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Chapter 4

Bioactivity and Synthesis of Diarylheptanoids From Alpinia officinarum

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INTRODUCTION

Alpinia officinarum Hance (Zingiberaceae), known as lesser galangal, is a well-known medicinal herb distributed in East Asia whose rhizomes are used for stomachic, analgesic, and antiemetic treatment [1]. The plant grows several feet tall and has long leaves and reddish-white flowers. Alpinia officinarum is widely cultivated throughout China, Thailand, India, Sri Lanka, Malaysia, Indonesia, Saudi Arabia, and Egypt. The species is native to Asia, Australia, and the Pacific Islands, where it occurs in tropical and subtropical climates. Alpinia is the largest genus of about 230 species in Zingiberaceae. Historically,
its rhizomes possess stimulant and digestive effects owing to their spicy flavor and aromatic scent, and as a result, it is widely used in curries and perfumes throughout Asia. Although it was previously used throughout Europe, its use has declined in recent years, and it is now mainly used in Eastern Europe. Homoeopaths use it as a stimulant. The rhizomes of *A. officinarum* have been used in traditional Japanese herbal prescriptions (Kampo medicine) mainly for dyspepsia, vomiting, flatulence, stomach trouble, and diarrhea. The plant is also used in traditional Chinese medicine as an aphrodisiac, abortifacient, carminative, antipyretic, antiinflammatory, and emmenagogue, as well as to treat disorders of the heart and kidneys, bronchitis, chronic enteritis, renal calculus, diabetes, and rheumatism. Furthermore, its rhizomes are used in various Asian cuisines (for example, in Thai and Lao tom yum and tom kha gai soups, Vietnamese Hu cuisine and throughout Indonesian cuisine). The rhizomes contain numerous active constituents, including essential oils [2], resin [3], flavonoids [4], diarylheptanoids [5], and phenylpropanoids [6,7]. As the main components distributed in this genus, diarylheptanoids possess cytotoxic, antiemetic, antiinflammatory, antivirus, and antiproliferative activities. The rhizomes of *A. officinarum* are an important medicinal herb recorded in Chinese, Korean, and Japanese Pharmacopoeias [8–10]. In this chapter, we discuss the biological activity of natural diarylheptanoids isolated from *A. officinarum*, as well as synthetic diarylheptanoids.

**STRUCTURES AND ISOLATION OF DIARYLHEPTANOIDS**

Diarylheptanoids are a major class of bioactive constituents in *A. officinarum* that are categorized into linear, cyclic, and dimeric diarylheptanoids, or diarylheptanoids bearing special moieties (Fig. 4.1, Table 4.1).

Diarylheptanoids isolated from *A. officinarum* are mainly linear diarylheptanoids. Diarylheptanoids 2–11 mostly possess a common structural moiety of 5-ene and 3-oxo or 3,5-dioxo groups on the heptane skeleton [11–28]. The main types of linear diarylheptanoids (13–43) possess 5-hydroxy and 3-oxo groups in their structure [11–19,22–30]. The other differences in structures lie in the pattern of substitution on aromatic rings. Some diarylheptanoids (47–53) possess a common structural moiety of 3,5-dihydroxy on the heptane skeleton [12,15,17,25,29,31]. In addition, compounds 1, 9, 12, and 44–46 are also linear diarylheptanoids that possess double bonds or ketone groups between C-1 and C-7 [15,19,32]. Sun et al. isolated 20 diarylheptanoids (2, 4, 6, 7, 12, 21, 24, 30, 32, 34–37, 45–47, 49, 54, 55, and 58) from *A. officinarum* [17,18], while compounds 2, 4–7, 13–15, 25, 26, 28, 29, 33, 39, 42, 43, 47, 51–53, 55, 56, and 63 were isolated from *A. officinarum* by An et al. [14,23–25]. Several novel dimeric diarylheptanoids (58–64) were isolated from the rhizomes of *A. officinarum* [19,32–34]. Some dimeric diarylheptanoids were connected through C—C or C—O—C bonds (58–61), and some were connected through the pyridine ring or six-numbered carbon ring (62–64). Both the pyridine and
FIGURE 4.1 The structures of diarylheptanoids from *Alpinia officinarum*. 
FIGURE 4.1—cont’d
FIGURE 4.1—cont’d
## TABLE 4.1 Diarylheptanoids From *Alpinia officinarum*

| No | Compound                                                                 | References                          |
|----|--------------------------------------------------------------------------|-------------------------------------|
| 1  | 7-(4-Hydroxyphenyl)-1-phenyl-3-heptanone                                 | [32]                                |
| 2  | 1,7-Diphenyl-4-en-3-heptanone                                           | [11–20,56,61,66]                    |
| 3  | 1-(4-Hydroxyphenyl)-7-phenyl-hept-4-en-3-one                            | [21]                                |
| 4  | 7-(4″-Hydroxyphenyl)-1-phenyl-4-hepten-3-one                             | [12,17,18,20,22,23,56,61,66]        |
| 5  | 7-(3,4-Dihydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-4-en-3-heptanone  | [24,25]                             |
| 6  | 1-Phenyl-7-(4-hydroxy-3-methoxyphenyl)-4E-en-3-heptanone                | [11,12,15,17–19,23,26–28,36,51,52,56,58,60–62,66,85] |
| 7  | 1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-4E-en-3-heptanone     | [17,23]                             |
| 8  | 7-(4″,5″-Dihydroxy-3″-methoxyphenyl)-1-phenyl-4-heptene-3-one            | [19]                                |
| 9  | 1,7-Diphenyl-5-heptene-3-one                                            | [19]                                |
| 10 | 1,7-Diphenyl-3,5-heptanedione                                           | [19,20]                             |
| 11 | 7-(4″-Hydroxy-3″-methoxyphenyl)-1-phenyl-3,5-heptadione                  | [28]                                |
| 12 | (2S)-1,7-Diphenyl-2-hydroxy-4E-hepten-3-one (alpinoid E)               | [17]                                |
| 13 | 1,7-Diphenyl-5-ol-3-heptanone                                          | [11,14,19,22,26–28]                |
| 14 | 7-(4″-Hydroxyphenyl)-1-phenyl-5-ol-3-heptanone                          | [12,14,19,26,28,29,44]              |
| 15 | 7-(4″-Methoxy-3″-hydroxyphenyl)-1-phenyl-5-ol-3-heptanone               | [11,14,15,19,22,26–28,59,71,76]     |
| 16 | 5-Hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone                | [15,22]                             |
| No. | Name                                                                 | References          |
|-----|----------------------------------------------------------------------|---------------------|
| 17  | 5-Methoxy-1,7-diphenyl-3-heptanone                                    | [15,22]             |
| 18  | 5-Methoxy-7-(4′-hydroxyphenyl)-1-phenyl-3-heptanone                   | [19,22]             |
| 19  | 5-Methoxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone          | [19,26–28]          |
| 20  | (5S)-Ethoxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone        | [27]                |
| 21  | (5R)-5-Hydroxy-1,7-diphenylheptan-3-one                               | [12,17,18,52,56,61,66] |
| 22  | 5-Hydroxy-7-(4′-hydroxyphenyl)-1-phenyl-3-heptanone                   | [13,44]             |
| 23  | 5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone | [29]                |
| 24  | (5R)-5-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenylheptan-3-one     | [12,13,17,18,30,32,36,52,56,58,61,62,66,85] |
| 25  | (5R)-5-Hydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-3-heptanone | [23,29]            |
| 26  | (5R)-5-Hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-3-heptanone | [24,25]         |
| 27  | (5R)-5-Hydroxy-1,7-bis(3-methoxy-4-hydroxyphenyl)-3-heptanone         | [12]                |
| 28  | (5R)-5-Hydroxy-7-(3-methoxy-3,5-dihydroxyphenyl)-1-phenyl-3-heptanone | [24,25]             |
| 29  | (5R)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)7-(4,5-dihydroxy-3-methoxyphenyl)-3-heptanone | [23]             |
| 30  | (5R)-7-(4-Hydroxy-3-methoxyphenyl)-5-methoxy-1-phenylheptan-3-one     | [17,18,51,56,61,66,85] |
| 31  | 1,7-Diphenyl-5-hydroxy-3-heptanone (dihydropyaphabishiketol)          | [13]                |
| 32  | (5S)-5-Hydroxy-7-(4′-hydroxyphenyl)-1-phenyl-3-heptanone              | [17,44,61,62]       |
| 33  | (5S)-5-Hydroxy-7-(3,4-dihydroxyphenyl)-1-phenyl-3-heptanone           | [24,25]             |
| 34  | (5S)-5-Hydroxy-7-(4′-hydroxy-3′-methoxyphenyl)-1-(4′-hydroxyphenyl)-3-heptanone | [17]             |
| 35  | (5S)-1,7-Diphenyl-5-methoxy-3-heptanone                               | [17,44,56,61,66]    |

Continued
| No | Compound                                                                 | References       |
|----|---------------------------------------------------------------------------|------------------|
| 36 | (5S)-7-(4-Hydroxyphenyl)-5-methoxy-1-phenylheptan-3-one                  | [17,18,61,66]    |
| 37 | (5S)-7-(4’-Hydroxy-3’-methoxyphenyl)-1-(4’-hydroxyphenyl)-5-methoxy-3-  | [17]             |
|    | heptanone                                                                 |                  |
| 38 | 5-Ethoxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone              | [32]             |
| 39 | 5(S)-Acetoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone                    | [23]             |
| 40 | 7-(4’-Hydroxy-3’-methoxyphenyl)-1-phenyl-3,5-heptadione                  | [26]             |
| 41 | 5-Hydroxy-1,7-diphenyl-6-heptene-3-one                                   | [19]             |
| 42 | trans, trans-1,7-diphenyl-5-ol-4,6-dien-3-heptanone                     | [14]             |
| 43 | trans, trans-1(3’-methoxy-4’-hydroxyphenyl)-7-phenyl-5-ol-4,6-dien-3-heptanone | [14,19,25,32]   |
| 44 | 6-Hydroxy-1,7-diphenyl-4-en-3-heptanone                                 | [16]             |
| 45 | (4E,6R)-6-Hydroxy-1,7-diphenylhept-4-en-3-one (alpinoid C)              | [18]             |
| 46 | (4E,6R)-6-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one (alpinoid B) | [18] |
| 47 | 7-(4-Hydroxy-3-methoxyphenyl)-1-phenylheptane-3,5-diol                   | [15,17,25,29]    |
| 48 | 7-(Hydroxy-3-methoxyphenyl)-1-(3,4-dihydroxyphenyl)-heptane-3,5-diol     | [15]             |
| 49 | 3,5-Dihydroxy-1,7-diphenylheptane                                       | [17,52,58,61,66] |
| 50 | (3R,5R)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol                    | [12,29,31]       |
|   | Formula                                                                 | Reference |
|---|------------------------------------------------------------------------|-----------|
| 51 | (3R,5R)-1,7-bis(4-Hydroxyphenyl)-3,5-heptanoidiol                      | [25]      |
| 52 | (3R,5R)-1-(4-Hydroxy-3-methoxyphenyl)-7-phenyl-3,5-heptanoidiol        | [25]      |
| 53 | (3R,5R)-1-(4-Hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)-3,5-heptanoidiol | [25] |
| 54 | 3,6-Furan-1,7-diphenylheptane                                         | [17]      |
| 55 | 3,6-Furan-7-(4’-hydroxy-3’-methoxyphenyl)-1-phenylheptane (alpinoid D) | [17,23]   |
| 56 | 1-(4-(4-Methoxylpent-3-enyl)-6-phenethylcyclohex-3-enyl)-3-phenylpropan-1-one (officinaruminane B) | [23] |
| 57 | 4-Phenethyl-1,7-diphenyl-1-heptene-3,5-dione                           | [19]      |
| 58 | (5R,5’R)-7,7’-(6,6’-Dihydroxy-5,5’-dimethoxy[1,1’-biphenyl]-3,3’-diyl)bis[5-methoxy-1-phenylheptan-3-one] (alpinoid A) | [18] |
| 59 | Alpinin D                                                              | [32]      |
| 60 | Alpinin C                                                              | [32]      |
| 61 | Alpinin B                                                              | [20]      |
| 62 | 2-Benzyl-3-hydroxy-3,5-diphenethyl-6-(3-phenylpropanoyl) cyclohexanone (alpinin A) | [33] |
| 63 | 2,6-Diphenethyl-3,5-di-(3-phenylpropanoyl)-pyridine (officinaruminane A) | [23] |
| 64 | (E)-3-[3-(3-Methoxy-4-hydroxyphenyl)prop-1-enyl]-2,4,6-triphenethylpyridine (officin B) | [34] |
| 65 | (5R)-5-(3,5,7-Trihydroxylavone)-7-(3-methoxy-4-hydroxyphenyl)-1-phenyl-3-heptanone (officin A) | [35] |
six-numbered carbon rings are derived from the heptane unit of linear diarylheptanoids. Liang et al. found that diarylheptanoid (65) has a novel skeleton bearing a flavonol moiety [35].

Pharmacological research found that diarylheptanoids exhibited antiproliferative, cytotoxic, antiemetic, antiinflammatory, and antivirus activities. Many related diarylheptanoids have been examined in order to study the structure–activity relationship (SAR).

Several research groups have developed techniques for the detection, isolation, and identification of the components from A. officinarum. Wong et al. isolated two diarylheptanoids (6 and 24) and two flavonoids using high-speed countercurrent chromatography (HSCCC) from chloroform extracts [36]. Ho et al. attempted to analyze the ethyl acetate extract directly by high-performance liquid chromatography (HPLC) with photodiode array and electrochemical detection (HPLC-ECD) techniques [37]. The HPLC-EDC method is also a very powerful tool for the detection of diarylheptanoid components at the nanogram level. Furthermore, Feng et al. discussed the separation and identification of diarylheptanoids in supercritical fluid extracts of A. officinarum using a UPLC-Q-TOF-MS-MS system [38].

SYNTHESIS OF DIARYLHEPTANOIDS

Diarylheptanoids are widely distributed in nature. Curcumin is the most common diarylheptanoid and possesses a range of bioactivities against human diseases, including antitumor, antiinflammatory, and antioxidant activities [39]. On the other hand, yashabushidiols were isolated from the male flowers of Alnus sieboldiana (Betulaceae) by Hashimoto et al. [40], and these compounds are also included in the diarylheptanoids from A. officinarum, such as compound (49) (Fig. 4.2).

Stereoselective synthesis of yashabushidiols and their derivatives has been reported by Venkateswarlu’s group, Shinde’s group, and Yikang’s group [41–43]. Each group used a sugar or derivative as a starting material; for example, d-mannitol, d-glucose, and d-gluconolactone. After several steps, acetal compounds were obtained, and nucleophilic addition or Wittig reactions then afforded yashabushidiols and their derivatives (Fig. 4.3).

We also synthesized yashabushidiols and their derivatives using kinetic resolution of Sharpless asymmetric epoxidation reaction [44] (Fig. 4.4). First, 4-phenyl-1-butyne was treated with n-BuLi followed by addition of 3-phenylpropionaldehyde...
FIGURE 4.3 Synthetic method for yashabushidiols and its derivatives using sugar as starting material.

to a lithiated alkynyl solution. Reduction of propargyl alcohol with Red-Al afforded the racemic allylic alcohol. Sharpless epoxidation reaction of allylic alcohol gave enantio-enriched antiepoxy alcohol through kinetic resolution, followed by reduction using Red-Al to afford both natural and unnatural types of yashabushidiol B (49). On the other hand, racemic allylic alcohol was treated with MCPBA and preferentially generated syn-epoxy alcohol followed by reductions using Cp₂TiCl₂, Zn, and ZnCl₂ to afford yashabushidiol A.

Compounds 35 and 32, and their enantiomers, were synthesized under almost the same conditions. Compound 32 showed particularly strong antiviral activity against respiratory syncytial virus (RSV) in vitro and in vivo [44]. Optically active compounds 35 and 32 were synthesized from racemic allylic alcohols according to the following procedure. First, kinetic resolution of optically active epoxy alcohol and chiral allylic alcohol was performed by Sharpless asymmetric epoxidation (Sharpless AE). Chiral allylic alcohol was subjected to Sharpless AE with L-DIPT to afford the opposite configuration epoxy alcohol. These epoxy alcohols were then oxidized by Dess–Martin periodinane oxidation to afford optically active α-epoxy ketones. Finally, compound 35 and
FIGURE 4.4  Synthesis of optically active yashabushidiol A via kinetic resolution of Sharpless asymmetric epoxidation.
its enantiomers were obtained by treating β-hydroxy ketone with MeOTf and 2,6-di-tert-butylpyridine; deprotection of β-hydroxy ketone by TBAF yielded compound 32 (Fig. 4.5).

Compound 50 was also isolated from A. officinarum. It resembled the structure of yashabushidiol B, which was synthesized by Das et al. [45]. They also used kinetic resolution of Sharpless AE reaction with the racemic allylic alcohol, followed by a ring opening reaction. The 3,5-dihydroxy compound was protected by 2,2-dimethoxypropane under acid conditions, followed by deprotection of the PMB group using DDQ reagent. Finally, the terminal hydroxyl group was oxidized by Swern oxidation to afford aldehyde compound, and it was then subjected to Wittig reaction followed by reduction using H₂ and Pd on carbon to yield compound 50 (Fig. 4.6).

Alpinoids B (46) and C (45) were also isolated from A. officinarum by Sun et al. [18]. Both compounds have a unique moiety in the skeleton of the γ-hydroxy-α-enone carbon chain. Generally, diarylheptanoids possess 3,5-diketo, 3-keto-5-hydroxy, or 3-keto-4-ene structures, but alpinoids B (46) and C (45) have a 3-keto-4-ene-5-hydroxy moiety. In addition, there is a chiral center at C-5, and its absolute configuration was determined as R by Mosher’s method.

Alpinoid C (45) and its analogues were synthesized by Venkateswarlu’s group and Miura’s group [46,47]. The synthetic strategy of Venkateswarlu’s group is described below (Fig. 4.7). First, 4-phenyl-2-buten-1-ol was treated with (+) DIPT, Ti(OiPr)₄, and cumene hydroperoxide to afford chiral epoxy alcohol. After two further steps, epoxy alcohol formed chiral allylic alcohol followed by olefin metathesis coupling using Grubb’s second generation catalyst to afford alpinoid C (45).

On the other hand, Miura et al. synthesized 45 using asymmetric 2,3-sigmatropic rearrangement of chiral α-sulfinyl enone (Fig. 4.8). Chiral α-sulfinyl enone was readily synthesized from l-menthyl sulfinate [48]. Chiral α-sulfinyl enone treated with catalytic amount of DBU and PPh₃, followed by oxidation with aqueous H₂O₂ solution afforded target compound 45 in high enantiomeric excess.

**ANTINEUROBLASTOMA ACTIVITY OF DIARYLHEPTANOIDs**

Neuroblastoma is a common extracranial pediatric solid tumor, accounting for 10% of all tumors in the pediatric age group. The clinical presentation of neuroblastoma is variable and advanced cases are often found to be highly resistant to conventional treatment modalities based on surgery, chemotherapy, transplantation, and radiotherapy [49]. Thus, development of new effective and safe therapeutic agents for the treatment of neuroblastoma is urgently needed.

In a recent publication, we discussed the antitumor activity of naturally occurring compounds against neuroblastoma [50].

Compounds 6, 24, and 30 exhibited the most potent activity against neuroblastoma IMR-32 cells (Table 4.2), with IC₅₀ values of 0.11, 0.83,
FIGURE 4.5 Efficient synthesis of optically active compounds 32, 35, and these enantiomers.
and 0.23 μM, respectively [17], and were more potent than cisplatin (IC\textsubscript{50}: 0.85 μM). Sun et al. found that diarylheptanoids containing the substituents of 3\textsuperscript{″}-OMe and 4\textsuperscript{″}-OH on the benzene ring or only a carbonyl (C-3) and a double bond (C-4/5) at the aliphatic chain possessed potent cytotoxicity against the IMR-32 cell line [17]. Compounds 6 and 30 showed significant cytotoxicity against neuroblastoma cell lines (IMR-32, SK-N-SH, and NB-39), induced nuclear shrinkage and fragmentation, and activated caspase-3 and -9 [51].

Tian et al. isolated nine diarylheptanoids (5, 26, 28, 33, 44, 47, 51–54) from \textit{A. officinarum} and evaluated their cytotoxicity by MTS assay. The diarylheptanoids inhibited the proliferation of neuroblastoma SHSY5Y cells in a
They found that 5 induces S phase arrest and apoptosis via upregulation of activating transcription factor 3 (ATF3) and stabilization of p53 in the SHSY5Y cell line [25]. Compound 5 also exhibited potent cytotoxicity against HepG2, MCF-7, and SF-268 (ATCC) human cancer cell lines (IC\(_{50}\): 6–10 \(\mu\)g/mL) [24].

Furthermore, Matsuda et al. also tested the inhibition of melanogenesis by 6, 21, 24, and 49 in theophylline-stimulated B16 melanoma 4A5 cells, and found IC\(_{50}\) values of 10–48 \(\mu\)M. Compound 6 showed the strongest activity among the four diarylheptanoids (IC\(_{50}\): 10 \(\mu\)M), and it also inhibited the mRNA expression of tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2, as well as protein levels of microphthalmia-associated transcription factor (MITF) [52].
ANTITUMOR-PROMOTING AND ANTIINFLAMMATORY ACTIVITIES OF DIARYLHEPTANOIDS

Chronic inflammation may be a causative factor in a variety of cancers. The longer the inflammation persists, the higher the risk of cancer. In general, inflammatory leukocytes such as neutrophils, monocytes, macrophages, and eosinophils provide soluble factors that are thought to mediate the development of inflammation-associated cancer, including the cancer cells themselves, although other cells also participate. Inflammatory mediators include metabolites of arachidonic acid, cytokines, chemokines, and free radicals. Chronic exposure to these mediators leads to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis. Emphasis will be placed on examining the role of the reactive oxygen (e.g., O$_2^-$) and nitrogen intermediates (e.g., NO), cytokines (e.g., interferons, interleukins, tumor necrosis factor-$\alpha$ (TNF-$\alpha$)), and prostaglandins (PGs). Increased cancer incidence is associated with increased duration of inflammation. Animal models have demonstrated experimentally that chronic inflammation can lead to the development of various forms of cancer, while providing further insights into possible mechanisms. Skin tumors are induced by administration of carcinogens such as 7,12-dimethylbenz[a]anthracene (DMBA), followed by repeated administration of tumor promoters such as 12-O-tetradecanoylphorbol-13-acetate (TPA) [53]. In recent publications, we discussed the inflammatory and tumor promotion, and its inhibitors from naturally occurring compounds [54,55].

Methanol extracts from the rhizomes of *A. officinarum* inhibited tumor promotion by TPA after initiation with DMBA in ICR mice [56].

Fig. 4.9A shows the percentage of tumor-bearing mice treated with DMBA plus TPA was 80% at week 20, whereas that in the group treated with DMBA plus TPA and methanol extract of *A. officinarum* was 20%. Treatment with methanol extracts of the rhizomes of *A. officinarum* caused an 85% reduction in the average number of tumors per mouse at week 20 (Fig. 4.9B). Using bioassay-guided isolation, seven diarylheptanoids (2, 4, 6, 21, 24, 30, and 35) were isolated from active fractions of the methanol extracts of *A. officinarum* [56]. The inhibitory effects against TPA-induced inflammation closely paralleled those of the inhibition of tumor promotion in two-stage carcinogenesis initiated by DMBA and TPA, a well-known tumor promoter, in a mouse skin model [57]. These diarylheptanoids inhibit tumor promotion in two-stage carcinogenesis in mouse skin. On the other hand, these diarylheptanoids inhibited TPA-induced inflammation in mice (Table 4.3). Compounds 4 and 30 were similar in activity to indomethacin, an inflammatory drug [56].

The antinflammatory mechanisms of diarylheptanoids have been reported by many researchers. Matsuda et al. found that compounds 6, 21, 24, and 49 inhibited nitric oxide (NO) production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages on bioassay-guided isolation, and compound 6 showed particularly strong inhibitory activity with an IC$_{50}$ value of 33 $\mu$M [58].
Bioassay-guided purification of ether extracts led to the isolation of a new diarylheptanoid (44), as well as two known diarylheptanoids (2 and 17). These compounds exhibited potent platelet-activating factor (PAF) receptor binding inhibitory activity with IC$_{50}$ values of 1.3, 5.0, and 1.6 μM, respectively [16]. Compound 15 also showed inhibitory and bactericidal activities against entero-pathogenic Escherichia coli (EPEC) clinical isolates and efficiently suppressed EPEC LPS-induced inflammation in human peripheral blood mononuclear cells.
Compound 6 exhibited antiinflammatory properties in a mouse macrophage cell line (RAW 264.7) (6.25–25 μM) and suppressed LPS-induced production of NO, interleukin (IL)-1β, and TNF-α by inhibiting nuclear factor-κB (NF-κB) activation and phosphorylation of p44/42 mitogen-activated protein kinases (MAPKs) [60]. Compounds 2, 6, 15, 16, 47, and 48 were tested for their inhibitory effects on NO production in the LPS-activated macrophage cell line RAW 264.7 [15]. Compounds 6 and 2 showed potent inhibitory activities with IC₅₀ values of 0.6 and 6.8 μM, respectively. Diarylheptanoid 3, isolated from the n-hexane extract, modulated NF-κB signaling involved in the inflammatory response, and inhibited LPS-induced expression of TNF-α, IL-1β, nitric oxide synthase (NOS), and cyclooxygenase-2 (COX-2) at the gene level in RAW 264.7 cells [21].

Kiuchi et al. examined the effects of diarylheptanoids (6, 11, 13–15, 19, and 40) against PG and leukotriene. This suggested that compounds lacking the methoxy group adjacent to the phenol were less active than those possessing the methoxy group, presumably owing to the decrease in acidity from the phenol group [26,28].

Thus, the reports cited above suggest that diarylheptanoids possess inhibitory effects against inflammatory and tumor-promoting activities.

ANTIVIRAL ACTIVITIES OF DIARYLHEPTANOIDS

Diarylheptanoids exhibited antiviral activities against influenza virus [61–65], RSV [44,66], poliovirus [44], measles virus [44], herpes simplex virus type 1 (HSV-1) [44], human immunodeficiency virus (HIV) [67], severe acute respiratory syndrome (SARS) virus [68], and Epstein–Barr virus in relation to carcinogenesis [69]. They are characterized as compounds possessing broad antiviral spectrum against DNA and RNA viruses. Most diarylheptanoids possessing antiviral activities have been evaluated in vitro. Antiviral activities in vivo have been documented for influenza virus and RSV using animal infection models [62,65,66].

Antiinfluenza Virus Activity

Sawamura et al. [61,62] examined the antiinfluenza virus activity and cytotoxicity of 10 diarylheptanoids (2, 4, 6, 21, 24, 30, 32, 35, 36, and 49) isolated from A. officinarum by plaque reduction assay and MTT assay, respectively, using Madin–Darby canine kidney (MDCK) cells (Table 4.4). In this study, influenza virus was more susceptible to 6 (EC₅₀ = 2.9 ± 0.3 μg/mL) and 32 (EC₅₀ = 0.7 ± 0.2 μg/mL) than to the others, and their therapeutic indexes (CC₅₀/ED₅₀) were 11.7 and 114.3, respectively [61]. Compound 32 has a 4-hydroxyphenyl moiety. Platypyllone and platypyllone-5-xylopyranoside contain two 4-hydroxyphenyl moieties and have been reported to be active against influenza virus with therapeutic indexes of >10 [64]. Thus, hydroxylation at the C-4
### TABLE 4.4 Antiviral Activity of Diarypheptanoids

| Diarylheptanoid | MDCK Cells<sup>a</sup> | HEp-2 Cells<sup>b,c</sup> | Vero Cells<sup>b</sup> |
|-----------------|----------------------|----------------------|----------------------|
|                 | Influenza Virus      | RSV                  | Measles Virus        | Polio Virus        | HSV-1                |
|                 | EC<sub>50</sub><sup>d</sup> | TI<sup>e</sup> | EC<sub>50</sub><sup>d</sup> | TI<sup>e</sup> | EC<sub>50</sub><sup>d</sup> | EC<sub>50</sub><sup>d</sup> | EC<sub>50</sub><sup>d</sup> | CC<sub>50</sub><sup>f</sup> |
| 2               | <30                  | >2.7                | 36.3(4.2)            | 1.3                | 17.3(1.2)            | 8.3(2.3) | 53.7(4.7) | 45.8(1.7) |
| 4               | <10                  | >3.0                | 5.0(0.0)             | 4.6                | –                   | –       | –        | –        |
| 6               | 2.9(0.3)             | >11.7               | 42.7(3.5)            | 0.9                | 47.0(4.6)            | 64.3(4.9) | 59.7(0.6) | 63.0(10.4) |
| 21              | 11.7(0.8)            | >4.5                | 21.7(0.6)            | 1.8                | 17.0(2.0)            | 22.7(1.5) | 54.0(5.6) | 69.5(5.2) |
| 22              | –                   | –                   | 44.7(1.5)            | 1.3                | –                   | –       | –        | –        |
| 22/32           | –                   | –                   | 24.3(0.6)            | 3.4                | –                   | –       | –        | –        |
| 24              | 22.4(1.8)            | >3.6                | 37.0(7.2)            | 2.3                | 18.3(1.2)            | 44.3(4.0) | 58.7(1.5) | >100     |
| 30              | <10                  | >3.6                | 13.3(3.8)            | 1.3                | 6.3(0.6)             | 3.7(0.6) | 5.7(0.6) | 10.8(1.3) |
| 32              | 0.7(0.3)             | >114.3              | 40.7(3.5)            | 2.1                | –                   | –       | –        | –        |
| 35              | 6.1(0.5)             | >13.1               | 16.3(3.5)            | >6.1               | 18.0(1.0)            | 16.7(2.1) | 18.3(0.6) | 40.5(5.4) |
| 36              | 7.0(0.2)             | >4.3                | 21.7(0.6)            | 1.5                | –                   | –       | –        | –        |
| 50              | 15.1(0.9)            | >3.3                | 22.3(0.6)            | 2.5                | –                   | –       | –        | –        |
| 76              | –                   | –                   | 7.0(1.4)             | 14.3               | –                   | –       | –        | –        |

<sup>HSV-1</sup>, herpes simplex virus type 1; <sup>MDCK</sup>, Madin–Darby canine kidney; <sup>RSV</sup>, respiratory syncytial virus.
<sup>a,b,c</sup>Antiviral activities were cited from [34], [79], and [84], respectively.
<sup>d</sup>Mean (SE) μg/mL of 50% effective concentration.
<sup>e</sup>Therapeutic indices (CC<sub>50</sub>/EC<sub>50</sub>).
<sup>f</sup>Mean (SE) μg/mL of 50% cytotoxic concentration.
position of the phenyl moiety may be important for antiinfluenza virus activity in vitro. However, in a murine influenza virus infection model, 6 significantly reduced virus titers in bronchoalveolar lavage fluids of the lungs and prolonged survival times of the infected mice without toxicity, whereas 32 did not show this activity [62]. Compound 6 possessed an unsaturated ketone and a methoxy group at the C-5 position of the 4-hydroxyphenyl moiety, but 32 did not. Thus, the ketone and methoxy groups may be necessary for antiinfluenza activity in vivo.

Compound 6 exhibited antiviral activity against H1N1 virus, H3N2 virus, and B type virus, as well as oseltamivir-resistant H1N1 virus [62]. This indicates that the mode of antiinfluenza virus action of 6 was different from that of the known agents, such as oseltamivir, and suggests that it is a candidate antiviral compound against more virulent strains than the pandemic H1N1. In fact, 6 was shown to have no effect on virus adsorption or invasion into cells, instead suppressing the expression of viral messenger RNA and antigens in infected MDCK cells [62]. It is probable that 6 selectively suppressed influenza virus mRNA synthesis in infected cells without cytotoxicity [62]. Diarylheptanoids isolated from Alpinia katsumadai such as katsumadain A and (E,E)-5-hydroxy-1,7-diphenyl-4,6-heptadien-3-one are reported to have inhibitory activity against the neuraminidase (NA) of influenza virus (A/PR/8/34) in vitro [65]. Some diarylheptanoids isolated from A. officinarum may therefore be effective in reducing NA activity.

### Antirespiratory Syncytial Virus Activity

Konno et al. [34,84] evaluated the anti-RSV activities of 12 diarylheptanoids (2, 4, 6, 21, 22, 22/32, 24, 30, 32, 35, 36, 49, and 66) by plaque reduction assay and trypan blue dye exclusion assay using HEp-2 cells (Table 4.4). Among these, 6 and 30 were not effective against the A2 strain of RSV [84]. The EC$_{50}$ values of 4 and 66 were 5.0±0.0 and 7.0±1.4 µg/mL (Table 4.4), respectively, and both compounds showed antiviral activity against the A2 strain of RSV with therapeutic indexes of 4.6 and 14.3, respectively, and were more potent than the other tested compounds [44,66]. Compound 4 was also active against influenza virus with an EC$_{50}$ value of <10 µg/mL [61], which suggests that 4 is an effective diarylheptanoid against both RSV and influenza virus in vitro. Compounds 22 and 22/32 were synthesized as an enantiomer and racemate, respectively, of 32, and compound 66 was synthesized as the enantiomer of 35 (Fig. 4.10) [44]. The therapeutic indexes of stereoisomers (22, 32, and 22/32) were similar (CC$_{50}$/EC$_{50}$: 1.3, 2.1, and 3.4, respectively) and their EC$_{50}$ values were 44.7±1.5, 40.7±3.5, and 24.3±0.6 µg/mL (Table 4.4), respectively [44]. However, the therapeutic indexes of 35 and 66 (6.1 and 14.3) were higher than those of the three stereoisomers, with the EC$_{50}$ values of 16.3±3.5 and 7.0±1.4 µg/mL, respectively [44,66]. The C-5 position of 35 and 66 is methoxylated with a saturated ketone at the C-3 position. Compound
also contained a methoxy group with a saturated ketone and its EC$_{50}$ value was 13.3 ± 3.8 μg/mL [66]. Thus, methoxylation in diarylheptanoids may contribute to anti-RSV activity in vitro. In a murine intranasal RSV infection model, compounds 22, 32, 22/32, and 66 were significantly effective in reducing virus titers, infiltration of lymphocytes and interferon-γ levels (marker of pneumonia severity) in the lungs of mice [44]. Among these, 66 showed the strongest anti-RSV activity in mice, as shown by anti-RSV assay in vitro, and this may be a lead compound for the development of anti-RSV drugs in the future.

Antiviral Activity Against Other Viruses

Six diarylheptanoids (2, 6, 21, 24, 30, and 35) were examined for their anti-RSV activity against poliovirus, measles virus, and HSV-1 by plaque reduction assay and trypan blue dye exclusion assay using Vero cells (Table 4.4). Among the six compounds, 6 and 30 did not exhibit any significant anti-RSV activity in HEp-2 cells [84]. However, 30 exhibited relatively stronger antiviral activities against all three viruses (poliovirus, measles virus, and HSV-1), but 6 was only effective against measles virus. All the examined diarylheptanoids except 6 exhibited antipoliovirus activity with EC$_{50}$ values between 3.7 ± 0.6 and 44.3 ± 4.0 μg/mL, and all except 2 and 6 exhibited anti-HSV-1 activity with EC$_{50}$ values between 5.7 ± 0.6 and 58.7 ± 1.5 μg/mL (Table 4.4). All six examined compounds were significantly effective against measles virus with EC$_{50}$ values between 6.3 ± 0.6 and 47.0 ± 4.6 μg/mL. Thus, diarylheptanoids appear to have a broad spectrum of antiviral activity.

Chareonkla et al. [67] reported that (3S,5S)-3,5-diacetoxy-1,7-bis(3,4,5-trimethoxyphenyl) heptane from Zingiber mekongense exhibited anti-HIV activity in the antisyncytium assay using ΔTat/revMC99 virus and 1A2 cell line system, but that it did not show activity on HIV-1 reverse transcriptase assay. Hirsute-none isolated from Alnus japonica has been shown to be a potent inhibitor of papain-like protease, which controls replication of the SARS coronavirus. This compound is therefore thought to be a potential compound for the treatment of SARS [68]. Some cyclic diarylheptanoids isolated from Acer nikoense and Myrica rubra are reported to strongly inhibit Epstein–Barr virus early antigen activation in Raji cells, and they also exhibit inhibitory activities on mouse skin tumor promotion in an in vivo two-stage carcinogenesis test [69]. It is possible that some diarylheptanoids from A. officinarum possess antiviral activity against these viruses.
OTHER ACTIVITIES OF DIARYLHEPTANOIDS

Obesity is a major health concern at present and is widely considered to be a global epidemic. Conventional or allopathic medicines used to treat obesity have high abuse potential and frequently exhibit side effects. Few botanicals included in natural weight loss products have been thoroughly researched on a basic or clinical level, and it is thus imperative to validate their widespread consumption for weight management. Many natural weight loss products are sold and used globally with little or no proof of efficacy and quality, and concerns regarding safety have surfaced with good reason. Orlistat inhibits pancreatic and gastric lipases that catalyze the hydrolysis of ingested fats, resulting in reduced dietary fat absorption and high fecal fat excretion [70]. It is certain that orlistat has a marked drug effect, as 35–45% of energy intake in Western diets is attributed to dietary fat. However, malabsorption of fat leads to rather uncomfortable side effects, such as flatus with discharge, oil spotting from the rectum, fecal incontinence, fecal urgency, loose or liquid stools, and malabsorption of fat-soluble vitamins [70].

The water extract of rhizomes from *A. officinarum* showed the strongest inhibitory activity against pancreatic lipase in vitro. The extract was subsequently fractionated using organic solvents, and the ethyl acetate fraction had the strongest inhibitory activity. The most potent inhibitor in this fraction was identified as galangin-3-methyl ether (Fig. 4.11) with an IC$_{50}$ value of 1.3 mg/mL, as compared with the positive control (orlistat) with an IC$_{50}$ value of 0.8 mg/mL using triolein as the substrate. After oral administration of corn oil, triglyceride levels in mice decreased significantly to less than those in the control group by administration of H$_2$O extract (1 g/kg) and the ethyl acetate fraction (0.5 g/kg). In Triton WR-1339-induced hyperlipidemic mice, galanin-3-methyl ether significantly decreased triglyceride and cholesterol levels at a 20 mg/kg dose to 81.3% and 81.0%, respectively, while it increased high density lipoprotein (HDL) when compared with the control group. Moreover, galanine-3-methyl ether did not show hypolipemic activity in high cholesterol diet-induced hyperlipidemic mice [71].

Compound 15 exhibited inhibitory activity against pancreatic lipase with an IC$_{50}$ value of 1.5 mg/mL using triolein as the substrate. The levels of serum triglyceride in corn oil fed mice were reduced significantly, while the levels of serum triglyceride and cholesterol were reduced in Triton WR-1339-induced hyperlipidemic mice. Hypolipidemic activity was not observed in the

![FIGURE 4.11 Structure of 3-methylgalangin and compound 15.](image)
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high-cholesterol diet-induced hyperlipidemic mice. Inhibition of pancreatic lipase for both compounds when compared with the positive control (orlistat) was good in terms of other parameters, such as triglyceride, cholesterol and HDL levels. However, orlistat remained the most effective drug [72].

Antiemetic drugs are effective against vomiting and nausea and may be used for severe cases of gastroenteritis, particularly if the patient is dehydrated. Antiemetics can also be used for morning sickness, but there is little information about their effects on the fetus. Some crude drugs inhibit vomiting among traditional Japanese herbal prescriptions, while *A. officinarum* is used as an antiemetic in traditional Chinese medicine.

Takahashi et al. reported that diarylheptanoids showed antiemetic activities in a copper sulfate (CuSO₄)-induced emesis assay in young chicks [12,29]. The SAR of diarylheptanoids was also investigated. Among 14 diarylheptanoids, two types of essential functional structure showed inhibitory activities against emesis. Diarylheptanoids 2, 4, 6, 21, 22, 24, 27 contained partial type A or B structures (Fig. 4.12), and they therefore concluded that diarylheptanoids of types A and B might be the main antiemetic components of *A. officinarum*.

5α-Reductase (reduced nicotinamide adenine dinucleotide phosphate: Δ⁴-3-ketosteroid 5α-oxidoreductase), which is present as type 1 and type 2 isozymes in humans and rats, catalyze the reductive conversion of testosterone to 5α-dihydrotestosterone [73]. 5α-Dihydrotestosterone acts as a more active androgen than testosterone in many tissues, such as the prostate. Therefore, inhibitors of this enzymatic conversion may be useful in the selective treatment of androgen-dependent diseases, such as benign prostate hyperplasia, male pattern baldness, and acne. Most 5α-reductase inhibitors are steroids binding to the steroid receptors, and these steroids may produce various undesirable hormonal effects acting as agonists or antagonists. It has been reported that diarylheptanoids possess inhibitory activity against 5α-reductase. The SAR of four diarylheptanoids (2, 22, 24, and 31) from *A. officinarum* was discussed [13]. It has been suggested that diarylheptanoids with unsaturated bonds, particularly the conjugated form in the alkyl structural moiety between the two aryl groups, had weak inhibitory activity, while diarylheptanoids with saturated counterpart bonds had potent inhibitory activity. Thus, the alkyl parts of the

![FIGURE 4.12 Structure of type A and B diarylheptanoids.](image)
diarylheptanoids appear to be important structural moieties for inhibitory activity against 5α-reductase.

_Helicobacter pylori_ is a Gram-negative, microaerophilic bacterium found in the stomach. It is also related to the development of duodenal ulcers and stomach cancer [74]. The eradication of _H. pylori_ is effective in preventing duodenal ulcers and stomach cancer.

Lee et al. examined the inhibitory effects of compound 15 against _H. pylori_ ATCC 43504, ATCC 700392, and ATCC 700824 using the paper-disc diffusion and agar dilution methods [75]. Rhizome-derived materials, particularly isolated diarylheptanoids, merit further study as potential antipylori functional food products or therapeutic products for preventing the diseases caused by _H. pylori_.

Zhang et al. reported that 13 diarylheptanoids (2, 6, 8–10, 13–15, 18, 19, 41, 43, and 57) showed antibacterial activity against _H. pylori_ [19]. The IC$_{50}$ values of these compounds were 9–20 μg/mL and 25–47 μg/mL against Hp-Sydney and 1 Hp-F44 strains, respectively.

**MOLECULAR PHARMACOLOGICAL EVALUATION BY TRANSLATION PROFILING**

From bacteria to vertebrates, cells change their patterns of gene expression to respond to their microenvironment. In addition to classical DNA microarray technology (transcriptome analysis), new analytical tools for high-throughput screening of whole transcriptome sequencing, polysome profiling (translatome analysis [76]) or ribosome profiling (ribosome protection assay [77]) have recently emerged and been applied to the analysis of gene expression (Fig. 4.13) [78]. In et al. reported that microarray global gene expression analysis showed 1′S-1′-acetoxyeugenol acetate (Fig. 4.14), a novel phenylpropanoid from _Alpinia conchigera_, enhanced the apoptotic effects of paclitaxel in MCF-7 cells through NF-κB inactivation [79]. This suggests that the induction of tumor cell death through apoptosis is modulated through dysregulation of the NF-κB pathway.

As genetic information transforms from DNA to proteins, the cellular abundance of proteins is predominantly controlled at the translation level [80]. Weak correlations between messenger RNA (mRNA) and protein levels [81] are observed because nontranslated mRNAs may be present in RNA granules, RNA particles, processing bodies, stress granules, and miRNA–RISC (miRISC) complexes in cytosol (Fig. 4.13). Analysis of the translatome can thus provide substantial and surprising new information [82].

Whole free polysome and/or membrane-bound polysome analysis has also been applied. Ribosome-associated mRNAs (usually >3) are separated from mRNAs associated with fewer ribosomes. These polysome-associated mRNAs are applied to label probes on DNA microarrays (translatome analysis) or are sequenced using next-generation sequencers (polysome profiling).
These polysome-associated mRNAs are then applied to ribosome-protection assay, and the resulting segments of RNA are sequenced using next-generation sequencers (ribosome profiling). In these analyses, active and stalled ribosomes have been shown to cosediment during isolation of polysome complexes through sucrose gradients [83], thus indicating that polysome profiling does not fully distinguish translationally active from repressed mRNAs.
Diarylheptanoids 6, 24, and 30 inhibit proinflammatory mediators and exhibit cytotoxic and antiviral activities. However, the precise mechanisms of action and their effects on expression of specific genes are unknown. Thus, we used translatome analysis to investigate the mechanisms and modes of action of these diarylheptanoids [84]. Polysome-associated mRNAs were prepared from diarylheptanoid-treated and control cells from a human B lymphoblastoid cell line; these mRNA samples were then used for microarray analysis. The number of downregulated inflammatory-related transcripts was ranked as follows: 30 > 24 > 6. Compound 6 showed greater influence on the translatome of BJAB cells, while 24 showed less efficacy, except when upregulating the expression of genes related to rhodopsin-like GPCRs, mRNA processing, and proteasome-related proteins of WiKiPathways [85]. It is possible that the same host factors, such as splicing factors or hnRNPs listed in mRNA processing WP411 45374 (WP; WiKiPathways), affect virus structure and/or replication. Sixteen transcripts were upregulated after treatment with 6, 24, or 30. Among these, transcripts of heterogeneous nuclear ribonucleoprotein C (C1/C2), heterogeneous nuclear ribonucleoprotein K, non-POU domain containing, octamer-binding, and polypyrimidine tract-binding protein 1 were identified as internal ribosome entry site trans-acting factors. All of these studies have provided new insights into the mode of action of diarylheptanoids from A. officinarum with regard to its antiinflammatory, antitumor promotion, and antiviral effects.

CONCLUSION

Humans have used plants as foods and natural medicines since ancient times, and while they are crude drugs, are typically safer than synthetic drugs, and have been used as both spices and supplements. Several active components have been isolated, and their chemical structures have been and continue to be determined. The diarylheptanoids of the rhizomes of A. officinarum are considered to be a particularly promising group of compounds. Diarylheptanoids are minor but ubiquitous components in our diet and have the advantage of being nontoxic or relatively nontoxic to humans. Natural diarylheptanoids have multiple physiological functions, including antiinflammatory, antitumor, cancer preventive, antiviral, antiemetic, and anti-pylori effects. Challenges that must be overcome in order to find functionally useful compounds that can be applied clinically are further screening of natural diarylheptanoid compounds, examination of SARs, elucidation of physiological action mechanisms, and the problems associated with supplying large quantities of compounds. In order to resolve these issues, collaboration between researchers in various fields will be necessary.

ABBREVIATIONS

AP-1 activator protein-1
ATF3 activating transcription factor 3
BJAB the human B-lymphoma cell line
COX  
cyclooxygenase
DMBA  
7,12-dimethylbenz[a]anthracene
EC_{50}  
50% effective concentration
EPEC  
Enteropathogenic *Escherichia coli*
HDLC  
high density lipoprotein
HIV  
human immunodeficiency virus
HPLC  
high-performance liquid chromatography
HPLC-ECD  
HPLC with photodiode array and electrochemical detection
HSCCC  
high-speed countercurrent chromatography
HSV-1  
herpes simplex virus type 1
IC_{50}  
50% inhibitory concentration
IL  
interleukin
iNOS  
inducible nitric oxide synthase
LOX  
lipoxygenase
LPS  
lipopolysaccharide
MALT  
mucosa-associated lymphoid tissue
MAPK  
mitogen-activated protein kinases
MDCK  
Madin–Darby canine kidney
MITF  
microphthalmia-associated transcription factor
miRISC  
microRNA-induced silencing complex
MMP  
matrix metalloproteinase
NA  
neuraminidase
NF-κB  
nuclear factor-kappaB
NO  
nitric oxide
PAF  
platelet-activating factor
PG  
prostaglandin
RSV  
respiratory syncytial virus
SARS  
severe acute respiratory syndrome
TNF-α  
tumor necrosis factor-α
TPA  
12-O-tetradecanoylphorbol-13-acetate
TRP  
tyrosinase-related protein

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