The search for, and chemistry and mechanism of, neurotrophic natural products

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Abstract
Neurotrophic factors, now termed neurotrophins, which belong to a class of polypeptidyl agents, have been shown to potentially be beneficial for the treatment of neurodegenerative diseases such as Alzheimer’s disease, because endogenous neurotrophic factors (NGF, BDNF, NT3, NT4) have been recognized to play critical roles in the promotion of neurogenesis, differentiation, and neuroprotection throughout the development of the central nervous system. However, high-molecular weight proteins are unable to cross the blood–brain barrier and are easily decomposed by peptidase under physiological conditions. To address this issue, small molecules that can mimic the functions of neurotrophic factors would be promising alternatives for the treatment of neurodegenerative disease. We have continued to search for natural products having typical neurotrophic properties, which can cause neurogenesis, enhance neurite outgrowth, and protect neuronal death using three cellular systems (PC12, rat cortical neurons, and MEB5 cells). In this review, we summarize the neurotrophic activities and synthesis of dimeric isocuparane-type sesquiterpenes from the liverwort, Mastigophora diclados, the mechanism of neurotrophic neolignans, magnolol, honokiol and their sesquiterpene derivatives, and introduce unique neurotrophin-mimic natural products, including seco-prezizaane-type sesquiterpenes from the Illicium species, vibansane-type diterpenes from Viburnum awabuki, and miscellaneous natural products with neurotrophic effects discovered by us.

Graphic abstract

Keywords Neurotrophin-mimic natural compound · Neurogenesis · Neurite outgrowth · Magnolia ovobata · Illicium species · Viburnum species · Garcinia subelliptica · Phytolacca americana

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Introduction

In recent years, the percentage of elderly people has increased. In Japan, the population ratio of people aged more than 65 years is estimated to reach 29.1% by 2020 and further increase to 38.5% by 2050 [1]. In a superaged society, people wish for healthy longevity and are eager for a fulfilling welfare society. On the other hand, with age, we suffer from various diseases, such as cardiovascular diseases, cancers, and dementia, and thus, it is essential to not only explore the etiology of these diseases but also develop therapeutic drugs and preventive methods.

In particular, the number of elderly individuals who suffer from senile dementia has increased through this superaged society. Senile dementias are regarded as neurodegenerative diseases, which are categorized as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), and amyotrophic sclerosis, and are characterized by nervous system dysfunction resulting from progressive neuronal degeneration [2]. In Japan, the elderly population with neurodegenerative diseases will increase to 8,300,000 by 2030 unless suitable medical treatments are not realized [3]. AD is the most prevalent form of dementia, accounting for 50–56% of cases at autopsy and in clinical settings, and AD combined with intracerebral vascular diseases accounts for another 13–17% of cases.

The principle risk for AD is age. The incidence of AD doubles for every 5 years of age, but AD is not necessarily the outcome of aging [4]. The brain regions involved in learning and memory processes are reduced in size in AD patients as a result of degeneration of synapses and death of neurons [5]. It has been more than 15 years since it was first proposed that AD might be caused by deposition of amyloid β-peptide (Aβ) in plaques in the brain [6]. Accumulation of Aβ in the brain triggers the remaining AD pathogenesis, including the formation of neurofibrillary tangles containing tau protein, causing the degeneration of neurons and resulting in AD. Although tremendous efforts have been made according to the amyloid hypothesis, new drugs for the treatment of AD have not been successfully developed [7, 8]. This is presumably because the underlying pathogenesis of AD still remains to be explored [9].

It is well known that following neuronal injury, adult neurons have an intrinsic ability and dynamic repair mechanism within the central nervous system to regenerate and produce neuronal cells and restore neuronal networks, although this capacity is limited and the regions that are able to regenerate neurons are restricted [10]. From this perspective, we initiated our research project to discover small molecule natural products that have the potential to act as neurotrophins to enhance neurogenesis, promote neurite outgrowth, and protect the death of neurons. In this review, we will introduce our own research program on the basis of neurotrophic properties and then highlight neurotrophic natural products, in particular, focusing on the chemistry and biological profiles of our discovered active compounds.

Neurotrophins and the screening system to search for neurotrophin mimetics

Neurotrophins (neurotrophic factors) have been shown to be potentially beneficial in the treatment of neurodegenerative diseases such as AD, Parkinson’s disease (PD) and Huntington’s disease (HD) because endogenous neurotrophic factors have been recognized to play critical roles in the promotion of neurogenesis, differentiation, and neuroprotection throughout the development of the central nervous system [10, 11]. In mammals, the known neurotrophins are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4) [11]. These neurotrophins bind selectively to their tyrosine kinase receptors TrkA, TrkB and TrkC, and all of them bind non-selectively to the neurotrophin receptor p75, resulting in activation of neuronal signal transduction related to the broad spectrum of biological activities exerted by neurotrophins [12, 13]. Therapeutic uses of NFs by intracranial injections, transplantation of cells secreting NFs, or gene therapy have shown promising results in animal models of neuronal degeneration as well as in clinical trials [14–16]. However, as NFs are high-molecular weight proteins, they have been unable to cross the blood barrier and are easily decomposed by peptidase under physiological conditions. To address this issue, small molecules that can mimic the functions of neurotrophic factors would be promising alternatives for the treatment of neurodegenerative disease [17, 18].

Our protocol of searching for small molecules with neurotrophic properties is how to discovery NT mimicking compounds as well as to implicate active compounds in the key physiological functions of NTs: differentiation (neurogenesis), development (neurite outgrowth promotion) and survival (protection of neuronal death) of neurons [19] (Fig. 1). We applied three cells to the assay system; rat pheochromocytoma PC12 cells [20], primary cultured rat cortical neurons [21] and mouse multipotent neural precursor cells (MEB5) [22]. Both PC12 cells and NGF-mediated PC12 cells are used as the primary screening to identify active candidates. PC12 cells generate and extend neurites in response to NGF though the direct activation of the TrkA receptor or enhancing the intercellular NT signal pathway to induce neuritogenesis; whereas, NGF-mediated PC12 cells can extend the length of neurites to show neurite outgrowth through various mechanisms. Withdrawal of NGF from the culture medium causes the death of PC12 cells.
This method is used to screen for protection against neuronal death. Primary cultured cortical neurons are used for the second screening to confirm neurite outgrowth promotion or protection of neuronal death under different culture conditions. Finally, MEB5 cell lines have been used to ascertain whether active compounds have the potential to induce the differentiation of stem cells into neurons. In this review, our chemical and biological studies on natural products with neurotrophic activity are compiled [23–25].

Mastigophorenes: isocuparane-type sesquiterpene dimers from the liverwort Mastigophora diclados

The liverworts elaborate a wide variety of terpenoids and lipophilic aromatic substances, which have been very often found to show different types of biological activity [26]. M. diclados (Brid.) Nees is a rather primitive liverwort and is commonly found in tropical Asiatic areas. Our independent study [27, 28] on the ether extract of M. diclados collected in Boruneo resulted in the isolation of four unique dimeric isocuparanes, mastigophorenes A (1), B (2), C (3), and D (4), together with their monomer unit, herbertenediol (5) [29] (Fig. 2). Mastigophorenes A (1), B (2), and D (4) were found to exhibit interesting neurotrophic properties at concentrations ranging from 0.1 to 10 μM, which could enhance neurite-sprouting and network formation in primary cell cultures derived from embryonic rat cerebral hemispheres [30]. On the other hand, mastigophorene C (3) and the monomeric compound, herbertenediol (5), suppressed the neurite outgrowth under the same conditions.

The dimeric compounds 1–4 could be derived from herbertenediol (5), a cometabolite in the plant, by phenolic oxidation. Compounds 1–4 are presumably biosynthesized via the phenoxy radical products formed from the one-electron oxidation of 5, and then the formed radicals are subsequently converted into radical A or benzyl radical B which would give rise to a quinone methide via one more oxidation along with the loss of a proton radical. Homocoupling between two radicals A would lead to mastigophorenes A (1) and B (2) followed by aromatization; whereas, mastigophorene D (4) could be produced from the direct coupling between two benzyl radicals B. An alternative heterocoupling between
radicals A and B would give rise to mastigophorene C (3) (Scheme 1) [28]. In fact, biomimetic oxidative coupling of 2-O-methylherbertenediol using (tert-BuO)₂ in chlorobenzene under refluxing gave, after O-methyl deprotection with BBr₃, two mastigophorenes A (1) and B (2) as an atrop-diestereomeric mixture (40:60) in 28% yield [31]. However, the direct oxidation of herbertenediol (5) with (tert-BuO)₂ failed to yield dimers 1 and 2, resulting in a complex mixture, and thus protecting the 1-hydroxy group of 5 was essential for successful oxidative coupling. We applied horseradish peroxidase (HRP)-catalyzed oxidative phenolic coupling to 5, which resulted in the direct formation of 1 (10%) and 2 (18%) with recovery of 5 (72%) [32, 33]. With a large amount of synthesized 1 and 2 in hand, the neurotrophic properties of 1 and 2 were evaluated in detail in primary cultured fetal rat cortical neurons. A neurite outgrowth assay was performed using 18-day-old fetal rat cortical neurons in serum-free DMEM supplemented with B-27. Morphological evaluation, as shown in Fig. 3, indicated that mastigophorenes A (1) and B (2) not only promoted significant neurite outgrowth but also formed a network of neurons at 0.1 and 1 μM. A neuronal survival assay was carried out

Scheme 1 Biosynthetic route to dimeric isocuparenes 1, 2, 3 and 4 based on one-electron oxidative coupling from (-)-herbertenediol (5)

(a) (b) (c)

Fig. 3 Enhancement of neurite outgrowth by mastigophorenes A (1) and B (2) in primary cultured rat cortical neurons in serum-free DMEM medium supplemented with B-27. a 0.5% EtOH, b 1μM mastigophorene A, c 1μM mastigophorene B
using the same neuronal cultures in serum-free DMEM supplemented with N-2, and the neuronal viability was assessed by the WST-8 assay. As summarized in Fig. 4, compounds 1 and 2 maintained neuronal survival at 0.1 and 1.0 μM, but lost their survival effect at 10 μM. These results suggest that mastigophorenes A (1) and B (2) can protect neurons from being insulted by toxic substances such as oxygen free radicals [32].

In addition, it should be noted that diastereoselective syntheses of mastigophorenes A (1) and B (2) with an atrop- enantioselective construction of the biaryl axis have been achieved by Bringmann [34], Meyers [35], and Feringa [36].

**Magnolol, honokiol and sesquiterpene-neolignans from Magnolia bark**

The bark of the *Magnolia* tree, *Magnolia obovata* Thumb. and *M. officinalis* Rhed. have been used in traditional herbal medicines in China, Korea and Japan. *Magnolia* bark is an important ingredient in Hange-kobokuto and Sai-boku-to preparations for the treatment of gastrointestinal disorders, important ingredient in Hange-kobokuto and Sai-boku-to *Magnolia* Magnolia obovata Thumb. from bark and sesquiterpene-neolignans termed sesquiterpene-neolignan, eudesmaganolol (9), eudeshonokios A (11) and B (10), eudesobovatols A (13) and B (12), clovanemagnanolol (14), and caryolanemagno- lol (15) [42-44]. Among them, clovanemagnanolol (14) and caryolanemagnanolol (15) could not only accelerate neurite outgrowth but also activate choline acetyltransferase activity (ChAT) at the concentration of 0.01 μM [45].

Clovanemagnanolol (14) and caryolanemagnanolol (15) are most likely to be converted from caryophyllene β-oxide and caryophyllene α-oxide, respectively, according to Barton’s results [45, 46]. The proposed biosynthetic pathway as shown in Scheme 2 is initiated by the oxidation of (–)-caryophyllene, providing caryophyllene β-oxide or caryophyllene α-oxide. Acide activation of both epoxides leads to an intramolecular attack of the exocyclic alkenes, generating the diastereomeric tricyclic cation intermediates A or B. Cation A is trapped by magnolol (6), directly forming clovanemagnanolol (14), whereas cation B is trapped by 6, giving rise to caryolanemagnanolol (15). Siegel et al. synthesized 14 and 15 in two steps according to the postulated biosynthetic pathways [47, 49]. Synthesized 14 and 15 were confirmed to significantly promote neuronal growth at 0.01 μM in the primary cultured embryonic cortical neurons, similar to the neurotrophic effects of natural products [48, 49].

These results suggest that the lipophilic derivatives of simple biphenyl neolignans, magnolol (6) and honokiol (7) can enhance neurotrophic activity. Comparing the neurotrophic properties between 6 and 7, 7 was found to be more potent than 6 [50]. For further developments of more effective derivative, honokiol (7) was synthesized in 21% yield over 14 steps by utilizing a Pd-catalyzed Suzuki–Miyaura reaction [51]. In addition, the structure–activity relationship between neurite outgrowth-promoting activity and the O-methylated and/or the hydrogenated analogs 7a-7f, as summarized in Fig. 6, was examined in the primary cultured rat cortical neurons.

As a result, honokiol (7), 2-O-methylhonokiol (7a), and 3′-dihydroallylhonokiol (7d) had striking effects on the morphology of cortical neurons as shown in Fig. 7. Analogs 7b, 7c and 7f showed no enhancement of neurite extension. As shown in Fig. 8, quantitative analysis of the longest neurite length affected by each compound at the concentrations of 0.1 and 1 μM indicated that 7a and 7d have the potential to enhance neurite extension in cultured rat cortical neurons with a potency that is as high as that of 7; whereas, analogs 7b, 7c, and 7f showed diminished neurotrophic efficiency. Thus, these results suggest that

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**Fig. 4** Neuroprotective activity of mastigophorenes A (1) and B (2) in primary cultured rat cortical neurons in serum-free DMEM medium supplemented with N-2. After the neuronal cells (2 × 10^5 cells cm^-2) were cultured for 3 days in the presence of 0.5% EtOH (control) and compounds 1 and 2, neuronal viability was assessed by the WST-8 reduction assay. The data are expressed as means SE (n=4); *p < 0.05, **p < 0.015, ***p < 0.005 versus control.
the 4′-hydroxy group and the 5-allyl group are essential for honokiol-mediated neurite outgrowth-promoting activity (Figs. 7, 8). Based on the results of this SAR study, Gree and Chandrasekhar et al. synthesized 24 derivatives with various substituents at the 3′-allyl position of 7 and evaluated their neurotrophic effects in neurite outgrowth of differentiated Neuro2a cells after treatment with NGF but could not find new analogs that were more potent than...
Recently, we successfully synthesized honokiol (7) in 74% yield over five steps [53], thereby a large amount of honokiol is now available for assessing its in vitro/in vivo biological activities and preparing a variety of derivatives.

Next, after preparing several compounds and assessing their neurotrophic activity, we found two fluorescently labeled derivatives, 7-MCM (7-methoxycoumarin-3-carbonyl) (7g) and NBD (7-nitrobenzyl-2-oxa-1,3-diazolyl) (7h) that were suitable to be probe molecules to identify the intra/intercellular targets of 7. Rat cortical neurons were incubated with 5 μM 7h, 7g, and 7MCM for 1 h, and then their distributions in cortical neurons were monitored by fluorescence imaging under a microscope. As shown in Fig. 9, the apparent fluorescence was observed in intercellular regions, but the fluorescent molecule itself, 7MCM, showed no fluorescence in any of the neurons. Taking a closer look at the fluorescent images, it is interesting to note the fluorescent vesicles assembled at the neck and/or branch of the dendrites in each cell body. These results suggest that honokiol could be taken up into cells and interact with specific targets, which would be associated with neurite outgrowth [54].

Pharmacological studies of honokiol (6) and magnolol (7) have revealed that their effects on central nerves, such as depressant, muscle-relaxant, and anxiolytic effects, are mainly ascribed to their actions on GABA_A receptors [55]. In our search for neurotrophic compounds, 6 and 7 were identified as neurotrophic compounds that upregulate the activity of choline acetyltransferase in neuronal culture [45]. Furthermore, we found that 6 and 7 could promote neurite outgrowth and neuronal survival under serum-free conditions in cultured rat cortical neurons [50]. Additionally, it should be noted that magnolol could prevent the decrease in age-dependent neuronal loss in the hippocampus of senescence-accelerated mice (SAMP1) [56]. The intriguing effects of honokiol and magnolol prompted us to investigate the mechanisms underlying their neurotrophic actions using the cultured neurons. In general, neurotrophins such as NGF, BDNF, and NT-3 bind to the extracellular domain of the tyrosine kinase receptors TrkA, TrkB, and TrkC, respectively, and thereby activate the respective tyrosine kinase in the intracellular domain [57]. When target signal proteins bind to tyrosine kinases, they are phosphorylated to adopt active forms, and then transfer signals to their downstream. Among the NT-activated signaling molecules, Ca^{2+}, MAPK (ERK), and Akt, are indispensable for transferring intracellular signals to nuclei [58]. First, we examined the intracellular Ca^{2+} response in primary cultured rat cortical neurons and human neuroblastoma SH-SY5Y cells by fluo-3 fluorescence imaging analysis. Magnolol and honokiol increased cytoplasmic free Ca^{2+} with a characteristic lag phase. The cytoplasmic free Ca^{2+} increase was independent of extracellular Ca^{2+} but dependent on the activation of phospholipase C and inositol 1,4,5-triphosphate (IP3) receptors, indicating an increase in cytoplasmic free Ca^{2+} through a phospholipase C-mediated pathway. Thus, 6 and 7 cause the release of Ca^{2+} from intracellular stores, resulting in an increase in cytoplasmic Ca^{2+} [59]. Regarding the effects of 6 and 7 on extracellular signal-regulated kinase (ERK1/2) and Akt, honokiol-induced neurite outgrowth in the cultured rat cortical neurons was significantly reduced by PD98059, a mitogen-activated protein kinase inhibitor, but not by LY294002, a phosphoinositide 3-kinase inhibitor. Honokiol also enhanced the phosphorylation of ERK1/2 in a dose-dependent manner; whereas, the effect of 7 on Akt phosphorylation was characterized by transient enhancement of 10 min and lasting inhibition after 30 min. The phosphorylation of ERK1/2 enhanced by 7 was inhibited by KN93, a Ca^{2+}/calmodulin-dependent kinase II (CaMKII) inhibitor. Moreover, the products of the phosphoinositide-specific C (PLC)-derived inositol 1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG)
**Fig. 6** Structure of honokiol (7) and its analogs 7a–7f, and florescent derivatives 7g–7h

**Fig. 7** Morphology of cultured rat cortical neurons demonstrated with anti-MAP2 immunohistochemical staining. a Neurons in the presence of 0.5% ethanol as vehicle control; b neurons in the presence of 0.1μM 7; c neurons in the presence of 1μM 7a; d neurons in the presence of 0.1μM 7d
were measured after honokiol treatment. Taking these results with our previous findings, as depicted in Fig. 10, signal transduction from PLC, IP3, Ca2+, and CaMKII to ERK1/2 has been proposed for a mechanism involved in honokiol-induced neurite outgrowth [60].

Furthermore, magnolol and honokiol were shown to be able to prevent age-related learning and memory impairment and cholinergic deficits in senescence-accelerated mice (SAMP8) [61]. Magnolol and honokiol were orally administered to 2-month-old SAMP8 mice once a day for 14 days. The SAMP8 mice showed significant impairment of learning and memory at 4 and 6 months of age. This age-related learning and memory impairment was prevented by pretreatment with either 6 (10 mg/kg) or 7 (1 mg/kg). In addition, 6 and 7 prevented age-related cholinergic defects and enhanced phosphorylation of Akt, a member of the prosurvival pathway, in the forebrain at 2 months of age (Fig. 11).

Recently, it was reported that 6 and 7 showed antidepressant-like effects on unpredictable chronic mild stress (UCMS)-treated rats by enhancing BDNF expression and serotonergic activity in the hippocampus [62, 63]. Matsui et al. reported that 6 significantly improved depressive behavior in olfactory bulbectomized (OBX) mice in the tail suspension test, significantly enhanced hippocampal neurogenesis and increased phosphorylation of Akt and cyclic AMP-responsive element-binding protein (CREB) [64]. These data demonstrate that magnolol (6) has antidepressant-like effects on behaviors and actions by enhancing hippocampal neurogenesis and neurotrophin-related intracellular signaling in mice.

Magnolol (6) and honokiol (7) are well known to have potent antioxidant effects [65]. Oral administration of 6 to C57BL/6N mice after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium (MPTP) treatment, an in vivo model of Parkinson's model, almost completely prevented MPTP-induced lipid peroxidation in the stratum [66], suggesting that 6 has protective effects on the onset of cognitive impairments via an antioxidative mechanism. This is also consistent with the increasing lipid hydroperoxide level in the brain of SAMP8 at 2 months of age, which may be a cause of the age-related impairments and degeneration seen in the brain [67].

**Neurotrophic compounds from *Illicium* species**

The genus *Illicium*, belonging to the family Illiciaceae, consists of approximately 40 species around the world. This genus is mainly distributed in the eastern North America, Mexico, the West Indies and eastern Asia. The fruits of the
Illicium species are distinctive star-shaped follicles that emit a characteristic refreshing flavor. In particular, the fruits of *I. vernum* Hook, Chinese star anise, are the source of economically important product derived from this genus, which is widely used as a spice for flavoring food and beverages. Hence, essential oils have been the primary subject of chemical research on *Illicium* species, and the presence of volatile phenols has been reported as constituents of various parts of all *Illicium* species studied so far. The chemical constituents of the *Illicium* species are classified into three groups; sesquiterpenes, prenylated C₆-C₃ compounds, and triphenyleolignan (sesquineolignan). Some of these compounds are not only unique in their architectural structure but also exert intriguing bioactive effects on the neuronal system [68, 69].

We reported the isolation and structure of tricycloillicinone (16) [70] and (2R)-12-chloro-2,3-dihydroillicinone E (18) [71] from the woods of *I. tashiroi*. Compounds 16 and 18 were found to increase choline acetyltransferase (ChAT) activity by 143% and 228% at 30 μM in cultured P10 rat septal neurons, respectively. Lately, both compounds were shown to promote neurite outgrowth in NGF-mediated PC12 cells and primary cultured rat cortical neurons at concentrations as high as 50, 100 μM. On the other hand, compounds 19–21, without a chlorine atom, did not have neurotrophic activity [72]. Another bicyclic nonaromatic phenylpropanoid, bicycloillicinone asarone acetal (17), was isolated from the same plant source as 16 and was found to enhance ChAT activity at 30 μM, which catalyzes the synthesis of acetylcholine from its precursor [73]. Acidic hydrolysis of 17 led to its core aldehyde, bicycloillicinone 17a, and catechol portion 17b (Scheme 3).

The syntheses of 16 and the core structure 17a were achieved by Danishefsky’s group [74]. Cholinesterase inhibitors such as donepezil and tacrine, which are capable of increasing neurotransmitter acetylcholine levels by inhibiting acetylcholinesterase (AChE) activity, are now in use for the treatment of AD [75]. Thus, compounds 16–18, which can induce ChAT, an enzyme responsible for the biosynthesis of acetylcholine, should contribute to increased acetylcholine levels and support the survival of cholinergic neurons. As prenylated phenylpropanoids with neurotrophic activity, illicinin A (22) and compound 23 were isolated from *I. anisatum* [76]. Compounds 22 and 23 were found to significantly promote neurite outgrowth at concentrations ranging from 0.1 to 10 μM in primary cultured rat cortical neurons. Illicinin A (22) and its derivatives 22a–22c were synthesized for structure–activity relationship studies by applying Pd-catalyzed Stille reactions and then were assessed for the neurite length of rat cortical neurons at 1 μM. As a result, compound 22c showed reduced activity, whereas the others 22a and 22b showed comparative activity to illicinin A (22) or were more potent, thereby indicating that an allyl group in 22 is essential for exerting neurotrophic activity. In addition, the presence and position of the prenyl group in 22 were shown to play an important role in neurotrophic activity.

Typical neolignans, magnolol (6) and honokiol (7), were introduced in the early section of this review as having interesting neurotrophic properties. Macranthol (25) [77] and isodunnianol (24) [78], another neolignans bearing one phenyl group called sesquineolignan, showed neuroprotective activity at 5–10 μM [79] and neurite outgrowth-promoting...
activity at 0.1–10 μM in primary cultured rat cortical neurons [80] along with anti-AChE activity with an IC50 value of 13.0 μM [84]. In addition, macranthol (25) exerted an antidepressant-like activity in mice by increasing the expression of hippocampal BDNF [81], and the mechanism of its mediated antidepressant-like action was verified to be associated with BDNF-TrkB and downstream activation of the PI3K/Akt-Bcl-2/caspase-3 signal pathway [82]. Merrillianoid (26), a unique caged-shaped neolignan possessing a benzo-2,7-dioxa[3,2,1]octane moiety that was isolated as a racemic form from the leaves of Illicium merrillianum, influenced the NGF-induced neurite outgrowth of PC12 cells at concentrations from 1 to 10 μM, possibly by interacting with the TrkA receptor and downstream activation of ERK1/2 and MEK in the Ras/ERK signal cascade [83].

The fruits of Illicium anisatum (Japanese star anise, “shikimi”) are known to be very toxic. Ingestion of these fruits causes convulsive symptoms, frequently leading to death. In 1952, Lane succeeded in the isolation of the pure toxic principle named anisatin (27), and its complete structure was later established by Yamada and Hirata [85]. Kawano et al., who continued to investigate the toxic substance in Illicium anisatum, succeeded in systematic studies on the chemical components in Illicium plants. Later, Schmidt and our group joined the
chemical and biological studies of *Illicium* plants. A number of unique seco-prezizaane-type sesquiterpenes or so-called *Illicium* sesquiterpenes have been reported exclusively by the above three groups, and the occurrence of *Illicium* sesquiterpenes has been found to be limited to the genus *Illicium* [69]. Following the extensive chemical studies on *Illicium* sesquiterpenes, we turned our attention to neurotrophic properties but not neurotoxic activity for these sesquiterpenes. The isolation of sesquiterpenes from *Illicium* species, guided by the enhancement of ChAT activity, neurite outgrowth promotion and neuroprotective activity in primary cultured rat cortical neurons resulted in the discovery of a number of neurotrophic sesquiterpenes as shown in Fig. 12.

Isodunnianin (28) was the first neurotrophic *Illicium* sesquiterpene isolated from the wood of *Illicium tashiroi* collected in Ishigaki Island, Japan, and it was shown to moderately enhance neurite-sprouting during the development of neurons and increase ChAT activity at 10 μM in primary fetal rat cortical neurons [86]. The structure of 28 was elucidated on the basis of the published NMR data of dunnianin [87], but later was corrected to 28 according to the revised structure of dunnianin [88]. Two majucin-type sesquiterpenes, (2S)-hydroxy-3,4-dehydroneomajucin (29) and jiadifenin (31), isolated from *Illicium jiadifengpi*, significantly promote the neurite outgrowth of primary cultured rat cortical neurons at concentrations ranging from 0.1 to 10 μM [89]. Jiadifenin (31) could be transformed from (2S)-hydroxy-3,4-dehydroneomajucin (29) if the C-10 hydroxyl group is oxidized to a ketone. Thus, compound 30, which was derived from 29 by DMP, was exposed to epimerization conditions at C-1 with DBU, leading to the thermodynamically more stable product (1R)-30. Next, DMP or Jones oxidation of (1R)-30 [90] gave rise to jiadifenin (31) as an equilibrated mixture at the C-10 position in good yield, followed by the addition of MeOH to the reaction mixture (Scheme 4). This chemical transformation confirmed the absolute configuration of jiadifenin.

![Scheme 4 Conversion from 29 to 31](image)

**Fig. 12** Anisatin (27) and *Illicium* sesquiterpenes having neurotrophic properties
Another interesting majucin-subtype sesquiterpene, jiadifenolide (32), and jiadifenoxolanes A (33) and B (34), were isolated from the same plant [91]. Jiadifenolide (32) and jiadifenoxolane A (33) were found to significantly enhance the neurite outgrowth in primary cultured rat cortical neurons, in particular, jiadifenolide exhibited more potent activity at concentrations as low as 0.01 μM as shown in Fig. 13. These majucin-subtype sesquiterpenes were reported to promote neurite outgrowth of NGF-mediated PC12 cells but have no effect on PC12 cells in the absence of NGF [90]. Moreover, jiadifenolide (32) promoted neurite extension and significantly increased the total neurite area and length in neuronal cells derived from human induced pluripotent stem (iPS) cells at concentrations ranging from 1 to 10 μM [92].

MEB5 is a multipotent stem cell line that can differentiate into neurons, astrocytes, and oligodendrocytes and, thus, is regarded as a potential tool to investigate compounds effective for the differentiation of CNS multipotent neuronal stem cells [22, 93, 94]. Furthermore, we attempted to assess the induction of differentiation of MEB5 cells by jiadifenolide. As shown in Fig. 14A, jiadifenolide significantly induced neuronal differentiation of MEB5 cells at 10 μM rather than astrocytic differentiation, with leukemina inhibitory factor (LIF) specifically induced as shown in Fig. 14A-b. The number of neurons at all the tested concentrations was greater in cultures treated with jiadifenolide than in control cultures (Fig. 14B). These results demonstrate that jiadifenolide promotes neuronal differentiation in the same manner as NGF.

Jiadifenolide (32) can be obtained straightforwardly from neomajucin (40) by DMP oxidation presumably through the proposed mechanism in Scheme 5 [91]. Jiadifenolide (32) and the other majucin-subtype sesquiterpenes 29–31 and 33 have attracted great attention from organic chemists due to their complex caged structural architecture and remarkable neurotrophic properties. Taking the structural similarity of the majucin-subtype sesquiterpenes into consideration, most synthetic strategies are divergent and comprehensive [18, 95–100].

Studies on seco-prezizaane-type sesquiterpenes from the Illicium species have culminated in their classification into further subgroups on the basis of a lactone type as follows: anisatin-subtype, pseudanisatin-subtype, minwanensin-subtype, majucin-subtype, pseudomajucin-subtype, cyclopavifloralone-subtype, anislactone-subtype and allo-cedrane-subtype consisting of rare carbon skeletons. Merrilactone A (37), of the anislactone-subtype, from the pericarps of Illicium merrillianum was found to exhibit neurotrophic activity in primary cultured rat cortical neurons at a concentration as low as 0.1 μM [101]. The limited amount of 37 has prevented further biological studies. This encouraged us to attempt partial synthesis of merrilactone A (37) from anislactone B (42), which was available in a large quantity from the same plant [102]. First, a solution of 42 in trifluoroacetic acid (TFA) was refluxed to bring about the lactone transformation to the C-4 hydroxyl group with dehydration of the C-1 hydroxyl group, giving rise to 43 in good yield. Then, epoxidation of 43 with m-chloroperoxybenzoic acid (m-CPBA) proceeded in a highly stereoselective fashion to give 44, which was treated with p-toluenesulfonic acid (p-TsOH) to produce merrilactone A (37) in 78% yield (Scheme 6). Following our reports, a number of excellent total syntheses of merrilactone A were published, and one should take a look at references [103, 104] for the details of each synthesis.

Tashironin (35) and 11-O-debenzyoltashironin (36) were isolated from I. tashiroi [105] and I. merrillianum [106]. Tashironin and its congeners [107] have a tricyclic skeleton corresponding to the key intermediate, allo-cedrane in the biosynthesis of seco-prezizaane-type sesquiterpenes. Among allo-cedrane-type sesquiterpenes 11-O-debenzyoltashironin (36) exhibits solely neurotrophic features in primary cultured rat cortical neurons at 0.1–10 μM and the presence of a free acetal group at the C-11 position is essential for having neurotrophic activity [106]. In 2017, illisimonin A...
(38), which could be classified as a rare rearranged allo-cedrane, was isolated from the fruits of I. simonsii and was reported to show neuroprotective effects against oxygen–glucose deprivation-induced cell injury in SH-SY5Y cells with an EC50 value of 27.72 μM [108]. Recently, the absolute configuration of 38 was revised by its enantioselective synthesis [109]. The first example of a seco-prezizaane-type norsesquiterpene, (2R)-hydroxy-norneomajucin (39) was isolated from I. jiadifengpi and was added to a list of Illicium sesquiterpenes with neurotrophic activity [110]. The biosynthesis of 39 could be initiated by oxidation of the hydroxyl group at the C-10 position of neomajucin 40 to give a highly strained α-keto-δ-lactone, which would cause decarboxylation to lose one carbon, thereby leading to the less strained five-membered lactone 39. As shown in Scheme 7, when 2-O-acetyl-(2S)-hydroxyneomajucin (45) was oxidized with Jones reagent, decarboxylation occurred spontaneously resulting in direct formation of the γ-lactone 46, from which 39 was readily accessible after several reactions [110].

Fig. 14 Effects of jiadifenolide on the neuronal differentiation of MEB5 cell line. A Morphological changes of MEB5 cells; blue, red, and green express nucleus, neuron, and astrocyte, respectively. a Control (0.5% EtOH), b leukemia inhibitory factor (LIF, 10 ng/mL), c nerve growth factor (NGF, 50 ng/mL), d jiadifenolide (10 μM). MEB5 cells were first cultured in the presence EGF at the density of 1.8×10⁴ cells/cm², and then medium was changed to EGF-free medium. After 4 days in the absence of EGF, the cells were double labeled with antibodies to class III β-tubulin (Tuj-1, red) and glial fibrillary acidic protein (GFAP, green). B The percentage of the neuronal (red) and astrocytic (green) cells; the cells were maintained for 1 day in the proliferation medium, and then transferred to the differentiation medium containing vehicle (control) or jiadifenolide and cultured another 7 days. After immunostaining for Tuj-1 and GFAP, neuron, astrocyte, and total cell numbers were counted, and the ratio to total cells was calculated. Data were expressed as means±SE (n = 5).
Neurotrophic sesquiterpenes 28–33 and 36–39 (Fig. 12) have significant structural homology with anisatin (27) and picrotoxinin (49) which cause convulsions but do not have neurotrophic properties. Picrotoxinin has been validated to elicit convulsion by binding to the GABA<sub>A</sub> receptor and chloride anion blockade of the Cys-loop family of glutamate-gated chloride channels. Anisatin (27) and veranisatin (48) were also identified as picrotoxin-like, noncompetitive GABA-antagonists [111, 112]. Many of these convulsant terpenes contain γ- or δ-lactone motifs. Even the simple β-alkyl lactone β-EMGB exhibits convulsive activity by binding to the same site as picrotoxin. Based on structural homology with picrotoxinin (49) and anisatin (27) (Fig. 15), it has been postulated that neurotrophic <i>Illicium</i> sesquiterpenes would enhance neurite outgrowth by modulation of the Cys-loop family of GABA<sub>A</sub> receptors, and a mechanistic link may exist between convulsant terpenes and neurotrophic <i>Illicium</i> sesquiterpenes [113].

In 2017, Shenvi et al. succeeded in the synthesis of (–)-11-<i>O</i>-debenzoyltashironin (36) and compared the effects of neurotrophic compounds 32 and 36, and convulsive compounds 27 and 49 on primary cultures of rat cortical neurons in terms of the hyperexcitation expected from the antagonism of inhibitory channels. Although all four compounds similarly caused hyperexcitation of cortical neurons and inhibited GABA-evoked currents, the GABA antagonistic effects of 32 and 36 were tenfold weaker than those of 27 and 49. Neurite outgrowth enhancement by 32 and 36 might be accounted for by a mechanism of chronic depolarization...
but more data are needed to validate this hypothesis in which convulsive and neurotrophic sesquiterpenes share a common target [114].

In 2018, Witkin et al. reported that jiadifenolide (32) and 11-O-debenzoyltashironin (36) did not cause convulsions in mice nor did they enhance or diminish convulsions induced by pentylenetetrazole (PTZ) although picrotoxinin (49) and tetramethylenedisulfotetramine (TETS) both induced convulsions. Furthermore, jiadifenolide and 11-O-debenzoyltashironin were verified to be less potent and less efficacious antagonists of GABA receptors than either picrotoxinin or TETS [115].

The underlying molecular mechanisms by which jiadifenolide (32) and its analogous *Illicium* sesquiterpenes exert their neurotrophic effects remain unknown despite the abovementioned hypothesis that they share a common target with the convulsant compounds including anisatin and picrotoxinin. We previously reported that jiadifenolide significantly promotes neurite outgrowth and cell growth as well as prevents death of neuronal precursor cells derived from human pluripotent stem cells (hiPSCs) [92]. By in silicon molecular network analysis of our comprehensive RNA sequencing results on 32-treated human neuronal cells using KeyMolnet software, 32 was found to activate cellular communication network factor (CCN) signaling pathways by upregulating the mRNA expression of CCN2. In addition, the CCN2 protein was confirmed to exhibit neurotrophic activity because the acetonide loses activity at the same concentration. This result suggests that the molecular mechanism by which 32 exerts its neurotrophic effect is linked with CCN signaling [116]. It should be noted that this is the first discovery to connect neurotrophic effects with CCN signaling.

Miscellaneous natural products with neurotrophic effects

Vibsane-type diterpenoids rarely occur as natural products and have been limited to the isolation from *Viburnum* species thus far. The carbon skeletons of these diterpenes are further classified into three subtypes: those with an eleven-membered ring, those with a seven-membered ring, and the rearranged types (neovibsans) [117, 118]. Among the three subtypes of vibsane-type diterpenoids, neovibsans A (50) and B (51) and their congeners 52-55 with modifications on the prenyl group, as shown in Fig. 16, significantly enhanced the neurite outgrowth of NGF-mediated PC12 cells at concentrations ranging from 5 to 40 μM [119, 120]. A good synthetic achievement of neovibsain B was accomplished by Imagawa et al. [121], who then extended their synthetic efforts to structure–activity relationship studies, resulting in elucidation of the minimum structure required for displaying neurite outgrowth activity in NGF-mediated PC12 cells (compound 56) [122].

The Brazilian medicinal plant *Psychopetalum olacoides* is known as a nerve tonic and is used for the treatment of chronic degenerative conditions of the central nervous system [123]. From the MeOH extract of this plant, a number of clerodane diterpenes 57-62 and 64-65 were isolated, among which ptychonal hemiacetal (57), ptychonal (58), 6α,7α-dihydroxyannone (61), and 7α,20-dihydroxyannone (62) exhibited NGF-potentiating activity in PC12 cells in the presence of NGF (20 ng/mL) at concentrations ranging from 0.1 to 40 μM [124, 125]. On the other hand, compounds 59, 60, and 63-65 had no effect on PC12 cells in the presence or absence of NGF. Compound 61 is the most potent NGF potentiator of these active compounds. The adjacent hydroxyl groups in 61 presumably contribute to its increased activity because the acetonide 63 loses activity at the same concentrations. In addition, the furan ring plays an important role in the appearance of NGF-potentiating activity since 64 and 65, with modifications to the furan ring, showed no activity at all.

Four spirocyclic nortriterpenes, leonurusoleanolides A (67), B (68), C (69), and D (70) were isolated from the fruits of *Leonurus heterophyllus*. Compounds 67 and 68, and compounds 69 and 70 exist as equilibrium mixtures of E and Z isomers. Mixtures of 67 and 68, and 69 and 70, significantly enhanced the neurite outgrowth of NGF-treated PC12 cells at concentrations ranging from 1 to 30 μM and also the parent compound, phlomistetraol B (66), possessed...
NGF-potentiating activity. However, 67–70 seemed to be more potent NGF potentiators than 66, which had toxicity at concentrations higher than 30 μM [126].

The polycyclic prenylated acylphloroglucinol (PPAP) family comprises a highly oxygenated and densely substituted bicyclo[3.3.1]nonane skeleton bearing prenyl or geranyl side chains that are rich in the family Clusiaceae (Guttiferae). Hypericum perforatum, commonly known as St. John’s wort, has attracted attention due to its antidepressant activity [127]. In the course of chemical studies on PPAPs of Garcinia subelliptica (Guttiferae) [128, 129], we found that garsubellin A (71) could increase the ChAT activity, a key enzyme for physiologic acetylcholine synthesis in the nervous system, by up to 154% at 10 μM in comparison with the control in primary cultured P10 rat septal neurons [130]. Owing to its important biological activity and architectural structure, garsubellin A (71) stimulated substantial synthetic effort, and the excellent synthetic achievements have been reported [127, 131–133]. More efficient synthetic methods of 71, however, still have to be developed to supply sufficient quantities to explore its full biological characterization (Figs. 17, 18).

A unique group of the neolignans, such as americanol A (72), isoamericanol A (73), americanin A (72a), isoamericanin A (73a), americanoic acid A methyl ester (76) and isoamericanic acid A methyl ester (77), which are characterized by having a 1,4-benzodioxane ring and have diverse and significant biological activities, occur exclusively in the seeds of Phytolacca americana L. (Phytolaccaceae) [134, 135]. In particular, americanol A and isoamericanol A were found to enhance not only ChAT activity but also neurite outgrowth at 10 μM in primary cultured fetal rat hemispheres [136]. Neolignans 72 and 73 would be formed by oxidative dimerization of the corresponding monomeric unit, coniferyl alcohol. In fact, caffeic acid was subjected to horseradish peroxidase (HRP)-catalyzed oxidative conditions to give rise to dicarboxylic acids 74 and 75, which were converted to 72 and 73, respectively, followed by sequential reductions [137]. We reexamined the neurotrophic activities of 72–77 in primary cultured rat cortical neurons. In addition to 72 and 73, americanoic acid A methyl ester (76) was found to exhibit potent neurite outgrowth activity at 0.1 μM; whereas, the activities of compounds 74, 75 and 77 were comparable with control cultures. Although compounds 74 and 75 had no effects on neurite outgrowth, they induced significant neuritogenesis such as increasing the number of neurite branches in the concentration range from 0.1 to 10 μM in a similar manner to basic fibroblast growth factor (bFGF) as shown in Fig. 19 [138].

Novel polyoxygenated benzofuran derivatives, namely, ribisin A (78), ribisin B (79), ribisin C (80), and ribisin D (81), were isolated from the fruiting bodies of Phellinus ribis, which is used in the East Asian countries as a traditional medicine for enhancing immunity and gastrointestinal cancer. Beznofurans 78–81 showed marked neurite outgrowth-promoting activity in NGF-mediated
PC12 cells at concentrations ranging from 1 to 30 μM; whereas, none of these four compounds had morphological effects on PC12 cells in the absence of NGF. Their absolute configurations on the chiral positions were elucidated by applying the CD exciton chirality method to the readily derived p-bromobenzoate [139]. Chemoenzymatic total syntheses of 78–81 were achieved by two groups [140, 141], and therefore, the absolute stereochemistry of ribisin C (80) was revised as its ent-form.

A prenylated and geranylated biphenyl derivative, clusiparalicoline A (82), was isolated from the roots of Clusia paralicola and showed modest cytotoxicity in the KB cell line [142]. We achieved the first synthesis of 82 by applying sequential palladium-catalyzed Stille and Suzuki reactions, and synthetic 82 was assessed by our neuronal cell assay. As a result, 82 was found to exhibit potent neurite outgrowth-promoting activity at concentrations from 0.1 to 1.0 μM in primary cultured rat cortical neurons, but the application of a higher dose than 10 μM induced the death in all neurons [143]. Although 82 shows cytotoxicity at high concentrations, the biaryl moiety of 82 may have some positive effects on the development and survival of neurons in the same manner as honokiol and magnolol, which have a specific affinity for neuronal cells [45].

Piperine (1-piperoylpiperidine), a pungent nitrogenous substance, is a main alkaloid in various piper species. These piper plants are commonly used as household spices as well as important traditional medicine in many Asian countries. With regard to piperine on cognitive function, recent pharmacological studies have shown that piperine possesses cognitive-enhancing activity [144] and improves both memory impairment and neurodegeneration in rats with cognitive defects induced by the ethylcholine aziridinium ion (AF64A) [145]. These reports prompted us to evaluate the neurotrophic properties of the fruits of the Javanese long pepper, Piper retrofractum, which are called Cabe Jawa and are used as one of the ingredients in the Indonesian natural medicine jamu. The methanolic extract of P. retrofractum

![Fig. 17 Other terpenes that enhance neurite outgrowth of NGF-mediated PC12 cells](image-url)
fruits exhibited neurite outgrowth-promoting activity in NGF-mediated PC12 cells. Bioassay-guided fractionation resulted in the isolation of the active component, piperodione (83), which is the first example of piperine oxidized at the C-2 and C-5 positions. Compound 83 showed potent NGF-potentiating activity in PC12 cells at concentrations ranging from 0.1 to 10 μM, but piperine had no effect on PC12 cells at the same dose as 83 [146]. Our study has demonstrated that piperine is not the active constituent responsible for the observed neurotrophic activity of *P. retrofractum* fruits. Recently, the total synthesis of piperodione (83) was reported from two groups, and 83 was verified to have NGF-potentiating activity but not cytotoxicity at all [147, 148]. Now, with large quantities of 83 in hand, further pharmacological studies of 83 are in progress.
Finally, it should be noted that a comprehensive review on (–)-talaumidin, a neurotrophic 2,5-biaryl-3,4-dimethylhydrofuran lignan, has been published quite recently [149]. Given the increasing interest in neurotrophin-mimic compounds, we suggest that readers refer to a recent review covering another topic of neurotrophic natural products.

Conclusions

In this review, we have introduced neurotrophin-mimicking natural products discovered by our group and have focused on the chemical and biological features of neurotrophic compounds but have not emphasized their synthetic achievements, because there are already some excellent reviews on this subject [18, 104, 150] that summarize the overview of their organic syntheses. Endogenous neurotrophins (NGF, BDNF etc.) are a class of polypeptidyl agents that promote neurogenesis, neuron survival, process outgrowth, and synaptic connectivity in the development of the neuronal system and neuronal plasticity in adult neurons. As mentioned in the introduction, the application of neurotrophins to treat neurodegenerative diseases suffers serious drawbacks in practice due to their unfavorable properties. Consequently, a small molecule non-peptidyl agent that mimics the functions of neurotrophic factors would be an attractive alternative for the treatment and/or protection of neurodegenerative diseases. This idea prompted us to search for plant-derived small molecules that have neurotrophic effects on three neuronal cells: PC12 cells, primary cultured rat cortical neurons, and MEB5 neuronal stem cells. Beginning in 1988, structurally unique isocuparane dimers, mastigophorenes A (1) and (2) were discovered as neurotrophic compounds by our group. Since then, a number of compounds with neurotrophic activity have been discovered from various plants. However, many active compounds have not gained access to detailed biological investigations, in particular, to in vivo animal models and their underlying neurotrophic mechanisms remain obscure because insufficient quantities of material are an often-encountered problem associated with natural products. To overcome this issue, many groups have been engaged in the synthesis of neurotrophic natural products. Jiadifenolide (32) is a good example. Chemical synthesis has supplied a sufficient quantity of 32 to undertake detailed biological studies, which leads to the possibility of clinical utility for jiadifenolide.

Through this review, we hope that organic chemists and medicinal chemists will share their interests and efforts with neurotrophin-mimicking small molecules, which are expected to not only play a critical role in chemical control over each step in the neural circuit life model (neurogenesis, differentiation, neurite outgrowth, death), as proposed in Fig. 1, but also make a positive contribution to protecting cognitive impairment in a superaged society.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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References

1. Data from “Welfare White Paper 2018 Edition”. www.mhlw.go.jp/wpbakususyo/kouei/16/backdata/01-01-01-02.html
2. Thompson LM (2008) Neurodegeneration: a question of balance. Nature 452:707–708
3. Data from “Dementia Policy Promotion Comprehensive (New Orange Plane) 2018. www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000076236.html
4. Querfurth HW, Lafera FM (2010) Alzheimer’s disease. N Engl J Med 362:329–344
5. Mattson MP (2004) Pathways towards and away from Alzheimer’s disease. Nature 430:631–639
6. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science 297:353–356
7. Reardon S (2015) Alzheimer’s drugs show progress. Nat Digest 523:509–510
8. Lang AE (2010) Clinical trials of disease-modifying therapies for neurodegenerative diseases: the challenge and the future. Nat Med 16:1223–1226
9. Xu X, Warrington AE, Bieber AJ, Rodriguez M (2012) Enhancing central nervous system repair—the challenges. CNS Drugs 25:555–573
10. Levitan IB, Kaczmarek LK (2002) The neuron: cell and molecular biology. Oxford University Press, Oxford, pp 395–433
11. Gibon J, Barker PA (2017) Neurotrophins and proneurotrophins: focus on synaptic activity and plasticity in the brain. Neuroscientist 23:587–604
12. Huang E (2003) TRK receptors: roles in neuronal signal transduction. Annu Rev Biochem 72:609–642
13. Dechant G, Barde Y-A (2002) The neurotrophin receptor p75NTR: novel functions and implications for disease of the nervous system. Nat Neurosci 5:1131–1136
14. Hefti F (1998) Nerve growth factor treatment for Alzheimer’s disease: the experience of the first attempt at intracerebral neurotrophic factor therapy. Handb Exp Pharmacol 134:175–187
15. Tuszynski MH, Thal L, Pay M, Salmon DP, Sang UH, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J (2005) A phase I clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med 11:551–555
16. Nagahara AH, Tuszynski MH (2011) Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat Rev Drug Discov 10:209–219
17. Swain C, Harper S, Pollack S, Smith R, Hefti F (1998) Neurotrophic natural products: chemistry and biology. Angew Chem Int Ed 37:956–987
18. Xu J, Lacoske MH, Theodorakis EA (2014) Neurotrophic sesquiterpene-neolignans from Magnolia family. Pharmacol Ther 130:157–176
19. Abe K, Takayanagi M, Saito H (1990) Effects of recombinant human basic fibroblast growth factor and its modified protein CS23 on survival of primary cultured neurons from various regions of fetal rat brain. Jpn J Pharmacol 53:221–227
20. Nakagaito Y, Sato M, Kuno H, Iwama T, Takeuchi M, Hakura A, Yoshida T (1998) Establishment of an epidermal growth factor-dependent, multipotent neural precursor cell line. In Vitro Cell Dev Biol Animal 34:585–592
21. Abe K, Takayanagi M, Saito H (1990) Effects of recombinant human basic fibroblast growth factor and its modified protein CS23 on survival of primary cultured neurons from various regions of fetal rat brain. Jpn J Pharmacol 53:221–227
22. Nakagaito Y, Sato M, Kuno H, Iwama T, Takeuchi M, Hakura A, Yoshida T (1998) Establishment of an epidermal growth factor-dependent, multipotent neural precursor cell line. In Vitro Cell Dev Biol Animal 34:585–592
23. Fukuyama Y, Kiriyama Y, Kodama M (1996) Novel neurotrophic isocuparane sesquiterpenoids from the medicinal plants of Paraguay and Thailand. Yakugaku Zasshi 124:417–424
24. Fukuyama Y, Kiriyama Y, Kodama M (1996) Novel neurotrophic isocuparane sesquiterpenoids from the medicinal plants of Paraguay and Thailand. Yakugaku Zasshi 124:417–424
25. Kudo M (2015) Search for neurotrophin-mimic natural products for prevention and treatment of neurodegenerative disease. Yakugaku Zasshi 135:1147–1152
26. Greene LA, Tischler AS (1976) Establishment of a noradrenergic clonal line of rat adrenal pheochromocytoma cells which respond to nerve growth factor. PNAS 73:2424–2428
27. Swain C, Harper S, Pollack S, Smith R, Hefti F (1998) Neurotrophic factor mimetics. Handb Exp Pharmacol 134:281–309
28. Xu J, Lacoske MH, Theodorakis EA (2014) Neurotrophic natural products: chemistry and biology. Angew Chem Int Ed 53:956–987
29. Lee YJ, Lee YM, Lee CK, Jung JK, Han SB, Hong JT (2011) Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther 130:157–176
30. Buter J, Heijnen D, Vila C, Hornillos V, Otten E, Giannerini M, Minnaard AJ, Feringa BL (2016) Palladium-catalyzed, tert-butylthiullium-mediated dimerization of aryl halides and its application in the atropselective total synthesis of mastigophorene A. Angew Chem Int Ed 55:3620–3624
31. Bringmann G, Pabst T, Henschel P, Kraus J, Peters K, Peters E-M, Rycroft DS, Connolly JD (2000) Nondynamic and dynamic kinetic resolution of lactones with stereogenic centers and axes: stereoselective total synthesis of herbertenolid and mastigophorenes A and B. J Am Chem Soc 122:9127–9133
32. Fukuyama Y, Kiriyama Y, Kodama M (1996) Total synthesis of herbertenolid, an isocuparane sesquiterpene isolated from liverworts. Tetrahedron Lett 37:1261–1264
33. Fukuyama Y, Kiriyama Y, Kodama M (1996) Total synthesis of herbertenolid, an isocuparane sesquiterpene isolated from liverworts. Tetrahedron Lett 37:1261–1264
34. Fukuyama Y, Kiriyama Y, Kodama M (1996) Total synthesis of herbertenolid, an isocuparane sesquiterpene isolated from liverworts. Tetrahedron Lett 37:1261–1264
35. Degnan AP, Meyers AL (1999) Total syntheses of (−)-herbertenolid, (−)-mastigophorene A, and (−)-mastigophorene B. Combined utility of chiral bicyclic lactams and chiral aryl oxazolines. J Am Chem Soc 121:2762–2769
36. Buter J, Heijnen D, Vila C, Hornillos V, Otten E, Giannerini M, Minnaard AJ, Feringa BL (2016) Palladium-catalyzed, tert-butylthiullium-mediated dimerization of aryl halides and its application in the atropselective total synthesis of mastigophorene A. Angew Chem Int Ed 55:3620–3624
37. Lee YJ, Lee YM, Lee CK, Jung JK, Han SB, Hong JT (2011) Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther 130:157–176
38. Guerra-Araiza C, Alvarez-Mejia AL, Sanchez-Torres S, Farfan-Garcia E, Mondragon-Lozano R, Pinto-Almazan R, Salgado-Ceballos H (2013) Effect of natural exogenous antioxidants on aging and on neurodegenerative diseases. Free Radic Res 47:451–462
39. Yang C, Zhi X, Xu H (2016) Advances on semisynthesis. Total synthesis, and structure-activity relationships of honokiol and magnolol derivatives. Mini Rev Med Chem 16:404–426
40. Sarrica A, Kirika N, Romeo M, Salamina M, Diomedes L (2018) Safety and toxicology of magnolol and honokiol. Planta Med 84:1151–1164
41. Fukuyama Y, Nakade K, Minoshima Y, Yokoyama R, Zhai H, Matsumoto Y (2002) Neurotrophic activity of honokiol on the cultures of fetal rat cortical neurons. Bioorg Med Chem Lett 12:1163–1166
42. Fukuyama Y, Otoshi Y, Kodama M (1989) Novel neurotrophic sesquiterpene-neolignans from Magnolia obovata. Tetrahedron Lett 30:5907–5910
43. Fukuyama Y, Otoshi Y, Kodama M (1990) Structure of clovamagnolol, a novel neurotrophic sesquiterpene-neolignan from Magnolia obovata. Tetrahedron Lett 31:4477–4480
44. Fukuyama Y, Otoshi Y, Nakamura K, Kodama M, Sugawara M, Nagasawa M (1990) Structure of eudesmagnolol and eudesho-nolol and clovanemagnolol. Org Lett 12:1304–1307
45. Aebi A, Barton DHR, Lindsey AS (1953) Sesquiterpenoids. Part III. The stereochemistry of caryophyllene. J Chem Soc (C) 3124–3129
46. Cheng X, Harzdorf NL, Shaw T, Siegel D (2010) Biomimetic syntheses of the neurotrophic natural products caryolanemagnolol and clovamagnolol. Org Lett 12:1304–1307
48. Khaing Z, Kang D, Camelo AM, Schmidt CE, Siegel D (2011) Hippocampal and cortical neuronal growth mediated by the small molecule natural product clavemagnolol. Bioorg Med Chem Lett 21:4808–4812
49. Cheng X, Harzdorf N, Khaing Z, Kang D, Camelo AM, Shaw T, Schmidt CE, Siegel D (2012) Neuronal growth promoting sesquiterpene-neolignans; syntheses and biological studies. Org Biomol Chem 10:383–393
50. Fukuyama Y, Nakada K, Minoshima Y, Yokoyama R, Zhai H, Mitsumoto Y (2002) Neurotrophic activity of honokiol on the cultures of fetal rat cortical neurons. Bioorg Med Chem Lett 12:1163–1166
51. Êsumi T, Makado G, Zhai H, Shimizu Y, Mitsumoto Y, Fukuyama Y (2004) Efficient synthesis and structure–activity relationship of honokiol, a neurotropic biphenyl–type neolignan. Bioorg Med Chem Lett 14:2621–2625
52. Kumar VP, Reddy RG, Vo DD, Chakravarty S, Chandrasekar S, Gee R (2012) Synthesis and neurite growth evaluation of new analogues of honokiol, a neolignan with potent neurotrophic activity. Bioorg Med Chem Lett 22:1439–1444
53. Harada K, Arioik C, Miyakata A, Kubo M, Fukuyama Y (2014) Efficient synthesis of neurotrophic honokiol using Suzuuki-Miyaura reactions. Tetrahedron Lett 55:6001–6003
54. Zhai H, Nakade K, Mitsumoto Y, Fukuyama Y (2003) Neurotrophic activity and mechanism of honokiol and magnolol. Yakugaku Zasshi 123(S3):98–101
55. Ai J, Wang X, Nielsen M (2001) Honokiol and Magnolol selectively interact with GABA<sub>A</sub> receptor subtypes in vitro. Pharmacology 63:34–41
56. Matsui N, Nakashima H, Ushio Y, Tada T, Shirono A, Fukuyama Y, Nakade K, Zhai H, Yasui Y, Fukuishi N, Akagi R, Alagi M (2005) Neurotrophic effect of magnolol in the hippocampal CA1 region of senescence-accelerated mice (SAMP1). Biol Pharm Bull 28:1762–1765
57. Levitan IB, Kaczmatek LK (2002) The neuron, cell and molecular biology. Oxford University Press, Oxford, pp 408–427
58. Pollack SJ, Harper SJ (2002) Small molecule Trk receptor agonists and other neurotrophic factor mimetics. Curr Drug Targets CNS Neural Disord 1:59–80
59. Zhai H, Nakade K, Mitsumoto Y, Fukuyama Y (2003) Honokiol and magnolol induce Ca<sup>2+</sup> mobilization in rat cortical neurons and human neuroblastoma SH-SY5Y cells. Eur J Pharmacol 474:199–204
60. Zhai H, Nakade K, Oda M, Mitsumoto Y, Akagi M, Sakurai J, Fukuyama Y (2005) Honokiol-induced neurite outgrowth promotion depends on activation of extracellular signal-regulated kinases (ERK1/2). Eur J Pharmacol 516:112–117
61. Matsui N, Takahashi K, Takeichi M, Kurosita T, Noguchi K, Yamazaki K, Tagashira H, Tsutsui K, Okada H, Kid Y, Yasui Y, Fukuishi N, Fukuyama Y, Akagi M (2009) Magnolol and honokiol prevent learning and memory impairment and cholinergic deficit in SAMP8 mice. Brain Res 1305:108–117
62. Li LF, Lu J, Li XM, Xu CL, Deng JM, Qu R, Ma SP (2012) Antidepressant-like effect of magnoiol on BDNF up-regulation and serotonergic system activity in unpredictable chronic mild stress treated rats. Phyrother Res 26:1189–1194
63. Wang C, Gan D, Wu J, Liao M, Liao X, Ai W (2018) Honokiol exerts antidepressant effects in rats exposed to chronic unpredictable mild stress by regulating brain derived neurotrophic factor level and hypothalamus-pituitary-adrenal axis activity. Neurochem Res 43:1515–1528
64. Matsui N, Akai H, Hiroshima N, Kid Y, Tanabe S, Koseki M, Fukuyama Y, Akagi M (2016) Magnolol enhances hippocampal neurogenesis and exerts antidepressant-like effects in olfactory bulbectomized mice. Phyrother Res 30:1856–1861
65. Haraguchi H, Ishikawa H, Shirataki N, Fukuda A (1997) Antioxidative activity of neolignans from Magnolia obovata. J Pharm Pharmacol 49:209–212
66. Muroyama A, Fujita A, Ly C, Kobayashi S, Fukuyama Y, Mitsumoto Y (2012) Magnolol protects against MPTP/MPP<sup>+</sup>-induced toxicity via inhibition of oxidative stress in <i>in vitro</i> and in vivo models of Parkinson’s disease. Parkinson’s Dis 2012:985157. https://doi.org/10.1155/2012/985157
67. Yasui F, Ishihashi M, Matsu S, Kojo S, Oomura Y, Sasaki K (2003) Brain lipid hydroperoxide level increases in senescence-accelerated mice at an early age. Neurosci Lett 350:66–68
68. Fukuyama Y, Huang J-M (2004) Chemical constituents of the genus Illicium. In: Jordal MM (ed) Illicium, Pimpinella and Foeniculum. CRC Press, Boca Raton, pp 31–68
69. Fukuyama Y, Huang J-M (2005) Chemistry and neurotrophic activity of seco-prezizaane- and anislatone-type sesquiterpenes from <i>Illicium</i> species. In: Atta-ur-Rahman (ed) Studies in natural products chemistry. Bioactive natural products (part L), vol 32. Elsevier, Amsterdam, pp 395–428
70. Fukuyama Y, Shida N, Kodama M, Chaki H, Yagami T (1995) Tricycloillicinone, a novel prenylated C<sub>5</sub>C<sub>2</sub>C<sub>1</sub> compound increasing choline acetyltransferase (ChAT) activity, isolated from <i>Illicium tashiroi</i>. Chem Pharm Bull 43:2270–2272
71. Fukuyama Y, Okamoto K, Kubo M, Shida N, Kodama M (1994) New chlorine-containing prenylated C<sub>5</sub>C<sub>2</sub>C<sub>1</sub> compounds increasing choline acetyltransferase (ChAT) activity in culture of postnatal rat septal neurons from <i>Illicium tashiroi</i>. Chem Pharm Bull 42:2199–2201
72. Fukuyama Y, Shida N, Hata Y, Anzaki S, Kodama M (1994) Prenylated C<sub>5</sub>C<sub>2</sub>C<sub>1</sub> compounds related to illicicine E from <i>Illicium tashiroi</i>. Phytochem 37:1653–1657
73. Fukuyama Y, Hata Y, Kodama M (1997) Bicycloillicinone asarone acetal: a novel prenylated C<sub>5</sub>C<sub>2</sub>C<sub>1</sub> compound increasing choline acetyltransferase (ChAT) activity from <i>Illicium tashiroi</i>. Planta Med 63:275–277
74. Pettus TRR, Inoue M, Chen X-T, Danishefsky SJ (2000) A fully synthetic route to the neurotrophic illicinones: syntheses of tricycloillicinone and bicycloillicinone aldehyde. J Am Chem Soc 122:6160–6168
75. Giacobini E (1998) Cholinesterase inhibitors for Alzheimer’s disease therapy: from tacrine to further applications. Neurochem Int 32:413–419
76. Takaoka S, Takaoka Y, Minoshima Y, Huang J-M, Kubo M, Harada K, Hioki H, Fukuyama Y (2009) Isolation, synthesis, and neurite outgrowth-promoting activity of illicinin A from the flowers of <i>Illicium anisatum</i>. Tetrahedron 65:8354–8361
77. Kouno I, Hashimoto A, Kawano N, Yang C-S (1989) New sesqui-neolignans from the pericarps of <i>Illicium macranthum</i>. Chem Pharm Bull 37:1291–1292
78. Kouno I, Morisaki T, Hara Y, Yang C-S (1991) Two new sesquiquinolignans from the bark of <i>Illicium dunnianum</i>. Chem Pharm Bull 39:2606–2608
79. Moriyama M, Huang J-M, Yang C-S, Hioki H, Kubo M, Harada K, Fukuyama Y (2007) Structure and neurotrophic activity of novel sesqui-neolignans from the pericarps of <i>Illicium fargessii</i>. Tetrahedron 63:4243–4249
80. Moriyama M, Huang J-M, Yang C-S, Kubo M, Harada K, Hioki H, Fukuyama Y (2008) Two new sesquiterpenoids and two new prenylated phenylpropanoids from <i>Illicium fargessii</i>, and neuroprotective activity of macranthol. Chem Pharm Bull 56:1201–1204
81. Li J, Geng D, Xu J, Weng LJ, Liu Q, Yi LT (2013) Antidepressant-like effect of macranthol isolated from <i>Illicium dunnianum</i>utch in mice. Eur J Pharmacol 707:112–119
82. Luo L, Liu XL, Li J, Mu RH, Liu Q, Yi LT, Geng D (2015) Macranthol promotes hippocampal neuronal proliferation in.
mice via BDNF-TrkB—PI3K/Akt signaling pathway. Eur J Pharmacol 762:357–363
83. Tian X, Yue R, Zeng H, Li H, Shan L, He W, Shen Y, Zhang W (2015) Distinctive effect on nerve growth factor-induced PC12 cell neurite outgrowth by two unique neolignan enantiomers from Illicium merillanum. Sci Rep 5:16982
84. Dong C-F, Liu L, Luo H-R, Li X-N, Guan Z-Y, Wang Y-F (2012) Sesquigignans and sesquiterpenoid from the stem barks of Illicium simonii and their anti-AChE activity. Nat Prod Bioprospect 2:133–137
85. Takada S, Nakamura S, Yamada K, Hirata Y (1966) Isolation and structure of neoaosatcin. Tetrahedron Lett 7:4739–4744
86. Fukuyama Y, Shida N, Kodama M (1993) Isodussinanin: a new sesquiterpene enhancing neurite outgrowth in primary culture of fetal rat cerebral hemisphere from Illicium tashiroi. Planta Med 59:181–182
87. Kouno I, Kawasaki N, Yang C-S (1988) New pseudoaosatin-like sesquiterpene lactones from the bark of Illicium dunnianum. J Chem Soc Perkin Trans 1:1537–1539
88. Schmidt TJ, Schmidt HM, Müller E, Peters W, Frönckez FR, Truesdale A, Fischer NH (1998) New sesquiterpene lactones from Illicium floridanum. J Nat Prod 61:230–236
89. Yokoyama R, Huang J-M, Yang C-S, Fukuyama Y (2002) New seco-preziizaane-type sesquiterpenes, jiadifenin with neurotrophic activity and 1,2-dehydroxemaunjacin from Illicium jiadifengpi. J Nat Prod 65:527–531
90. Carcache DA, Cho YS, Hua Z, Tian Y, Li Y-M, Danishefsky SJ (2006) Total synthesis of (+)-jiadifenin and studies directed to understanding its SAR: probing mechanistic and stereochemical issues in palladium-mediated allylation of enolate-like structures. J Am Chem Soc 128:1016–1022
91. Kubo M, Okada C, Huang J-M, Harada K, Hioki H, Fukuyama Y (2009) Novel pentacyclic seco-preziizaane-type sesquiterpenoids with neurotrophic properties from Illicium jiadifengpi. Org Lett 11:5910–5913
92. Shoji M, Nishiooka Minato H, Harada K, Kubo M, Fukuyama Y, Kuzuhara T (2016) Neurotrophic activity of jiadifenolide on neuronal precursor cells derived from human induced pluripotent stem cells. Biochem Biophys Res Commun 470:798–803
93. Satoh M, Sugino H, Yoshida T (2000) Actiniv promotes astrocytic differentiation of a multipotent neural stem cell line and an astrocyte progenitor cell line from murine central nervous system. Neurosci Lett 284:143–146
94. Nakagaito Y, Yoshida T, Satoh M, Takeuchi M (1995) Effects of leukemia inhibitory factor on the differentiation of astrocyte progenitor cells from embryonic mouse cerebral hemispheres. Dev Brain Res 87:220–223
95. Trzoss L, Xu J, Lacoske MH, Mobley WC, Theodorakis EA (2013) Illicium sesquiterpenes: divergent synthetic strategy and neurotrophic activity studies. Chem Eur J 19:6398–6408
96. Harada K, Imai A, Uto K, Carter RG, Kubo M, Hioki H, Fukuyama Y (2015) Synthesis of jiadifenin using Mizoroki-Heck and Tuji-Trost reactions. Tetrahedron 71:2199–2209
97. Lu H-H, Martinez MD, Sheniv RA (2015) An eight-step gram-scale synthesis of (+)-jadifenolide. Nat Chem 7:604–607
98. Shen Y, Li L, Pan Z, Wang Y, Li J, Wang K, Wang X, Zhang Y, Hu T, Zhang Y (2015) Protecting-group-free total synthesis of (+)-jadifenolide: development of [4+1] annulation toward multisubstituted tetrahydrofurans. Org Lett 17:5480–5483
99. Cheng X, Micalizio GC (2016) Synthesis of neurotrophic seco-preziizaane sesquiterpenes (1R,10S)-2-oxo-3,4-dehydrohemaunjacin, (2S)-hydroxy-3,4-dehydrohemaunjacin, and (+)-jadifenin. J Am Chem Soc 138:1150–1153
100. Hung K, Condakes ML, Novaes LFT, Harwood SJ, Morikawa T, Yang Z, Maimone TJ (2019) Development of a terpene feedstock-based oxidative synthetic approach to the Illicium sesquiterpenes. J Am Chem Soc 141:3083–3099
101. Huang J-M, Yokoyama R, Yang C-S, Fukuyama Y (2000) Merrilactone A, a novel neurotrophic sesquiterpene dilactone from Illicium merillanum. Tetrahedron Lett 41:6111–6114
102. Huang J-M, Yang C-S, Tanaka M, Fukuyama Y (2001) Structures of merrilactones B and C, novel anislactone-type sesquiterpenes from Illicium merillanum, and chemical conversion of anislactone B to merrilactone A. Tetrahedron 57:4691–4698
103. Urabe D, Io Re MO (2009) Total syntheses of sesquiterpenes from Illicium species. Tetrahedron 65:6271–6289
104. Greaney MF, Shi L, Nazef N (2013) Total synthesis of (+)-anislactone A and (+)-merrilactone A. In: Harmata M (ed) Strategies and tactics in organic synthesis, vol 9. Elsevier, London, pp 105–147
105. Fukuyama Y, Shida N, Kodama M (1995) Tashironin, a plausible biosynthetic precursor of anisatin-type sesquiterpenes. Tetrahedron Lett 36:583–586
106. Huang J-M, Yokoyama R, Yang C-S, Fukuyama Y (2001) Structure and neurotrophic activity of seco-preziizaane-type sesquiterpenes from Illicium merillanum. J Nat Prod 64:428–431
107. Song W-Y, Ma Y-B, Bai X, Zhang X-M, Gu Q, Zheng Y-T, Zhou J, Chen J-J (2007) Two new compounds and anti-HIV active constituents from Illicium verum. Planta Med 73:372–375
108. Ma S-G, Li M, Lin M-B, Li L, Liu Y-B, Qu J, Li Y, Wang X-J, Wang R-B, Xu S, Hou Q, Yu S-S (2017) Ilissimonin A, a caged sesquiterpenoid with tricyclo[5.2.1.01,6]decane skeleton from the fruits of Illicium simonii. Org Lett 19:6160–6163
109. Burns AS, Rychnovsky SD (2015) Total synthesis and structure revision of (–)-llisimonin A, a neuroprotective sesquiterpene from the fruits of Illicium simonii. J Am Chem Soc 141:13295–13300
110. Kubo M, Kobayashi K, Huang J-M, Harada K, Fukuyama Y (2012) The first examples of seco-preziizaane-type norsesquit-erpenoids with neurotrophic activity from Illicium jiadifengpi. Tetrahedron Lett 53:1231–1235
111. Kudo Y, Oka J, Yamada K (1981) Anisatin, a potent GABA antagonist, isolated from Illicium anisatum. Neurosci Lett 25:83–88
112. Nakamura T, Okuyama E, Yamazaki M (1996) Neurotropic components from star anise (Illicium verum Hook, fil.). Chem Pharm Bull 44:1908–1914
113. Shevi RA (2016) Neurite outgrowth enhancement by jiadifenolide: possible target. Nat Prod Rep 33:535–539
114. Ohtawa M, Krambis MJ, Cerne R, Schkeryantz JM, Witkin JM (2017) Synthesis of (–)-11-O-debenzoyltashironin: neurotrophic sesquiterpenes cause hyperexcitation. J Am Chem Soc 139:9637–9644
115. Witkin JM, Shenvi RA, Li X, Gleason SD, Weiss J, Morrow D, Gatow JT, Wakulchik M, Ohtawa M, Lu H-H, Martinez MD, Schkeryantz JM, Carpenter TS, Lighthouse FC, Cerne R (2018) Pharmacological characterization of the neurotrophic sesquiterpene jiadifenolide reveals a non-convulsant signature and potential for progression in neurodegenerative diseases studies. Biochem Pharmacol 155:61–70
116. Shoji M, Ueda M, Nishioka M, Minato H, Seki M, Harada K, Kubo M, Fukuyama Y, Suzuki Y, Aoyama E, Takigawa M, Kuzuhara T (2019) Jiadifenolide induces the expression of cellular communication network factor (CCN) genes, and CCN2 exhibits neurotrophic activity in neuronal precursor cells derived from human induced pluripotent stem cells. Biochem Biophys Res Commun 519:309–315
117. Fukuyama Y, Kubo M, Esumi T, Harada K, Hioki H (2010) Chemistry and biological activities of vibsane-type diterpenoids. Heterocycles 81:1571–1602
118. Miwa K, Esumi T, Imagawa H, Fukuyama Y (2014) Chemical diversity of vibsane-type diterpenoids and neurotrophic activity and synthesis of neovibsanin. In: Atta-ur-Rahman (ed) Studies in natural products chemistry, vol 43. Elsevier, Amsterdam, pp 41–78
119. Kubo M, Kishimoto Y, Harada K, Hioki H, Fukuyama Y (2010) NGF-potentiating vibsane-type diterpenoids from Viburnum sieboldii. Bioorg Med Chem Lett 20:2566–2571
120. Kubo M, Nakai M, Harada K, Fukuyama Y (2019) Structure of seven new vibsane-type diterpenoids from Viburnum awabuki. Tetrahedron 75:2379–2384
121. Imagawa H, Saijo H, Kurisaki T, Yamamoto H, Kubo M, Fukuyama Y, Nishizawa M (2009) Total synthesis of (+)-neovibsanin B. Org Lett 11:1253–1255
122. Imagawa H, Saijo H, Yamaguchi H, Maekawa K, Kurisaki T, Yamamoto H, Nishizawa M, Oda M, Kubara M, Nagahama M, Sakurai J, Kubo M, Nakai M, Makino K, Ogata M, Takahashi H, Fukuyama Y (2012) Syntheses of structurally-simplified and fluorescently-labeled neovibsanin derivatives and analysis of their neurite outgrowth in PC12 cells. Bioorg Med Chem Lett 22:2089–2093
123. Hashimoto G (1996) Illustrated encyclopedia of Brazilian medicinal plants. Maruzen, Tokyo, p 891
124. Tang W, Hioki H, Harada K, Kubo M, Fukuyama Y (2008) Clerodane diterpenoids with NGF-potentiating activity from Pterygodolatum alocaoides. J Nat Prod 71:1760–1763
125. Tang W, Kubo M, Harada K, Hioki H, Fukuyama Y (2009) Novel NGF-potentiating diterpenoids from a Brazilian medicinal plant, Pterygodolatum alocaoides. Bioorg Med Chem Lett 19:882–886
126. Liu Y, Kubo M, Fukuyama Y (2012) Spirocyclic nortriterpenoids with NGF-potentiating activity from the fruits of Leonurus heterophyllus. J Nat Prod 75:1353–1358
127. Ciochina R, Grossman RB (2006) Polycyclic polypropenylated acylphloroglucinols. Chem Rev 106:3963–3986
128. Fukuyama Y, Kaneshi A, Tani N, Kodama M (1993) Subellinone, a polyisoprenylated phloroglucinol derivative from Garcinia subelliptica. Phytochemistry 33:483–485
129. Fukuyama Y, Minami H, Kuwayama A (1998) Garsubellins, a polyisoprenylated phloroglucinol derivatives from Garsubellin A, a neurotrophic activity from the fruits of Viburnum awabuki. Tetrahedron Lett 40:3185–3188
130. Liu Y, Kubo M, Fukuyama Y (2012) Nerve growth factor-potentiating benzofuran derivatives from the medicinal fungus Phellinus ribis. J Nat Prod 75:2152–2157
131. Lan P, Banwell MG, Willis AC (2014) Chemoenzymatic total syntheses of ribisins A, B, and D, polyoxgenated benzofuran derivatives displaying NGF-potentiating properties. J Org Chem 79:2829–2842
132. Boyd DR, Sharma ND, McGivern CJ, Stevenson PJ, Hoering P, Allen CCR (2019) Chemoenzymatic synthesis of (–)-ribisins A and B from dibenzo[b,d]furane. J Org Chem 84:15165–15172
133. Tao-K, Huang L, Wall ME, Wani MC, Navarro H, Mukherjee R, Farnsworth NR, Kinghorn AD (1999) New biphenyl compounds with DNA strand-scission activity from Clusia parallilcola. J Nat Prod 62:1484–1487
134. Takaoka S, Nakade K, Fukuyama Y (2002) The first total synthesis and neurotrophic activity of clusiparalicolone A, a prenylated and geranylated biaryl from Clusia parallilcola. Tetrahedron Lett 43:6919–6923
135. Wattanarthorn J, Chomphopnikulnert P, Muchimapura S, Piprem A, Tankanmerthai O (2008) Piperine, the potential functional food for mood and cognitive disorders. Food Chem Toxicol 46:3106–3110
136. Chomphopnikulnert P, Wattanarthorn J, Muchimapura S (2010) Piperine, the main alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer’s disease. Food Chem Toxicol 48:798–802
137. Kubo M, Ishii R, Ishino Y, Harada K, Matsui N, Akagai M, Kato E, Hosoda S, Fukuyama Y (2013) Evaluation of constituents of Piper pseudoaxiliforme on neurotrophic activity. J Nat Prod 76:769–773
138. Sommerwerk S, Kern S, Heller L, Csek R (2014) First total synthesis of piperodione and analogs. Tetrahedron Lett 55:624–6244
139. Tiwari PK, Ballav H, Aidhen IS (2018) Total synthesis of natural product piperodione and its analogues. ChemistrySelect 3:5975–5980
140. Harada K, Kubo M, Fukuyama Y (2020) Chemistry and neurotrophic activities of (–)-talaumidin and its derivatives. Front Chem. https://doi.org/10.3389/fchem.2020.00301
141. Wilson RM, Danishefsky SJ (2006) Application of total synthesis to problems in neurodegeneration: fascinating chemistry along the way. Acc Chem Res 39:539–549

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