitors. Nevertheless no toxicity for **24-26** while a noticeable one for **27** (52 % cell viability at 30 μM) were observed. The absence of known positive control value in the NO assay is regrettable.²⁷

Independently, in 2013, H Morita collaborators studied also aceroside VII (**26**) isolated from barks of *Acer nikoense* (Aceraceae) used in Japanese folk medicine for hepatic disorders and eye diseases. They confirmed that **26** displayed no toxicity at 50 μM and poor effect on LPS-induced NO production with an IC₅₀ value above 100 μM in J774.1 macrophages.⁴⁶

In 2017, platyphyllenone (**23**), equally isolated from *Alnus sibirica*, was again tested against NO production in LPS-activated RAW 264.7 macrophages with IC₅₀ value of 15.9 μM (compared to AA : IC₅₀ = 12.3 μM) and for antioxidant activity through DPPH assay with IC₅₀ values of 101.2 μM (compared to AA : IC₅₀ = 3.1 μM).²³

The same year, further studies on (-)-centrolol (**27**) reported an IC₅₀ values of 27.8 μM for NO production inhibition in LPS-activated RAW 264.7 macrophages (compared to L-NMMA : IC₅₀ = 41.9 μM), and 44.4 μM for DPPH radical scavenging activity (compared to AA : IC₅₀ = 46.1 μM).²³ **27** was equally tested *in vivo* for its anti-inflammatory effect against TPA-induced inflammation in mice (1 mg/ear) with an ID₅₀ value of 0.66 mg/ear, compared to those of quercetin (ID₅₀ = 1.6 mg/ear).⁴⁷

Its enantiomer (+)-centrolol (**28**) isolated from *Nidus vespae* was tested against NO release with an IC₅₀ value above 25 μM compared to the positive control MG132 with IC₅₀ value = 0.1 μM in LPS-activated RAW 264.7 macrophages.²⁶ The same study reported the isolation from *Nidus vespae* of diarylheptanoids **29** and **30**. Their NO production inhibitory effect was evaluated with IC₅₀ values of 13.8 and 13.2 μM respectively in LPS-activated RAW 264.7 macrophages.²⁶ The presence of a ketone or alcohol function in position 3 and the number of phenol functionalities (2 or 3) do not influence the NO production inhibitory activity.

In 2013, Kang Ro Lee and coworkers⁴⁸ identified from rhizomes of *Dioscorea nipponica* (Dioscoreaceae) linear diarylheptanoids **31-35** along with five compounds embedding an 1,5-oxy bridge in the carbon chain **134-138**. Tsaokoarylone **31**, compounds **32** and **138** significantly decreased the NO production with IC₅₀ values of 3.4, 14.4 and 18.6 μM respectively in LPS-activated BV-2 cells, compared to L-NMMA (IC₅₀ = 18.3 μM), without any cell toxicity. **33** and **34** revealed more active (IC₅₀ = 7.8 and 8.5 μM respectively) but a significant cell toxicity was detected (24.8 and 18.5 % cell viability at 20 μM), whereas **35**, diosniponol A (**134**), diosniponol B (**135**), **136** and **137** were found less efficient with IC₅₀ values of 57.1, 95.1, 45.9, 39.7 and 38.1 μM respectively. The NO inhibitory activity of **33** was moreover evaluated with an IC₅₀ value of 8.6 μM (no reported reference) and a moderate cytotoxicity (IC₅₀ = 36.4 μM) in LPS-activated RAW 264.7 macrophages.²⁷

The genus *Alpinia* is an important member of Zingiberaceae family widely distributed in Asia from which 143 diarylheptanoids were isolated in 2017.⁴⁹

From the 1980's, anti-inflammatory activities of yakuchinone A (**36**) and yakuchinone B (**37**), isolated from *Alpinia oxyphylla* (Zingiberaceae) used for centuries in traditional medicine for inflammatory disorders, have attracted interest. They initially were identified by Sankawa et al.⁵⁰ as strong PG biosynthesis inhibitors with IC₅₀ values of 0.5 and 2.3 μ M respectively (compared to indomethacin: IC₅₀ = 4.9 μ M). **36** and **37** were reported to inhibit 5-hydroxyeicosatetraenoic acid (5-HETE) production with IC₅₀ values of 5.4 and 4.0 μ M respectively from intact human neutrophils and PGE₂ formation by bovine seminal vesicles (BVS) cyclooxygenase with IC₅₀ values of 16 and 23 μ M respectively (compared to BW-756C : IC₅₀ = 32.0 μ M and phenidone: IC₅₀ = 11.8 μ M as references).⁵¹ They were further shown to inhibit the TNF- α production with 43 and 52 % rates respectively at 20 μ M in TPA-treated mouse skin and the COX-2 expression in TPA-stimulated mouse skin.⁵²

Yamazaki et al.⁵³ also assayed yakuchinone B (**37**) against TNF- α and IL-1 β -induced VCAM-1 expression with 0 to 95 % and 0 to 100 % inhibition respectively, and against TNF- α and IL-1 β -induced ICAM-1 expression with 0 to 51 % and 0 to 85 % inhibition respectively the range 1-50 μ M in HUVECs cells (indomethacin used as positive control had no effect up to 100 μ M).

Among linear diarylheptanoids, the natural compounds **38** to **51** were isolated from *Alpinia officinarum* (Zingiberaceae) originally from China, widely cultivated in south-east Asia and employed as flavoring agent.⁵⁴ Diarylheptanoid **38** was proved efficiently active against mice TPA-induced ear inflammatory edema with ID₅₀ value of 0.8 μ mol/ear, compared to indomethacin (ID₅₀ = 0.9 μ mol/ear).⁵⁵ A comprehensive study devoted on the anti-inflammatory potential of this compound showed its inhibitory activity against NO release with IC₅₀ value of 5 μ g/mL, against IL-1 β , TNF- α , COX-2, NF- κ B and iNOS expression with 70, 71, 69, 50 and 69% inhibition rates respectively at 5 μ g/mL in LPS-stimulated RAW 264.7 macrophages without any toxic effect.⁵⁶

In 1982, Sankawa et al.⁵⁰ identified **39** as a PG biosynthesis inhibitor with IC₅₀ value of 50 μ M which is 10 fold higher than the one of indomethacin used as positive control. It was latter shown that, at 25 μ M, **39** inhibited NO release in LPS-activated RAW 264.7 macrophages with 50% rate, IL-1 β , TNF- α production in LPS-induced human peripheral blood mononuclear (PBM) cells with 85 and 43% rates respectively, and iNOS and COX-2 gene expression by 75.5 and 54.6% in LPS-activated RAW 264.7 macrophages by inhibiting NF- κ B activation and phosphorylation of p44/42 MAPK.⁵⁷ An IC₅₀ value of 0.6 μ M for NO release in LPS-activated macrophages⁵⁸ and an ID₅₀ value of 2.2 μ mol/ear against mice TPA-induced ear inflammatory edema⁵⁵ were further reported. Recently, *in silico* studies suggested that **39** interacted with P38 α MAPK. It was shown to reduce IL-1 β , IL-6 and TNF- α expression with 86, 52 and 85% inhibition rates respectively at 10 μ g/mL in LPS-induced HepG2 cells.⁵⁹ Moreover, **39** displayed significant inhibitory activity against TNF- α production with 54% rate at 0.02 mg/mL (concentration for which cell viability of diarylheptanoid **39** was more than 80 % by MTT assay) in Kdo2-lipid (KL) A-stimulated RAW 264.7 macrophages.⁶⁰

In 1982, diarylheptanoids **40** and **41** were proved to inhibit PG biosynthesis with IC₅₀ values of 2.0 and 4.4 μ M respectively in the same range than indomethacin.⁵⁰

Hydroxyketone **41** was thereafter comprehensively evaluated for its anti-inflammatory activity. In 2008, (*R*)-**41** was assayed *in vivo* against mice TPA-induced ear inflammatory edema with ID₅₀ value of 1.8 µmol/ear compared to indomethacin (ID₅₀ = 0.9 µmol/ear).⁵⁵

41 was moreover reported by Ryu et al.⁵⁸ to inhibit NO production with 40% rate at 10 µg/mL (IC₅₀ >30 µM) in LPS-activated macrophages. In 2016, Bodhankar, Rojtkar, Natu and co-workers⁶¹ showed that **41** displayed antioxidant properties in a concentration-dependent manner with DPPH scavenging activity with an IC₅₀ value of 93.5 µg/mL (compared to AA : IC₅₀ = 58 µg/mL), hydroxyl radical HO• scavenging assay with an IC₅₀ value of 77 µg/mL (compared to AA : IC₅₀ = 47 µg/mL) and *in vivo* anti-inflammatory one against carrageenan induced hind paw edema in rats with 1.53% (after 1h), 33.1% (after 3h) and 42 % (after 5h) inhibition rates at a dose of 10 mg/kg. The molecular docking study revealed affinity towards COX-2 active site of which **41** could be a selective inhibitor.

The same authors⁶² recently showed that oral administration of this diarylheptanoid reduced the serum levels of TNF-α, IL-1β and IL-6 levels with 0 to 18%, 3 to 5% and 0 to 2.5% inhibition rates at doses ranging from 5 mg/kg to 20 mg/kg in Freund' complete adjuvant (FCA)-induced arthritis in rats on day 28 (compared to diclofenac: 47%, 7% and 2.5% inhibition rates respectively at 5 mg/kg). More interestingly, diarylheptanoid **41** significantly inhibited the increase in paw volume of Freund' complete adjuvant (FCA)-induced arthritic rats with 20.1 and 21.3% rates at 10 mg/kg and 20 mg/kg respectively on day 28 (compared to diclofenac with 28.3% rate at 5 mg/kg). Docking study indicated good *in-silico* binding with active site of TNF-α. Another comprehensive study on anti-inflammatory activity of **41** in LPS-induced RAW 264.7 macrophages was conducted by Wu and Feng's team.⁶³ Cytotoxicity assays revealed that up to 20 µg/mL the cell viability was above 80%. Thus, **41** was evaluated for its potency to reduce NO production, PGE₂, TNF-α and IL-1β expression level with 12 to 44%, 57 to 85%, 10 to 87% and 4 to 64% inhibition rates respectively in the range 5-20 µg/mL. **41** was further shown to inhibit the expression of iNOS and COX-2 and to reduce the phosphorylation of NF-κB p65 in a dose dependent manner. The same team reported latter that **41** acted against TNF-α expression with 43% inhibition rate at 0.05 mg/mL (cell viability >80%) in KLA-stimulated RAW 264.7 macrophages.⁶⁰ Following preliminary molecular docking studies, **41** was also proved by Elgazar's team⁵⁹ to exhibit cytotoxicity with an IC₅₀ value 26.6 µg/mL and anti-inflammatory activities against IL-1β, IL-6 and TNF-α expression with 83, 65 and 89 % inhibition rates respectively at 10 µg/mL in LPS-induced HepG2 cells. Investigations on β-methoxyketone **42** according to the same experiments than hydroxyketone **41** showed better anti-inflammatory activity with PG biosynthesis inhibition IC₅₀ value of 2.3 µM⁵⁰ and reduction of mice TPA-induced ear inflammatory edema with ID₅₀ value of 0.9 µmol/ear (compared to indomethacin : ID₅₀ = 0.9 µmol/ear).⁵⁵

In 2006, low to moderate NO release inhibitory activities were reported for diarylheptanoids **43-45** in LPS-activated RAW 264.7 macrophages as for **41**.⁵⁸ Derivatives **43** and **44** only induced 32 and 27 % inhibitory rates at 10 µg/mL respectively (IC₅₀>30 µM). An IC₅₀ value of 22.8 µM was evaluated for **45** which reduced iNOS expression level with 32% inhibition rate at 25 µM (no reported reference).

Five non phenolic diarylheptanoids **46-50**, also isolated from *Alpinia officinarum*, were equally found to display anti-inflammatory activities. In 2007, Fan et al.⁶⁴ proved that compounds **46-47-48** exhibited potent platelet-activating factor (PAF) receptor binding activities with IC₅₀ values of 1.3, 1.6 and 5.0 µM respectively and concluded that diarylheptanoid represented a new class of potent PAF receptor binding inhibitory compounds. Moreover, *in vivo* assays on TPA-induced mice inflammation showed

that compounds **47**, **48** and **49** inhibit edema with ID₅₀ value of 2.7, 2.1 and 2.7 $\mu\text{mol/ear}$ respectively (compared to indomethacin : ID₅₀ = 0.9 $\mu\text{mol/ear}$).⁵⁵ Further studies showed that **48** inhibited NO release with an IC₅₀ value of 6.8 μM and reduced iNOS expression level with 71% inhibition rate at 25 μM in LPS-activated RAW 264.7 macrophages.⁵⁸ In another report, **48** and **49** were evaluated *in vivo* as for **41** against carrageenan induced hind paw edema in rats. They showed no significant inhibition in the increase of paw edema from 1h to 5h after injection of carrageenan at 10 mg/kg (6.9 % and 4.7 % inhibition respectively after 5h compared to for 39.5 % diclorofenac).⁶¹ **49** was also noted to exhibit weak effect against PG biosynthesis with IC₅₀ value of 170 μM .⁵⁰

Moreover **48**, **50** and **51** displayed moderate inhibitory activity against TNF- α production with 38, 35 and 37% rates respectively at 0.06 mg/mL in Kdo2-lipid (KL) A-stimulated RAW 264.7 macrophages.⁶⁰ The numerous studies cited here show that *Alpinia officinarum* is an important source of diarylheptanoids with proven anti-inflammatory properties.

In 2003, a series of new original diarylheptanoids were isolated from seeds of *Alpinia blepharocalyx* (Zingiberaceae), one of the most important Chinese medicinal plants and their structures elucidated. In particular *in vitro* NO inhibitory activity of linear compounds **52-62** and tetrahydropyran enclosing diarylheptanoids **139** and **140** was evaluated in LPS-activated J774.1 macrophages by Kadota et al.⁶⁵ All the tested compounds inhibited the NO release in a dose dependent manner more efficiently than curcumin (IC₅₀ = 190 μM) as positive control. Diarylheptanoid **52** showed a moderate activity with an IC₅₀ value of 181 μM . More potent were hydroperoxide calyxin A (**53**), calyxin B (**54**), epicalyxin B (**55**) and calyxin F (**139**) bearing a chalcone moiety displaying IC₅₀ values of 49, 39, 84 and 51 μM respectively. calyxin C (**56**), epicalyxin C (**57**) (stereoisomeric to each other at C9''), calyxin D (**58**), epicalyxin D (**59**) (stereoisomeric to each other at C9'') and calyxin E (**60**) bearing a flavanone moiety inhibited NO release with IC₅₀ values of 84, 95, 103, 83 and 76 μM respectively. 6-Hydroxycalyxin F (**140**) showed 37.6% inhibition rate at 10 $\mu\text{g/mL}$. Stronger activity was found for dimeric diarylheptanoids blepharocalyxin A (**61**) and B (**62**) with IC₅₀ values of 39 and 36 μM without any cytotoxicity.

Note that in 1997, the same team initially reported that compounds **54-59** inhibited the production of NO in activated murine macrophages J774.1 at a range of 90-94% at 100 $\mu\text{g/mL}$ with a cell viability of 85-90% at this concentration.⁶⁶

Curcuma, a genus of flowering plants of the Zingiberaceae family, contains about forty species of tropical origin well known for containing various polyphenolic compounds with used as medicines and food ingredients. In 2017, 97 diarylheptanoids were extracted from *curcuma* genus.⁶⁷

In 1993, three non-phenolic diarylheptanoids, alnustone (**63**), **64** and **65** isolated from rhizomes of *Curcuma xanthorrhiza* (Zingiberaceae), by Taylor et al.⁶⁸ were shown to exhibit significant anti-inflammatory activity in the *in vivo* assay of carrageenan-induced hind paw edema in rats with 44, 30 and 39% inhibition rates 3h after injection at 100 mg/kg, compared to aspirin (80% inhibition).

In 1996, the same team tested diarylheptanoids **63-65** against ethyl phenylpropiolate-induced rat ear edema. Alnustone (**63**) showed an ID₅₀ value of 63 $\mu\text{g/ear}$ and 67 $\mu\text{g/ear}$, 30min and 1h after edema induction respectively, compared to oxyphenbutazone : ID₅₀ = 12 $\mu\text{g/ear}$ and 46 $\mu\text{g/ear}$, 30 min and 1h after edema induction respectively as positive reference drug. Compound **64** exhibited ID₃₀ values of 35 $\mu\text{g/ear}$ and 28 $\mu\text{g/ear}$, 30 min and 1h after edema induction (compared to oxyphenbutazone : ID₃₀ = 0.2 $\mu\text{g/ear}$ and 0.3 $\mu\text{g/ear}$, 30 min and 1h after edema induction respectively), while **65** displayed ID₅₀ values of 129 $\mu\text{g/ear}$ and 312 $\mu\text{g/ear}$, 30 min and 1h after edema induction respectively. Thus,

alnustone (**63**) was thus identified as the most potent in the series with an activity in the same dose-range than the reference compound at 1h after induction.⁶⁹

Very recently, (*R*)-**65**, isolated from *Curcuma comosa* (Zingiberaceae), was further evaluated *in vivo* in thioacetamide-induced mice hepatotoxicity assay and its protective effect highlighted by Piyachaturawat's team.⁷⁰ In particular pretreatment with **65** significantly attenuated TNF- α expression (53% rate at dose of 1 mg/ kg). This data could be related to an anti-inflammatory potential.

Comprehensive studies were conducted by Qiu's Chinese team⁷¹ aiming at isolating, identifying and evaluating extracts from rhizomes of *Curcuma kwangsiensis* (Zingiberaceae), which are one then most important crude drugs used in traditional Chinese medicine. In 2010, these authors evaluated 12 new and 6 known diarylheptanoids **66-83**. They made efforts to separate enantiomers by chiral HPLC and determined the absolute configuration using the modified Mosher's method. Their inhibitory effect on NO production in LPS-stimulated RAW 264.7 macrophages was evaluated compared to indomethacin (IC_{50} = 12.9 μ M) and hydrocortisone (IC_{50} = 40.6 μ M) as positive controls. Compounds **70**, **71**, **72**, **77**, **78**, **80** and **81** displayed moderate activities close to that of reference compounds with IC_{50} values of 16.1, 42.0, 20.6, 49.5, 28.5, 15.6 and 10.6 μ M respectively. Derivatives **66**, **67**, **68**, **69**, **73**, **74**, **75**, **76**, **79**, 3-platyphyllone (**82**) and **83** showed strong inhibition with IC_{50} values of 2.7, 7.0, 8.9, 9.8, 3.9, 7.3, 9.7, 5.8, 6.5, 5.6 and 4.8 μ M respectively. Noteworthy, for each pair of enantiomers, the inhibitory effects of each enantiomer are not significantly different.

It should be pointed out an IC_{50} value of 32.1 μ M for NO release inhibition of 3-platyphyllone (**82**) in LPS-activated RAW 264.7 macrophages was later found by other authors (compared to L-NMMA : IC_{50} = 41.9 μ M).²³

Moreover, **83** was widely tested by He and Lu's team⁷² against imiquimod-stimulated production of IL-1 β , IL-6 and IL-12 with 86, 61 and 69% inhibition rates respectively in mRNA level and with 56, 58 and 31% inhibition rates respectively in protein level at 10 μ M in BMDCs.

In their continuing search for bioactive constituents from *Curcuma kwangsiensis*, Qiu et al.⁷³ identified in 2011 a series of 11 new diarylheptanoids **84-94** and 7 known ones **95-101** which were examined for their inhibitory activity on NO production in LPS-activated RAW 264.7 macrophages. Diols **84**, **85** and **86** showed strong activity with IC_{50} values of 3.1, 2.8 and 2.4 μ M respectively, compared to indomethacin (IC_{50} = 12.9 μ M). Derivatives **92**, enantiomeric mixture of **93-94**, **95**, **96**, and **97** exhibited activity close to the reference compound with IC_{50} values of 10.7, 9.5, 9.4, 11.5 and 8 μ M. Diarylheptanoid **89**, **90**, **91**, **98** and hanokinin (**99**) displayed moderate activity with IC_{50} values of 37.5, 32, 35.5, 25.8 and 46.4 μ M respectively. Moreover, other studies described for **98** an IC_{50} value of 89.7 μ M (in LPS-activated BV2 microglial cells compared to L-NMMA : IC_{50} = 18.3 μ M)⁴⁸ and for **99** an IC_{50} value of 30 μ M (in LPS-activated RAW 264.7 macrophages compared to L-NMMA : IC_{50} = 41.9 μ M).²³ Derivatives **87** and **88** showed weak activity with IC_{50} values of 75.7 and 82.8 μ M respectively, while IC_{50} values of meso-hanokinol (**100**) and (+)-hanokinol (**101**) were found above 100 μ M.⁷³ Note that **84** was tested in 2018 against NO production with an IC_{50} value of 27.0 μ M compared to indomethacin (IC_{50} = 32.3 μ M) in LPS-activated RAW 264.7 macrophages.⁷⁴

Diarylheptanoids **99**, **100**, **101** and **102** were furthermore isolated from the fruits of *Amomun tsao-ko* (Zingiberaceae) and showed to attenuate NO production in LPS-activated BV2 microglial cells with respectively 66.3, 65.2, 51.3 and 76.7% inhibition rates at 10 μ M (compared to 70.5% inhibition rate for ω -nitro-L-arginine methyl ester used as a positive control).⁷⁵

Compounds **103-106** were isolated from *Curcuma comosa* rhizomes, cultivated and used in traditional Thai medicine, and studied by many teams. Thus, **103** and **104** were found to dose-dependently strongly inhibit the NO release in LPS-treated RAW 264.7 macrophages with IC₅₀ values of 0.66 and 0.42 μ M respectively by Suksamrarn and coworkers.⁷⁶ No numerical data was mentioned for BAY 11-7082 used as positive control. In 2016, a comprehensive study was conducted on **104** to evaluate its potency as therapeutic agent against osteoporosis tightly linked to inflammation. It exhibited both anti-inflammatory activity with an IC₅₀ value of 1.1 μ M for NO inhibition in LPS-activated RAW 264.7 macrophages with no cytotoxicity. An anti-osteoclastogenic activity was displayed by strongly inhibiting RANKL-mediated osteoclast differentiation in BMDCs (IC₅₀ = 325 nM), which may be due, at least in part, to inhibition of the MAPK pathway.⁷⁷ In the search of new treatment against neurodegenerative diseases, **104** was further shown at 5 μ M (no toxic concentration) to inhibit NO production with 91 % rate, suppress iNOS expression with 85% rate, attenuate the activation of NF- κ B with 52% rate and lower ROS production with 90% rate and p38 MAPK activation with 44% rate in LPS-activated aggressive proliferating immortalized (HAPI) microglial cells.⁷⁸ Evaluation of **105** and **106** revealed that these compounds decreased secretion of cytokines TNF- α with 19 and 44% inhibition rates respectively and IL-1 β with 20 and 30 % inhibition rates respectively, reduced TNF- α protein expression with 58 and 64% inhibition rates respectively at 1 μ g/mL and suppressed IKK β expression and NF- κ B activation in phorbol-12-myristate-13-acetate (PMA)-stimulated human monocytes U937 cells.⁷⁹

In 2018, tetrahydroxy compound **107** was isolated from *Curcuma zedoaroides* A. (Zingiberaceae) rhizomes as a new diarylheptanoid by Tewtrakul et al.⁸⁰ Its anti-inflammation activity was investigated on NO production with an IC₅₀ value of 32.6 μ M compared to indomethacin (IC₅₀ = 26.3 μ M) in LPS activated RAW 264.7 macrophages. **107** did not inhibit TNF- α production (IC₅₀ >100 μ M), and suppressed iNOS and COX-2 mRNA expressions in dose-dependent manner.

In a search for new inhibitors of STAT3 (a major actor of inflammation activated by the pleiotropic cytokine IL-6), extracts of *Curcuma phaeocaulis* (Zingiberaceae) recently provided five non-phenolic compounds **108-112** along with two phenolic diarylheptanoids **113** and **114**. These compounds were evaluated for their inhibitory effect on IL-6-stimulated STAT3 expression in Hep3B cells. Whereas **108** was found inefficient with an IC₅₀ value above 50 μ M, **109-114** gave IC₅₀ values of 37.6, 19.9, 12.9, 11.1, 4.1 and 21.5 μ M respectively (compared to stattic as positive control: IC₅₀ = 0.67 μ M). Particular attention was paid for compound **112** as the more potent. Therefore, derivative **112** was evaluated for its effect on ICAM-1, C-reactive protein (CRP), IL-1 β and suppressor of cytokine signaling 3 (SOCS3) mRNA expression with 76, 91, 91 and 91% inhibition rates respectively at 30 μ M.⁸¹

In 2012, three new diarylheptanoid glycosides plantagineoside A (**115**), plantagineoside B (**116**) and unusual cyclic plantagineoside C (**141**) were characterized by Kim's team⁸² along with three known ones **117-118-119** after isolation from *Tacca plantaginea* (Taccaceae), whose rhizomes have been widely used in traditional medicine. Compounds **115** and **116** were found inactive (IC₅₀ > 10 μ M) to inhibit TNF- α -induced NF- κ B transcriptional activity in HepG2 cells, whereas derivatives **117-119** and **141** proved significantly active with IC₅₀ values of 6.2, 0.9, 9.4 and 8.0 μ M respectively compared to sulfasalazine (IC₅₀ = 0.9 μ M) as positive control. Moreover all compounds **115-119** and **141** significantly activated the transcriptional activity of peroxisome proliferator-activated receptors (PPARs) in a dose-

dependent with IC₅₀ values of 7.0, 10.4, 1.2, 0.3, 9.9 and 5.2 μ M respectively, compared to benzafricate (IC₅₀ = 1.0 μ M) as positive control. Evaluation on three individual PPAR subtypes, including PPAR α , γ , and β (δ) was equally performed and showed that these compounds essentially enhanced the transcriptional activity of PPAR β (δ) which is particularly important for inflammation regulation with IC₅₀ values of 11.0, 13.1, 29.3, 15.6, 23.1 and 30.1 μ M respectively, compared to L-165041 (IC₅₀ = 0.65 μ M) as positive control. No significant toxicity was noticed at the tested concentration.

Many other plant genus have been explored for diarylheptanoids with anti-inflammatory properties. Linear compounds **120-121-122** and cyclic rhoiptelol B (**142**) isolated from roots of *Juglans mandshurica* (Juglandaceae), an important medicinal plant primarily distributed throughout Northeastern Asia, showed anti-inflammatory activities in a dose-dependent manner in LPS-stimulated RAW264.7 cells. It inhibited NO production with 43 to 88 %, 39 to 89 %, 39 to 87 %, 34 to 85% rates respectively, TNF- α production with 39 and 77 %, 36 to 95 %, 34 to 78 % and 41 to 94% rates respectively and IL-6 expression with 57 to 89 %, 43 to 90 %, 43 to 95 % and 40 to 95% rates in the range 10-100 μ M.⁸³ Cell viability determined by MTT assay, showed that compounds **120-122** and **142** had no significant cytotoxicity. Rhoiptelol B (**142**) had also been evaluated in 2007 after isolation from *Alnus hirsuta* for its inhibitory activity against LPS-induced NO and TNF- α production and NF- κ B activation in RAW 264.7 cells. However, it showed very weak activity with IC₅₀ values above 100 μ M.²⁹

Compounds **123-124-125** were isolated as new diarylheptanoids from hemiparasitic shrub *Viscum album* L. (Santalaceae) and tested for their inhibitory effects on the LPS-stimulated production of TNF- α , IL-6 and IL-12p40 in BMDCs. With IC₅₀ values of 0.32, 0.68 and 0.09 μ M respectively, **123** revealed potent efficiency, compared to SB203580 (IC₅₀ = 7.53, 3.45 and 5.21 μ M respectively) used as positive control. **124** showed moderate activity with IC₅₀ values above 50 μ M for TNF- α , IL-6 and 11.8 μ M for IL-12p40, whereas **125** proved inefficient (all IC₅₀ > 50 μ M).⁸⁴

Seeds from *Aframomum melegueta* (Zingiberaceae), a commonly used African spice, allowed isolation of diarylheptanoids **126** and **127** which were tested for their hepatoprotective effect against CCl₄-induced liver toxicity. They significantly decreased the levels of serum alanine amino transferase (ALT) which is an enzyme associated to liver diseases and considered as pertinent marker of inflammation,⁸⁵ TBARS, TNF- α and IL-1 β , with 61.1, 67.1, 38.6 and 63.6% inhibition rates respectively for **126**, and 56.3, 60.4, 43.8 and 58.8% inhibition rates respectively for **127** at 1 μ M in rats liver hepatocytes 180 min after CCl₄ addition (compared to curcumin : 57.6%, 39.2%, 37.1% and 63.3% inhibition rates respectively).⁸⁶ Moreover, the experimental results did not show any toxicity for the hepatocytes. **126** and **127** showed same range of anti-inflammatory efficiency as curcumin.

Recently, He and co-workers⁷⁴ characterized new pentaol **128**, cyclic diarylheptanoids **143-146** from *Kaempferia galanga* L. (Zingiberaceae) rhizomes and evaluated their inhibitory effect against LPS-induced NO production in RAW 264.7 macrophages. **143** and **145** proved particularly efficient with IC₅₀ values 27.9 and 17.3 μ M respectively, compared to indomethacin (IC₅₀ = 32.3 μ M). **128** (IC₅₀ = 46.7 μ M) and **144** (IC₅₀ = 79.9 μ M) exhibited moderate activity, while **146** proved inefficient (IC₅₀>100 μ M).

In the course of investigation on the therapeutic effect of ginger on cardiovascular diseases, it was shown that gingerenone A (**129**) efficiently inhibited TNF- α and LPS- induced VCAM-1 expression with 26 to 89 % and 17 to 94 % rates respectively and attenuated TNF- α and LPS-induced NF- κ B

transactivation with 7 to 46 % and 8 to 40 % rates respectively in the range 5-20 μM in HUVECs, showing its potential in prevention for atherosclerosis.⁸⁷

Phenolic **130**, **131** and non-phenolic **132**, **133** diarylheptanoids isolated from rhizomes of *Pleuranthodium racemigerum* (Zingiberaceae), an endemic plant of New Guinea, were tested for their anti-inflammatory activity against NO production and TNF- α downregulation in LPS-activated RAW 264.7 macrophages and N-11 microglial cells. These compounds inhibited the NO release with IC₅₀ values of 47, 25.1, 28.3 and 47.0 μM respectively in RAW 264.7 macrophages (compared to curcumin : IC₅₀ = 12.3 μM as reference) and IC₅₀ values of 63.2, 41.3, 12.7 and 44.2 μM respectively in activated N-11 microglial cells (compared to apigenin : IC₅₀ = 15 μM as positive control). Concerning the TNF- α level, these derivatives showed IC₅₀ values of 29.6 , 15.9, 5.3 and 9.9 μM respectively in RAW 264.7 macrophages (compared to curcumin : IC₅₀ = 11.2 μM) and IC₅₀ values of 29.6, 23.3, 4.3 and 29.6 μM respectively in N-11 microglial cells (compared to apigenin : IC₅₀ = 20 μM) were found. Yet, they proved some degree of cytotoxicity, however lower than that of curcumin in RAW 264.7 cells for the same range of efficacy.⁸⁸

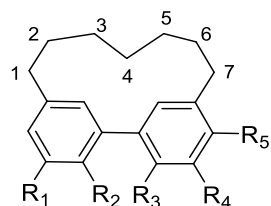
Recently extraction from the fruits of *Amomum kravanh* (Zingiberaceae) allowed the isolation and identification of new diarylheptanoids which were evaluated for their NO inhibitory effect in LPS-activated RAW 264.7 macrophages. In particular, new kravanol D (**147**), G (**148**) and H (**149**), embedding a tetrahydropyran ring in the seven carbon chain, and known renealtin A (**151**) with a tetrahydrofuran ring (Fig.3), with IC₅₀ values 23.6, 21.8 , 17.4 and 26.5 μM respectively (compared to dexamethasone: IC₅₀ = 32.5 μM as reference) showed moderate activity.⁸⁹

In 2013, kravanol B (**150**) and renealtin A (**151**) had been previously evaluated with IC₅₀ values of 38.9 μM and above 100 μM respectively (compared to L-NMMA: IC₅₀ = 40.4 μM) in LPS-induced RAW 264.7 macrophages).⁹⁰

4. Macrocyclic natural diarylheptanoids

The structures of the selected macrocyclic diarylheptanoids are compiled in Table 3 (compounds **152-171**) for *meta-meta* bridged biphenyl diarylheptanoids and Table 4 (compounds **172-182**) for *meta-para* bridged diphenyl ether diarylheptanoids. Macrocyclic diarylheptanoids are mainly found in genus *Myrica* (Myricaceae),⁹¹ *Alnus*, *Carpinus* (Betulaceae) and *Acer* (Acereaceae).⁹²

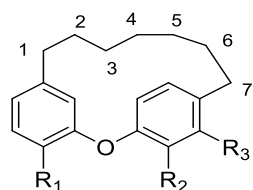
Table 3. Structures and sources of natural anti-inflammatory macrocyclic *meta-meta*-bridge biphenyl heptanoids.



Diarylheptanoids	Sources of evaluated diarylheptanoids	1	2	3	4	5	6	7	R ₁	R ₂	R ₃	R ₄	R ₅
Myricanenin A (152)	<i>Myrica nana</i> ⁹³	–	(S)-OH	(R)-OH	–	–	–		OH	OH	OH	OCH ₃	H
Myricanenin C (153)	<i>Myrica nana</i> ⁹³ <i>Myrica adenophora</i> ⁹⁴	–	–	O	–	–	–	–	H	OH	OH	OCH ₃	H
Myricanenin D (154)	<i>Myrica nana</i> ⁹³		Δ ¹ (E)	O	–	–	–	–	OH	OH	OCH ₃	OCH ₃	OH
Myricanenin E (155)	<i>Myrica nana</i> ⁹³	–	OH	O	–	–	–	–	OH	OH	OCH ₃	OCH ₃	OH
12-Hydroxymyricanone (156)	<i>Myrica nana</i> ⁹³	–	OH	O	–		–	–	H	OH	OCH ₃	OCH ₃	OH
Alnusonol (157)	<i>Myrica nana</i> ⁹³	–	–	O	–	OH	–	–	H	OH	OH	H	H
(R)-Myricanol (158)	<i>Myrica adenophora</i> ⁹⁴	–	–	(R)-OH	–	–	–		H	OH	OCH ₃	OCH ₃	OH
Porson (159)	<i>Myrica adenophora</i> ⁹⁴	–	OH	O	–		–	–	H	OH	OCH ₃	OCH ₃	OCH ₃
Myricanone (160)	<i>Myrica adenophora</i> ⁹⁴ <i>Alnus japonica</i> ⁹⁵	–	–	O	–	–	–	–	H	OH	OCH ₃	OCH ₃	OH
(S)-Myricanol (161)	<i>Alnus japonica</i> ⁹⁵	–	–	(S)-OH	–	–	–	–	H	OH	OCH ₃	OCH ₃	OH
Halnuheptanoid B (162)	<i>Alnus japonica</i> ⁹⁵	–	–	O	–	–	–	–	H	OAc	OCH ₃	OH	O-Glc
163	<i>Alnus japonica</i> ⁹⁵	–	–	O	–	–	–	–	H	OH	OCH ₃	OCH ₃	O-Glc
164	<i>Alnus japonica</i> ⁹⁵	–	–	(S)-OH	–	–	–	–	H	OH	OCH ₃	OCH ₃	O-Glc
Carpinontriol A (165)	<i>Carpinus cordata</i> ⁹⁶ <i>Carpinus turczaninowii</i> ⁹⁷	–	OH	O	OH	OH	OH		H	OH	OH	H	H

Carpinotriol B (166)	<i>Carpinus cordata</i> ⁹⁶ <i>Carpinus turczaninowii</i> ⁹⁷	–	OH	O	–	OH	OH	–	H	OH	OH	H	H
Juglanin B (167)	<i>Myrica rubra</i> ⁹⁸	–	–	(<i>R</i>)-OH	–	–	–	–	H	OH	OH	OCH ₃	H
Juglanin B-(11 <i>R</i>)-O-sulfate (168)	<i>Myrica rubra</i> ⁹⁸	–	–	(<i>R</i>)-OSO ₃ K	–	–	–	–	H	OH	OH	OCH ₃	H
169	<i>Micromelum integerrimum</i> ¹⁰⁰	–	–	(<i>S</i>)-OH	–	–	–	–	H	OH	OCH ₃	OH	OCH ₃
Acerogenin E (170)	<i>Acer nikoense</i> ¹⁰¹	–	–	O	–	–	–	–	H	OH	OH	H	H
Acerogenin K (171)	<i>Acer nikoense</i> ¹⁰¹	–	–	OH	–	–	–	–	H	OH	OH	H	H

Table 4. Structures and sources of natural anti-inflammatory macrocyclic *meta-para*-bridge diphenylether heptanoid.



Diarylheptanoids	Sources of evaluated diarylheptanoids	1	2	3	4	5	6	7	R ₁	R ₂	R ₃
Acerogenin A (172)	<i>Acer nikoense</i> ^{46, 47, 101}	–	–	–	–	(<i>R</i>)-OH	–	–	OH	H	H
Acerogenin B (173)	<i>Acer nikoense</i> ^{46, 47, 101}	–	–	(<i>R</i>)-OH	–	–	–	–	OH	H	H
Acerogenin C (174)	<i>Acer nikoense</i> ⁴⁶	–	–	–	–	O	–	–	OH	H	H
Acerogenin L (175)	<i>Acer nikoense</i> ⁴⁶	–	–	O	–	–	–	–	OH	H	H
Aceroside III (176)	<i>Acer nikoense</i> ⁴⁶	–	–	–	–	(<i>R</i>)-O-Api(1→6)-Glc	–	–	OH	H	H
Aceroside IV (177)	<i>Acer nikoense</i> ⁴⁶	–	–	(<i>R</i>)-O-Glc	–	O	–	–	OH	H	H
Aceroside B1 (178)	<i>Acer nikoense</i> ⁴⁷	–	–	–	–	(<i>R</i>)-OH	–	–	O-Glc	H	H
Myricatomentogenin (179)	<i>Alnus hirsuta</i> ²⁹	–	–	O	–	–	–	–	OH	OCH ₃	OH
180	<i>Alnus hirsuta</i> ²⁹	–	–	(<i>R</i>)-OH	–	–	–	–	OCH ₃	OCH ₃	OH
Tedarene A (181)	<i>Tedania ignis</i> ^{102, 103}	–	Δ ² (<i>E</i>)	–	–	Δ ⁴ (<i>Z</i>)	–	–	OH	H	H
182	<i>Juglans mandshurica</i> ⁸³	–	–	(<i>S</i>)-O-Glc	–	O	–	–	OH	OCH ₃	H

A series of biphenyl diarylheptanoids **152-157**, isolated from roots of *Myrica nana* (Myricaceae), were tested for their inhibitory effect on NO release. Myricananin A (**152**), myricananin C (**153**), 12-hydroxymyricanone (**156**) and alnusunol (**157**) displayed potent activity with IC₅₀ values of 45.3, 63.5, 30.2 and 46.2 μ M respectively in LPS-activated peritoneal macrophages, compared to L-NMMA (IC₅₀ = 64.2 μ M). In turn, myricanin D (**154**) and C (**155**) did not show any inhibitory effect on NO release (IC₅₀ > 100 μ M). Myricananin A (**152**) was moreover found to inhibit the iNOS expression.⁹³

Myricananin C (**153**) was equally found in the roots of *Myrica adenophora* (Myricaceae), along with (*R*)-myricanol (**158**), porson (**159**) and myricanone (**160**). They were tested for their antioxidant (DPPH, ABTS) and anti-inflammatory activities. Myricanin C (**153**), (*R*)-myricanol (**158**) and myricanone (**160**) exhibited strong ABTS radical scavenging activity (IC₅₀ (ABTS) = 12.0, 22.3 and 19.6 μ M respectively compared to 23.3 μ M for AA), associated with potent NO inhibitory activity (IC₅₀ values of 13.0, 7.5 and 1.0 μ M respectively, compared to 39.5 μ M for N-nitro-L-arginine as positive control) in LPS-activated RAW 264.7 macrophages. Porson (**159**) showed only a moderate ABTS antiradical scavenging activity (IC₅₀ = 73.7 μ M), no significant DPPH one (IC₅₀(DPPH) >250 μ M) and a modest anti-inflammatory activity under these conditions (NO inhibitory activity, IC₅₀ = 46.9 μ M).⁹⁴

Myricanone (**160**) was also isolated from *Alnus japonica* stem bark, along with (*S*)-myricanol (**161**), glucopyranosides halnuheptanoid B (**162**), O- β -D-glucoside macrocycles **163** and **164** by Ibrahim et al.⁹⁵ These compounds were tested for their antioxidant activity, they showed a moderate DPPH inhibitory activity in the range 41-70% at 50 μ M, compared to 97% inhibition for propyl gallate as positive control. Their anti-inflammatory activity was evaluated using carrageenan induced rat paw edema model at a dose 10 mg/kg. They displayed potent activity with 49.6, 51.5, 46.3, 46.9 and 47.1% inhibition after 4 hours, compared to indomethacin as reference (55.2% inhibition). The authors noticed that glucosidation of phenolic groups led to reduced activities.

The diarylheptanoids macrocycles carpinontriol A (**165**) and B (**166**) first identified by Y-S Lee and al.⁹⁶ from the stem of *Carpinus cordata* (Betulaceae) did not show any significant antioxidant activity in DPPH assay (IC₅₀ >100 and 80.2 μ g/mL respectively, compared to epigallocatechin gallate : IC₅₀ = 2.7 μ g/mL as positive control). Later, N-H Lee⁹⁷ also isolated macrocycles **165** and **166** from *Carpinus turczaniewii* branches and evaluated their anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophages. **165** and **166** reduced the NO release with high IC₅₀ values of 396 and 199.4 μ M respectively and IL-6 production in a dose dependent manner from 6.3 to 76.6% and 19 to 55.3% respectively in the range 50-500 μ M. No cell toxicity was observed during the experiments.

Juglanin B (**167**) initially identified from walnut husks *Juglans regia* L. (Juglandaceae)⁹⁸ and its O-sulfate derivative **168** found in leaves of *Myrica rubra* (Myricaceae) were evaluated against LPS-induced cytokines production in macrophage RAW 264.7 cells. Juglanin B (**167**) inhibiting TNF- α , IL-1 β and IL-6 production with IC₅₀ values of 19.5, 17.9 and 20.3 μ M respectively was slightly more potent than its sulfate counterpart with IC₅₀ values of 20.1, 22.9 and 22.7 μ M respectively, compared to quercetin as positive control with IC₅₀ values of 13.6, 16.9 and 16.8 μ M respectively. Moreover, these compounds dose-dependently reduced significantly the LPS-expression of iNOS and COX-2 proteins.⁹⁹

In 2019, diarylheptanoid **169** isolated from leaves of *Micromelum integerrimum* (Rutaceae) was studied in the context of retinitis pigmentosa, in which inflammation plays a key role by Zheng's

team.¹⁰⁰ **169** treatment (daily intraperitoneal injection at 5mg/kg) decreased NO production (21%) and IL-1 β , (22%), IL-6 (12%), IL-12 (12%), TNF- α (16%) levels in the retinas of Rd10 mice model. Macrocyclic **169** also decreased gene expression of IL-1 β (41%), IL-6 (31%), IL-12 (38%), TNF- α (49%) and protein expression of NF- κ B (50%) in the retinas of Rd10 mice. The authors concluded that a treatment with the diarylheptanoid **169** protected photoreceptor cells against degeneration in the Rd10 mouse model of retinitis pigmentosa.

The biphenyl macrocycles acerogenin E (**170**) and K (**171**) isolated from the stem bark *Acer nikoense* (Acereaceae), a tree indigenous to Japan, were shown to inhibit NO production with IC₅₀ values of 24 and 25 μ M respectively in LPS-activated mouse peritoneal macrophages, equivalent to that of L-NMMA (IC₅₀ = 28 μ M) as positive control. When compared to the inhibitory activities of diarylethers acerogenin A (**172**) and B (**173**) (IC₅₀ values of 74 and 88 μ M respectively), equally isolated, Yoshikawa and coworkers suggested that biphenyl-type structures display stronger NO production inhibitory activity than biphenyl-ether type ones.¹⁰¹ The two latter derivatives **172** and **173** were further assayed for their NO production inhibitory activity in LPS-activated J774.1 macrophages and showed only weak to no-activity with IC₅₀ values of 162.3 and above 200 μ M respectively (compared to L-NMMA : IC₅₀ = 73 μ M). In the same report, acerogenin C (**174**) was shown to exhibit moderate activity (IC₅₀ = 66.1 μ M), whereas acerogenin L (**175**) was inefficient (IC₅₀ >100 μ M). No cell cytotoxicity was observed at 50 μ M. ⁴⁶ *In vivo* assays were conducted by Akihisa et al. ⁴⁷ on acerogenin A (**172**) and B (**173**), glycosides aceroside III (**176**), IV (**177**) and B1 (**178**) still isolated from *Acer nikoense*. These compounds were evaluated for their anti-inflammatory effects against TPA-induced inflammation in mice (1 mg/ear) showing marked activity with ID₅₀ values of 0.32, 0.26, 0.81, 0.49 and 0.32 mg/ear, compared to those of quercetin (ID₅₀ = 1.6 mg/ear) and indomethacin (ID₅₀ = 0.30 mg/ear).

Myricatomentogenin (**179**) and alcohol **180** extracted from stem bark of *Alnus hirsuta* were investigated for their inhibitory activity against LPS-induced NF- κ B activation and NO and TNF- α production in LPS-activated RAW 264.7 macrophages. They showed similar potent inhibitory activity of NF- κ B gene expression with IC₅₀ values of 9.4 and 9.2 μ M respectively, on NO production with IC₅₀ values of 18.5 and 18.2 μ M, and TNF- α production with IC₅₀ values of 22.9 and 22.3 μ M respectively, in comparison with parthenolide, a known NF- κ B inhibitor (IC₅₀ = 3.4, 2.4 and 2.6 μ M respectively for NF- κ B, NO and TNF- α).²⁹

An unique cyclic diaryl heptadienoid tedarene A (**181**) was isolated from the unusual source marine sponge *Tedania ignis* (Tedaniidae) and showed 68% inhibition of NO production at 30 μ M in LPS-activated J774.1 cells.¹⁰² Moreover, it was proved by F Bedos-Belval et al.¹⁰³ to inhibit 65% of NO release, and respectively 40% and 75% of IL-1 β and IL-6 cytokines production at 30 μ M in LPS-stimulated RAW 264.1 macrophages. However, the authors noticed the self-toxicity of this compound with only 40% cell viability at 30 μ M.

Macrocyclic **182** was recently isolated from the roots of *Juglans mandshurica* and showed anti-inflammatory activity in a dose-dependent manner in LPS-stimulated RAW264.7 cells. It is active against NO production with 32.7 to 91.3% inhibition, TNF- α and IL-6 production with 44.1 to 95.7% and

29.2 to 95.6% inhibition respectively in the range 3-100 μ M. No significant cytotoxicity in RAW 264.7 cells at 100 μ M was observed.⁸³

5. Conclusion

This review summarizes the findings from 1982 to 2020 concerning the anti-inflammatory activities of a total of 182 diarylheptanoids, mainly isolated as secondary metabolites from plants used in traditional medicine. In our opinion, all natural diarylheptanoids with quantified anti-inflammatory properties have been considered. However, some works may not have been retrieved by the literature method used herein. This review suggests the potential of the diarylheptanoid scaffold for the treatment of chronic inflammatory diseases even if structure-activity outcomes are difficult to highlight due to the complexity of inflammation process and the data variability of *in vitro* and/or *in vivo* studies. Diarylheptanoids may act as anti-inflammatory agents affecting the arachidonic metabolism, the cytokines production or the modulation of pro-inflammatory gene expression. Thus, the diarylheptanoid scaffold represents an important basis for the development of new, safe, effective and side effect-free anti-inflammatory drug candidates.

Acknowledgments

We thank CNRS and University Toulouse 3 for financial support.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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