Oplopanax horridus: Phytochemistry and Pharmacological Diversity and Structure-Activity Relationship on Anticancer Effects

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Oplopanax horridus, well-known as Devil’s club, is probably the most important ethnobotanical to most indigenous people living in the Pacific Northwest of North America. Compared with the long history of traditional use and widespread distribution in North America, the study of O. horridus is relatively limited. In the past decade, some exciting advances have been presented on the phytochemistry and pharmacological diversity and structure-activity relationship on anticancer effects of O. horridus. To date, no systematic review has been drafted on the recent advances of O. horridus. In this review, the different phytochemicals in O. horridus are compiled, including purified compounds and volatile components. Animal and in vitro studies are also described and discussed. Especially, the potential structural-activity relationship of polyynes on anticancer effects is highlighted. This review aimed to provide comprehensive and useful information for researching O. horridus and finding potential agents in drug discovery.

1. Introduction

Oplopanax horridus (Sm.) Torr. & A. Gray ex Miq., well-known as Devil’s club, an ethnobotanical, exclusively originates and is distributed in northwestern North America. This understory shrub forming larger populations through layering usually grows in moist, well-drained, dense, and old-growth forests [1]. This herbal plant belongs to the genus Oplopanax, which only consists of three species, the remaining of which are O. japonicus Nakai and O. elatus (Nakai) Nakai [2]. O. elatus is mainly distributed in the temperate regions of Northern China, the south of Primorye, northern part of the Korean Peninsula, and Russia [3], while O. japonicus is endemic to central Japan [4]. The genus Oplopanax is classified to the Araliaceae family, which comprises some world-known botanicals such as Panax ginseng (Asian ginseng, Chinese or Korean ginseng), P. quinquenergy (American ginseng), and P. notoginseng (Sanqi) [5–8]. Occasionally, O. horridus is sometimes marketed as “wild armored Alaskan ginseng,” “Alaskan ginseng,” or “Pacific ginseng”, but the marketing is now forbidden in the United States due to the misleading [2]. Such marketing relies on the presumable speculation that O. horridus share similar chemical ingredients with the herbs in Panax, but the presumption is not supported by related phytochemical investigation [4].

O. horridus has a long history of use for 34 different medical ailments by the Pacific indigenous peoples from over 38 linguistic groups [7]. The extracts of Devil’s club are marketed in North America for respiratory stimulant and expectorant, rheumatoid arthritis, autoimmune conditions, eczema, type II diabetes, external infections, and internal infections [7]. The Pacific native tribes also use O. horridus for spiritual stimulant, while Shaman use it in their religion ceremonial practices. Table 1 summarizes that different part of O. horridus is used for various ailments by the indigenous people. It implies that the main phytochemicals in different parts of O. horridus are significantly varied.
TABLE 1: The uses of *O. horridus* for various treatments.

| Part of *O. horridus* | Application                          | Preparation        | References |
|------------------------|--------------------------------------|--------------------|------------|
| Inner barks            | Respiratory, cardiovascular, gastrointestinal, cold or infection, diabetes, arthritis, and cancer | Decoction; infusion | [2, 7, 92] |
| Stems                  | Respiratory                          | Decoction          | [2, 7, 93] |
| Roots                  | Respiratory, diabetes, and arthritis | Decoction; infusion | [2, 4, 94] |
| Berries                | Gastrointestinal                     | Paste              | [7, 19]    |
| Leaves                 | Arthritis                            | Decoction; infusion | [7, 29]    |

Recently, pharmacological studies showed that *O. horridus* possessed anticancer, antibacterial, antidiabetes, antipsoriasis, antiarthritis, and antifungal and anticonvulsant activities [2]. In the past five years, most of animal and in vitro studies on *O. horridus* focused on its anticancer effects. At the same time, extensive investigation on the chemical constituents of *O. horridus* has led to the isolation and identification of compounds I-47, which include polynes (polyacetylenes), phenylpropanoids (aglycones and glycosides), lignan glycosides, triterpenoids, sesquiterpenes, and some other compounds. Additionally, forty-eight volatile compounds were identified from the volatile oil by GC/MS. Among these components, polynes, e.g., falcarindiol (FAD), and oplopantriol A (OPT), have been mostly reported as potentially anticancer natural products from *O. horridus*.

In the past decade, some exciting advances have been presented on the phytochemistry, pharmacological diversity, and structure-activity relationship on anticancer effects of *O. horridus*. To date, no systematic review has been drafted on the recent advances of *O. horridus*. In this review, the different phytochemicals in *O. horridus* are compiled, including purified compounds and volatile components. Animal and in vitro studies are also described and discussed. Especially, the potential structural-activity relationship of polynes on anticancer effects is highlighted. This review aimed to provide comprehensive and useful information for researching *O. horridus* and finding potential agents in drug discovery.

2. Ethnobotanical and Ethnopharmacology

*O. horridus* is distributed from Alaska along the Pacific Coast down to Oregon, Idaho, and Montana in the south and east to the southwestern Yukon Territory, while some isolated populations grow around Michigan and the islands in Lake Superior (Figure 1) [7, 9]. *O. horridus* generally is from 1 to 1.5 m tall, while it can grow to 3 to 5 m in some undisturbed moist rainforest. The spines appear around the stems and along the upper and lower surfaces of its leaves, which are palmately lobed with 5-13 lobes, 20 to 40 cm across, and are spirally located on the stems (up to 3 cm diameter). The flowers are blooming in dense umbels from 10 to 20 cm diameter with five greenish-white petals. The fruit is a small red drupe with 4 to 7 mm diameter. The root without spines is similar to the stem [9]. The plant grows and reproduces slowly and take many years to reach seed bearing maturity, and it is very sensitive to human impact [10].

*O. horridus* has been used for both spiritual and medical practices by the native tribes of Alaska and British Columbia for centuries. Traditionally, the native tribes drink the aqueous decoction of the root or stem bark of *O. horridus* for the treatments of colds, fever, burns, stomach trouble, body pains, sore throats, swollen glands, constipation, and tuberculosis [11]. The inner bark of the root and stem has been used to stop infection on wounds and reduce swelling [12]. The Alaska Natives from the Alaskan southeast coast, Cook Inlet, Kodiak, Kenai, Prince William Sound, and Tanana Valley use the inner bark of the root and stem to treat colds, cough, and fever [13]. The traditional preparations of *O. horridus* include either applying the heated inner bark to the wounded area and bandaging it or chewing the root or stem bark.
and spitting the crude herb on the wound as an emergency analgesic and antiseptic [10]. The infusion of inner bark of O. horridus was described as a possible treatment for cancer by indigenous peoples in North America [7]. Although formal documentation of its traditional use for cancer is lacking, O. horridus extracts and its compounds exhibited the anticancer activities in preclinical investigations [2, 4].

3. Phytochemistry

The main chemical constituents of O. horridus are polyynes (polyacetylenes), phenylpropanoids (aglycones and glycosides), lignan glycosides, triterpenoids, sesquiterpenes, and volatile compounds [4]. Within the different structural skeletons of these groups, a variety of analogues are presented in the aerial and underground parts of the botanical. Generally, the secondary metabolites in O. horridus are consistent with the patterns of chemical constituents from the genus Oplopanax and the family Araliaceae. Polyynes have been mostly reported with high contents in both the stem and the root of O. horridus as potential anticancer and antimycobacterial (antituberculosis) natural products. Due to the limited number of analytical chemistry investigations that have been done, only six polyynes have thus far been quantified in the root of O. horridus [14, 15]. Phenylpropanoids and lignan glycosides are the other two main natural products from the genus Oplopanax. Sesquiterpenes and volatile compounds have also been extracted from the root of this herb. For this species, the chemical profile of the polyynes of the root may be useful for herbal identification since they are very different from the other species in this genus, O. japonicus and O. elatus.

3.1. Polyynes (Polyacetylenes). Polyynes, also known as polyacetylenes, possess a long chain of carbon atoms with alternating double and triple bonds between them, which occur in natural products containing more than two acetylene groups. Meanwhile, polyynes comprising two to four acetylene groups are usually found in higher plants, most of which contain conjugated diyne in the highly unsaturated lipid chains [16]. These highly unsaturated hydrophobic compounds are generated in the Araliaceae family, which have a high concentration in the roots and a small content in the stem barks. The polyynes which are unstable and oxidized in dried plant material, contain seventeen or eighteen carbons (C17 or C18) in the skeleton chain, and are mostly found in the Araliaceae.

To date, seven polyynes have been purified and identified from the root bark of O. horridus, five of which are also discovered from the stem bark of O. horridus [17, 18]. The identified C17 and C18 polyynes from O. horridus, 1–7, are oplopantriol A, oplopantriol B, (11S, 16S, 9Z)-9,17-octadecadiene-12,14-diyne-1,11,16-triol, 1-acetate, oplopandiol acetate, falcarindiol, falcarinol, and oplopandiol (Figure 2). Polyyne has not been reported to be found in the follower, berry, leaves, and seeds of O. horridus. For analytical investigation of polyynes in O. horridus, an HPLC fingerprint method was developed to evaluate the stem and berry extracts of O. horridus, which showed that polyynes are not major components in the stem and berries of O. horridus [19]. For the quantification of polyynes in O. horridus, an online solid-phase extraction HPLC (SPE-HPLC) and a modified reversed migration microemulsion electrokinetic chromatography were validated to quantify polyynes and one polyyne in O. horridus [14, 15]. The contents of polyynes in the root bark of O. horridus range from 0.029% to 0.15% (1), 0.025% to 0.13% (2), 0.077% to 0.31% (3), 0.24% to 0.43% (4), 0.26% to 0.67% (5), and 0.26% to 0.67% (6), respectively.

Although no evidence is found that O. horridus is used to cure cancer in North America in the long history, the extracts and polyynes from O. horridus exhibited their anticancer activities in recent pharmacological research. The extracts mainly containing polyynes from O. horridus root bark showed effective in the inhibition of the proliferation of several ovarian, breast, lung, and colorectal cancer cell lines [20, 21]. The mechanisms of polyynes on anticancer activities are still not well known. To the tested polyynes, Falcarindiol and Oplopantrol A showed the strongest inhibition on the growth of all the examined cancer cell lines [22, 23].

3.2. Phenylpropanoids (Aglycones and Glycosides). Phenylpropanoids are metabolized by plants from the amino acids phenylalanine and tyrosine. The basic chemical structure of phenylpropanoid consists of the aromatic phenyl group and the three-carbon propene tail of cinnamic acid. Phenylpropanoids are found commonly in the plant kingdom, where they play a vital role as essential components in biosynthesizing polymers, providing protection from ultraviolet light, defending against herbivores and pathogens, and mediating plant-pollinator interactions. Phenylpropanoids including aglycones and glycosides were also obtained from O. horridus [24]. As phenolic compounds, phenylpropanoids
and their derivatives were synthesized into thousands of different chemical structures including aromatic rings in several species in the Araliaceae family.

The phenylpropanoids from the root bark of *O. horridus* were isolated and purified by various chromatographic techniques including silica gel, reverse phase silica gel, sephadex LH-20, and pre-HPLC and identified by their physicochemical properties and spectral data. The phenylpropanoids are obtained and identified from the root bark of *O. horridus* include ferulic acid (8), 3-acetylcaffeic acid (9), caffeic acid (10), homovanillyl alcohol 4-O-beta-D-glucopyranoside (11), 3-hydroxyphenethyl alcohol 4-O-beta-D-glucopyranoside (12), 3, 5-dimethoxycinnamyl alcohol 4-O-beta-D-glucopyranoside (13), 3, 5-dimethoxycinnamyl alcohol 4-O-beta-D-glucopyranoside (14), oplopanhesides A-E (15-19), 3-[(6-O-acetyl-beta-D-glucopyranosyl)oxy]-3,5-dimethoxyphenylpropanoic acid (20), and glycer-2-yl ferulate (21), as well as three coumarins, scopoletin (22), esculetin (23), and 3'-angelyl-4'-acetyl-cis-knellactone (24) (Figure 3) [25–27]. Phenylpropanoids (15–19) are glycosides that possess a novel feature in their sugar moieties with a 3-hydroxy-3-methylglutaryl moiety connected with C-6 of the beta-D-glucopyranosyl group.

Although the phenylpropanoids are only discovered from the root bark of *O. horridus* several years ago, no phenylpropanoids have been qualitatively and quantitatively...
determined by any analytical method. Therefore, the contents of the phenylpropanoids in any part of O. horridus are still unknown. These phenylpropanoids showed no cytotoxic effects against human cancer cell lines (HCT-116, HT-29, MDA-231, and MCF-7) by MTT method [26]. Phenylpropanoids have not been found in other parts of O. horridus, while some phenylpropanoids are recently found in the root of O. elatus [28].

3.3. Lignan Glycosides. The lignans are a large group of natural products found in plants, which have also been obtained from the family Araliaceae. Usually, plant lignans are derived from phenylpropanoids via dimerization of substituted cinnamic alcohols, which is catalysed by oxidative enzymes and controlled by dirigent proteins. Due to the rarely investigation on the hydrophobic constituents from O. horridus, no lignan aglycone has been found in O. horridus. Meanwhile, lignan glycosides are firstly purified and identified from the hydrophilic constituents of the root bark of O. horridus [25, 27].

The isolated lignan glycosides from the root bark of O. horridus are identified as (+)-isolariciresinol-9′-O-beta-D-glucopyranoside (25), 3,3′-dimethoxy-4,9,9′-trihydroxy-4′,7-epoxy-5′,8-liganan-4,9-bis-O-beta-D-glucopyranoside (26), (+)-5,5′-dimethoxylicadinol 4′-O-beta-D-glucopyranoside (27), (-)-5,5′-dimethoxylicadinol 4′-O-beta-D-glucopyranoside (28), (-)–pinoresinol 4′-O-beta-D-glucopyranoside (29), (+)-5,5′-dimethoxylicadinol 9′-O-beta-D-glucopyranoside (30), and (+)-[5,6,7,8-tetrahydro-7-(hydroxymethyl)-10,11-dimehoxydibenzo[a, c][8]annulen-6-yl]methyl beta-D-glucopyranoside (31) (Figure 4). To date, lignan glycoside has not yet been
found in other parts of *O. horridus*, perhaps due to the limited phytochemical study of these parts. No analytical method has been developed to determine lignans in *O. horridus* so the contents of lignan glycosides in *O. horridus* are unclear. Little pharmacological research has been reported on the lignan glycosides from *O. horridus*, so the corresponding bioactivities of these lignan glycosides are yet to be determined.

3.4. Triterpenoids. Triterpenoids including saponins are the most representative constituents of the family Araliaceae, which have also been found in the genus *Oplopanax*. Except one dammara-type triterpenoid, all other triterpenoids belong to oleanane- and lupan-type, which are all only discovered in the leaves of the herbs in this genus. Unlike ginseng from the genus *Panax*, triterpenoids have neither been isolated nor identified from the root of the plants in *Oplopanax*, but triterpenoids are regarded to be the main bioactive substances in ginseng. Recently, one dammara-type triterpenoid and five lupan-type triterpenoids have been isolated and identified from the leaves of *O. horridus* [29, 30].

The purified triterpenoids from the leaves of *O. horridus* are elucidated as 3α-hydroxy-lup-20(29)-ene-23, 28-dioic acid (32), 3α-hydroxy-lup-20(29)-ene-23, 28-dioic acid-3β-D-glucopyranoside (33), 24-nor-3-oxo-lup-20(29)-en-28-oic acid-28-O-alpha-L-rhamnopyranosyl (1"→ 4")-beta-D-glucopyranosyl (1"→ 6")-beta-D-glucopyranoside (34), dammara-20, 24-dien-3beta-ol acetate (35), acankoreagenin (36), and acankoreoside A (37) (Figure 5). Although dammarane triterpenoid is very common in the family Araliaceae, especially in the genus *Panax*, this triterpenoid is the first time to be found in the family Araliaceae. Compared with 41 triterpenoids obtained from the leaves of *O. elatus*, only six triterpenoids isolated from *O. horridus* are limited. The contents of triterpenoids in the leaves of *O. horridus* are uncertain because of few reports about their determination. It is also blank about the pharmacological research on the triterpenoids from *O. horridus*.

3.5. Sesquiterpenes. Sesquiterpenes are a group of terpenes including sesquiterpenoids that consist of three isoprene units, which may be acyclic or contain rings, including many unique combinations. Sesquiterpenes are widely found in plants from Araliaceae, most of which were identified by gas chromatography coupled with mass spectrometry (GC/MS). To date, three sesquiterpenes have been purified from the inner stem bark and root bark of *O. horridus*, which were identified as 3,10-epoxy-3,7,11-trimethylundeca-1,6-dien-1-ol (neroplomacrol, 38), rel-(3S,6R,7S,10R)-7,10-epoxy-3,7,11-trimethylundec-1-ene-3,6,11-triol (neroplofurol, 39), and nerolidol (40) (Figure 6)[31]. Among them, neroplomacrol and neroplofurol were isolated from the anti-TB active fractions of the inner stem bark of *O. horridus*, which...
were not the main anti-TB active principles but may have synergistic behavior with them. Other sesquiterpenes were identified from the essential oil of *O. horridus* by GC/MS, the relative contents of which are also calculated.

3.6. Volatile Compounds. The volatile oil from *O. horridus* is regarded to be responsible for some clinical uses of the title plant. Volatile oils from natural medicines are very complicated, and volatile compounds could not be easily purified and obtained from volatile oil by modern chromatographic techniques due to their disadvantages such as lower boiling point, lower polarity, and thermal degradation. Therefore, most volatile compounds are identified before by GC/MS. Volatile oils have been extracted from stem and root of *O. horridus*.

Shao et al. used a supercritical fluid extraction method to extract the volatile oil from the root bark of *O. horridus* with a yield of 1.15%, which was much more than the yield of 0.22% when the oil was extracted by the steam distillation method. Then, the volatile oil was subsequently analyzed by GC/MS (Table 2) [32, 33]. Forty-eight volatile compounds were identified by GC/MS analysis and, among all the detectable constituents, (S,E)-nerolidol (52.5%) was the compound with highest content in the volatile oil, followed by τ-cadinol (21.6%) and bicyclogermacrene (4.5%). (S,E)-Nerolidol and τ-cadinol had been purified as simple compounds from the essential oil and their structures were identified by additional spectroscopic techniques. By comparison with the MS data from the Agilent Chemstation the library, one more polyyne, S-falcarinol (3.6%), was also detected and obtained from the essential oil by chromatographic separation. Except for some very common volatile compounds, e.g., α-pinene, β-phellandrene, linalool, 1,3,5-undecatriene, and 1,3,5,8-undecatetraene; most of the constituents identified in the essential oil were sesquiterpenes and oxygenated sesquiterpenes. Some minor constituents were not identified by GC/MS.

3.7. Other Compounds. Some fatty acids, steroid, and steroid glycosides were separated and identified from the root bark of *O. horridus*, i.e., heptacosane acid (41), ethacosane acid (42), *beta*-sitosterol (43), daucosterol (44), aralia cerebrosid (45), usnic acid (46), and protocatechoic acid (47) [24].

4. Biological Activities

Different parts of *O. horridus* are used to help cope with verified illnesses from type II diabetes to cancer problems by indigenous people, but the pertinent pharmacological researches are very limited. Compared to few biological activity report of the leaves, the extracts of the stem and berries have only been screened for their antiproliferation effects of four human cancer cell lines (SW-480, HCT-116, HT-29, MCF-7, and NSCLC) [19]. Meanwhile, the root has been researched on its antibacterial, antifungal, antidepressant, and anticancer effects [2, 34]. In the past decade, although no record was found that any part of *O. horridus* was used to cure cancer in the long history, the extracts and compounds from the root of *O. horridus* exhibited their anticancer activities in recent investigations [2, 4].

4.1. Antibacterial. The extracts and fractions from the root of *O. horridus* showed antibacterial activity related with *antimycobacterial*, the bacteria of which may cause leprosy and tuberculosis in humans [35–37]. The results showed that the ingredients of *O. horridus* displayed synergistic enhancement on antituberculosis effect [38]. From a methanol extract of the inner bark of *O. horridus* exhibited antibacterial activity, five polyynes, 1–4, 7, including falcaminol, falcarindiol, oplopandiol, oplopandiol acetate, and (Z)-9,17-octadecadiene-12,14-diyne-1,11,16-triol 1-acetate, are purified and identified. Specifically, falcarindiol and oplopandiol were the main positive antimycobacterial components from the extract [17]. Additionally, all the obtained polyynes displayed potential ability to inhibit the proliferation of *M. tuberculosis*, *M. avium* at 10 μg/disk in a disk diffusion assay, as well as two Gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus*, two Gram-negative bacteria, *Escherichia coli* DC2 and *Pseudomonas aeruginosa* Z61, and the yeast *Candida albicans*. Among them, falcarindiol has been proved to possess the strongest antibacterial activities [17].

4.2. Antifungal. The methanol extract of *O. horridus* inner bark was screened for antifungal activity against 9 fungal species, i.e., *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, *Fusarium tricinctum*, *Microsporum cocker*, *Microsporum gypseum*, *Saccharomyces cerevisiae*, *Trichoderma viridae*, and *Trichophyton mentagrophytes* [39, 40]. The extract was demonstrated antifungal activity against all the fungal strains assayed except *A. flavus*. The extract had only slight activity against *A. fumigatus*, *C. albicans*, *F. tricinctum*, *S. cerevisiae*, and *T. viridae*, but it had greater inhibition against *M. gypseum*. With the assayed fungi, the extract showed the greatest significant antifungal activity on *M. cooker* and *T. mentagrophytes* [39]. However, the
corresponding natural products with antifungal activity are still unknown.

4.3. Antidiabetes. *O. horridus* is extensively recommended for the treatment of diabetes in indigenous communities [41, 42]. Without any data, it was claimed that *O. horridus*, as a pancreatic tonic, is regarded to decrease blood sugar levels by improve the efficiency of insulin [41]. Therefore, it should be cautiously used for diabetes due to the perspective risk and uncertainty. In preclinical research on *O. horridus* for adult diabetes, a white precipitate isolated from root bark of *O. horridus* showed a slightly hypoglycemic effect in lab hares [43]. Inconsistently, the *O. horridus* tea at a certain dosage exhibited no significant hypoglycemic effects in a primary study [44]. Three new phenolic glycosides obtained from the root bark of *O. horridus*, oplopanhesive A-C, displayed negative activity for their α-glucosidase inhibition (IC$_{50}$ >50 μM, respectively) [26]. Unambiguously, more studies are requested in concerning its antidiabetic effects.

4.4. Anticancer Effect. The infusion of inner bark of *O. horridus* was described as a possible treatment for cancer by indigenous linguistic people including Alutiiq, Gitxsan, Haida, Tlingit, and Tsimshian [7]. To date, *O. horridus* has not been reported to have anticancer effects on human bodies, and no human clinical studies have been conducted on this herb. The extracts mainly containing polyynes from the root bark of *O. horridus* show anticancer effects on several colorectal, breast, lung, ovarian, pancreatic and acute myeloid leukemia cancer cell lines, and animal models [4, 45, 46].

4.4.1. Colorectal Cancer. The different extracts from *Oplopanax* root, stem, berry, root bark, and their fractions were investigated in vitro for their potential antiproliferative effects on human HCT-116, HT-29, and SW-480 colorectal cancer cell lines [19–21, 47]. The results showed that the stem, root, root bark extracts, and lipophilic fractions of root bark possessed potent antiproliferative effects. The observation of the cell cycle distribution suggested that G2/M phase is arrested by the extracts. However, the hydrophilic fractions had much weaker effects on the apoptotic cells [20].

Five polyynes were isolated and evaluated as the bioactive compounds from hydrophobic fractions [47]. Among these polyynes, FAD and OPT showed significant potent effects, and the primary structure-activity analysis suggested that these anticancer activities are related to the ethylenic bonds and acylations in the structures [48, 49]. Firefly luciferase-tagged HCT-116 cells were inoculated into the flanks of athymic nude mice used as the animal model to evaluate the in vivo antitumor potential of FAD and OPT from *O. horridus* [48]. The results showed that the FAD and OPT treatment groups exhibit significantly decreased xenogenic imaging signal intensities when compared with the control group. Quantitative analysis revealed that the FAD and OPT significantly inhibited xenograft tumor growth after the administration of FAD and OPT [22, 23]. A rat small intestine

| Compound           | Molecular formula | Compound           | Molecular formula |
|--------------------|-------------------|--------------------|-------------------|
| Pentanol           | C$_2$H$_5$O       | Germacrene D       | C$_{15}$H$_{24}$  |
| Hexanol            | C$_2$H$_5$O       | ar-Curcumene       | C$_{15}$H$_{22}$  |
| Heptanal           | C$_2$H$_7$O       | β-Sesquiphellandrene | C$_{15}$H$_{24}$ |
| Heptanol           | C$_2$H$_{15}$O    | β-Elemene          | C$_{15}$H$_{24}$  |
| Octanol            | C$_2$H$_6$O       | α-Murolene         | C$_{15}$H$_{24}$  |
| Benaldehyde        | C$_2$H$_6$O       | Allo-aromadendrene | C$_{15}$H$_{24}$  |
| 2-Octenal          | C$_6$H$_{14}$O    | γ -Cadinene        | C$_{15}$H$_{24}$  |
| 2-Methylpentenal   | C$_6$H$_7$O       | α -Farnesened      | C$_{15}$H$_{24}$  |
| α-Pinene           | C$_{10}$H$_{16}$  | 1,10-Di-epi-cubenol| C$_{15}$H$_{24}$O |
| β-Phellandrene     | C$_{10}$H$_{16}$  | δ -Cadinene        | C$_{15}$H$_{24}$  |
| Linalool           | C$_{10}$H$_{16}$O | Bicyclogermacrene  | C$_{15}$H$_{24}$  |
| 1,3,5-Undecatriene | C$_{11}$H$_{18}$  | Ishwarane          | C$_{15}$H$_{24}$  |
| 1,3,5,8-Undecatetraene | C$_{11}$H$_{20}$ | Gemmacrene B       | C$_{15}$H$_{24}$  |
| α-Ylangene         | C$_{15}$H$_{24}$  | (S, E)-Nerolidol   | C$_{15}$H$_{26}$O |
| Aromadendrene      | C$_{15}$H$_{24}$  | Spathulenol        | C$_{15}$H$_{24}$  |
| α-Zingiberene      | C$_{15}$H$_{24}$  | Gemmacrene D-4-ol  | C$_{15}$H$_{26}$O |
| β-Caryophyllene    | C$_{15}$H$_{24}$  | Gleenol            | C$_{15}$H$_{24}$  |
| (E)-α-Bergamotene  | C$_{15}$H$_{24}$  | Guaiol             | C$_{15}$H$_{24}$  |
| α-Copaene          | C$_{15}$H$_{24}$  | Endo-1-bourbonanol | C$_{15}$H$_{26}$O |
| α-Humulene         | C$_{15}$H$_{24}$  | τ -Cadinol         | C$_{15}$H$_{26}$O |
| α-Cadinene         | C$_{15}$H$_{24}$  | τ -Murolol         | C$_{15}$H$_{26}$O |
| Germacrene A       | C$_{15}$H$_{23}$  | S-Falcarinol       | C$_{17}$H$_{23}$O |
| (E)-β-Farnesene    | C$_{15}$H$_{23}$  | α-Eudesmol         | C$_{15}$H$_{26}$O |
| γ -Murolene        | C$_{15}$H$_{24}$  | Bulnesol           | C$_{15}$H$_{26}$O |

Table 2: The volatile compounds of essential oil from the root of *O. horridus*.
After one week following engraftment, the 70% ethanol Foxp3<sup>tm1Flv/J</sup>) were employed for in vivo anti-AML. Male and female transgenic C57BL/6J-Foxp3-RFP mice (C57BL/6-) were used for the study of the therapeutic potential of the extract. The extract was administered by oral gavage. In vivo assays were performed using the transplant model in order to evaluate the efficacy of the extract in vivo. The results showed that the extract significantly enhanced the survival rate of the mice and reduced the tumor size in the transplanted xenografts. The extract also inhibited the proliferation of the tumor cells. The data suggested that the extract possessed anti-AML activity.

4.4.2. Acute Myeloid Leukemia (AML). Male and female transgenic C57BL/6J-Foxp3-RFP mice (C57BL/6-Foxp3<sup>tm1Flv/J</sup>) were employed for in vivo anti-AML. After one week following engraftment, the 70% ethanol extract of <i>Oplopanax</i> root was diluted into the drinking water at a final concentration of 20 μM. The survival of both male and female mice was significantly increased upon the inclusion of the extract in the drinking water [45]. In addition, the extract decreased the Tregs and increased CD4<sup>+</sup> T cells and the ratio of CD8<sup>+</sup> T cells to Tregs. These changes are indicative of a responsive immune system correlated as expected with an increase in survival [45].

The 70% ethanol extract was assessed on AML cell line viability and to study the regulation of tyrosine phosphorylation and cysteine oxidation. The root extract displayed better in vitro anti-AML efficacy in addition to a noted anti-tyrosine kinase activity. The extract decreased the viability of murine C1498 cells and human U937, HL-60/VCR, and KG-1 cells with differential effects. In addition, the effect of the extract compared with nerolidol (a major essential oil component of <i>O. horridus</i>) yielded a better anti-AML activity [45].

4.4.4. Lung Cancer. The antiproliferative effects of nonsmall cell lung cancer (NSCLC) cells were evaluated. The IC<sub>50</sub> of the extract, 50, 70, and 100% ethanol fractions for antiproliferation on NSCLC cells, were 125.3, 271.1, 17.6, and 23.2 μg/mL, respectively [19]. In addition, the extracts from the stem and berry were evaluated. The stem extract had potent antiproliferative effects at a low concentration of 0.1 mg/mL compared to 1 mg/mL for the berry [21].

4.4.5. Ovarian Cancer. An ovarian cancer (Ovar 10 three-dimensional [3D]) model was utilized to evaluate the antiproliferation activity of 75% ethanol extract and its active compound, alone and in combination. Ovar 10 cells formed compact 3D spheroids after five days of culture in a rotary culture system [50]. The 3D spheroids were significantly more resistant to killing by the extract when compared to 2D cells. A number of apoptosis-related genes were differentially expressed in these cells. In 3D spheroids, the proportion of cells in the G2/M phase was slightly increased and the S phase was slightly decreased when compared to 2D cells [50].

4.4.6. Pancreatic Cancer. The 70% ethanol extract was investigated on pancreatic endocrine HP62 and pancreatic ductal carcinoma PANC-1 and BxPC-3 cells. The extract significantly inhibited the proliferation of HP62 at low IC<sub>50</sub>. Apoptosis focused antibody array profile indicated upregulation of cytochrome C, claspin, cIAP-2 and HTRA2/Omi apoptosis-related markers, suggesting that the effect was via targeting the intrinsic mitochondrial apoptosis pathway [51].

The extract was also assessed for its effect on human pancreatic cancer PANC-1 3D spheroids and 2D monolayer cells. PANC-1 3D spheroids were significantly more resistant to killing by this extract with IC<sub>50</sub> level closer to that observed in vivo. The extract also significantly enhanced the antiproliferation activity of the antineoplastic medications cisplatin (CDDP) and gemcitabine (GEM). The bioactive compound, identified as a polyene, showed strong antiproliferation activities. Cell cycle analysis showed that the proportion of cells in S phase was increased and in G2/M phase was reduced in 3D spheroids when compared with 2D cells [52].

5. Structure-Activity Relationship of Polynyes on Anticancer Effects

5.1. Length of Carbon Chain. The structure-activity relationship of carbon chain in polynyes with their anticancer potential is summarized in Table 3. Anticancer activities...
### Table 3: Possible structure–activity relationship of polyynes from *O. horridus* against cancer.

| Polyynes(a) | Structure characteristics | Cancer cell lines | Activity(b) | References |
|-------------|---------------------------|-------------------|-------------|------------|
|             | Carbon chain | Hydroxyl group | Double bond | HCT-116, HT-29, SW-480, A549, MCF-7, MDA-MB-231, HepG2 | Best | [22, 48, 49, 59] |
| 1           | 18          | 3               | 2          | A549, MCF-7, MDA-MB-231, HepG2 | Best | [48, 59] |
| 2           | 18          | 3               | 1          | A549, MCF-7, MDA-MB-231, HepG2 | Better | [48, 59] |
| 3           | 18          | 2               | 2          | A549, MCF-7, MDA-MB-231, HepG2 | Good | [47, 48, 59] |
| 4           | 18          | 2               | 1          | A549, MCF-7, MDA-MB-231, HepG2 | Good | [47, 48, 59] |
| 5           | 17          | 2               | 2          | A549, MCF-7, MDA-MB-231, HepG2, DU145 | Best | [23, 47, 48, 59] |
| 6           | 17          | 2               | 1          | A549, MCF-7, MDA-MB-231, HepG2 | Better | [47, 48, 59] |
| 7           | 17          | 1               | 2          | Not available | Not available | [95–97] |

(a) 1. oplopantrio A; 2. oplopantrio B; 3. (11S,16S,9Z)-9,17-octadecadiene-12,14-diyne-1,11,16-triol-1-acetate; 4. oplopandiol acetate; 5. falcarindiol; 6. oplopandiol; 7. falcarinol. (b) Stereoselectivity also affects the activities discussed in the text.

decrease with the increase of the length of carbon chain in the main chemical structural skeleton of polyynes. To date, hundreds of polyynes have been isolated from bacterial, fungi, microorganisms, marine invertebrates, and high plants, and most naturally occurring polyynes feature a long lipid chain covering from 10 to 42 carbons in their chemical structural skeleton [16, 53, 54].

Among them, C_{17} and C_{18}-polyynes were predominantly reported for their anticancer effects [55–58]. In the tested cancer lines, the antiproliferation effects of polyyne 1 displayed stronger effects than 3 and 5, while polyyne 2 exhibited greater activities than 4 and 6 [48, 59]. Among these polyynes, 1 (FAD) shows the strongest anticancer activity, suggesting that FAD is a candidate for chemical modification [60–62].

5.2. Ethenyl Group. As shown in Table 3, (R)-falcarinol, a C_{17}-polyyne, is obtained from some other plants, and it has been demonstrated to show antiproliferation effects on several cancer cell lines [63–67]. However, biological study has not been conducted on its derivative, cis-9-heptadecene-4,6-diyne-8-ol, which becomes an easier volatile compound when its terminal double bond is transferred to be single bond [68]. Regarding the chemical structures of these polyynes, they could be divided into three pairs grouped by their terminal bond moieties, i.e., 1 vs. 2; 3 vs. 4; and 5 vs. 6. With regard to their anticancer effects, polyyne 1, 3, and 5 showed greater potent activity, suggesting that the terminal ethenyl group improved anticancer activity [48, 59]. Recently, it is reported that the pharmacokinetic parameters between 1 and 2 had significant differences. Compared with 2, the terminal ethenyl group made 1 easier transformed into other metabolites in vivo [69]. It has been demonstrated that compound 1 could effectively join in chemical carcinogen detoxification by selectively mediating Phase II drug metabolism enzymes and quinone oxidoreductase [70]. Therefore, further studies should be employed to investigate the relationship between its terminal ethenyl group and anticancer behavior.
5.3. Hydroxyl Group. Since polar compounds interact with phospholipid substances in the hydrophilic domain of cell membrane, the entrance orientation of polyynes into membranes is affected by the number and location of alcohol hydroxyl groups [71]. The number and location of hydroxyl groups in polyynes influenced its anticancer activity [72, 73]. In the natural polyynes, if the hydroxyl group at C-1 was substituted with an acetyl group, the antiproliferative effect of polynye was decreased, but if the hydroxyl group at C-11 or C-16 was acetylated, the antiproliferative activity would be significantly suppressed [59]. The anticancer activities of polynye 3, 4, 5, and 6 have been systematically compared. Oplopantriol A (5) showed the strongest antiproliferative effects on selected colorectal cancer cell lines and greater inhibition of tumor growth in vivo [22, 49]. Among the four polyynes, oplopantriol A can be considered to be a prochemical.

In order to investigate the contribution of hydroxyl groups to the antiproliferation on cancer cells, sixteen more acetylated derivatives have been synthesized for the evaluation of potential anticancer activities. The polynyes do not have any inhibitory effects of the adopted cancer cells if all the hydroxyl groups of the polynyes were acetylated [59]. However, compared to hydroxyl group at C-1, the terminal ethenyl group contribute more significance for maintaining anticancer potential. For example, compound 5 has 3 to 5-fold relatively stronger antiproliferative effects than compound 6, while compound 5 possesses 1 to 3-fold relatively greater than compound 3 [48]. The elimination of hydroxyl groups of polynyes will yield acetylene alkanes, which have not been subjected to anticancer research.

5.4. Stereoselectivity. With the same planer chemical structures of the polynyes identified from O. horridus, each molecule is able to generate four stereoisomers with (3S, 8S)- or (11S, 16S)-, (3S, 8R)- or (11R, 16S)-, (3R, 8S)- or (11S, 16R)-, and (3R, 8R)- or (11R, 16R)-configuration. However, only (3S, 8S)- or (11S, 16S)- and (3R, 8S)- or (11S, 16R)- stereoisomers have been isolated and identified from natural resources [16]. According to the numbering sequence, the stereochemistry identified for polynyes purified from O. horridus with a (3S, 8S)- or (11S, 16S)-configuration seems to be very different from those with the (3R, 8S)- or (11S, 16R)-configuration reported from Apiaceae and Asteraceae [74–77].

To the (3S, 8S)- and (3S, 8R)-polyynes, (3S, 8S)-1 has only been found in the genus Oplopanax, while (3S, 8R)-1 has been isolated from several plants in different genus [78–81]. Although (3R, 8S)-1 and (3R, 8R)-1 have been synthesized [77], they have not been assayed for their anticancer effects. (3S, 8R)-1 showed the inhibitory activity on various tumor cells proliferation, e.g., K562, Raji, Wish, HeLa, Calu-1, MCF-7 in vitro [66, 82, 83], and tumor growth in different mouse model [67, 84]. Compared with (3S, 8R)-1, (3S, 8S)-1 showed stronger antiproliferative effects against MCF-7 cells [23, 83]. Due to the limited data, the stereochemistry on the anticancer effects of 1 needs further studies.

To the (11S, 16S)- and (11S, 16R)-polyynes, (11S, 16R)-3 has been isolated from the genus Angelica [85–87], while (11S, 16S)-4 has been synthesized [88, 89]. (11S, 16R)-5 has also been isolated from the genus Angelica [90, 91], but (11S, 16S)-6 has only been found in O. horridus. Among these existing C18-polyynes, only (11S, 16S)-polyynes isolated from O. horridus have been tested for their anticancer activities. Therefore, more researches are needed to confirm the stereoselectivity of polynyes on their anticancer effects.

6. Summary and Perspectives

O. horridus, well-known as Devil’s club, is probably the most important ethnobotanical to most indigenous people living in the Pacific Northwest of North America. Different part of O. horridus has a long history to be used for ailments by local people as traditional herbal medicines. In this review, the phytochemicals mainly including polyynes, triterpenoids, sesquiterpenes, diterpenoid, lignans, and phenylpropanoids from different part of O. horridus have been compiled. To date, approximately 47 compounds have been purified from O. horridus, and most of them are discovered for the first time from this genus. However, phytochemistry studies are relatively limited on each part of O. horridus except its root.

Polyynes identified from this herb exhibit pharmacological diversity. Especially, though this botanical has not been reported to have anticancer effects in human clinical studies, polynyes from O. horridus showed effects against colorectal cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, and acute myeloid leukemia in human cancer cell lines and different animal models. Regarding the anticancer effects and mechanisms of polynyes, it is pertinent to several molecular mechanisms and various signaling pathways. Because the bioavailability and metabolism of polynyes are critical important, their plasma concentrations that maybe significantly affect its biological activities in vivo are unknown. Moreover, the pharmacokinetic studies are blank to these polynyes except a few reported pharmacokinetic parameters of facarindiol and oploandiol in rat [69]. Therefore, in vivo preclinical models are essential and vital to evaluate and predict the clinical function of polynyes.

We propose that the length of lipid chain, terminal ethenyl group, number of hydroxyl groups, and stereoselectivity in polynyes affect their anticancer activity. These relationships could benefit chemical modification of polynyes for discovery of bioactive molecules. Due to the stability of polynyes, C17-polyynes are most researched for their anticancer activities [61]. Our former experiments showed that acetylation of polynyes decreased their activities, but cancer chemopreventive potential may be enhanced by employing other chemical functional groups into polynyes. Although different stereoisomers of polynyes could be synthesized, their potential anticancer effects have not been quantitatively compared. Further investigations are needed to develop novel anticancer candidate in drug discovery.

Conflicts of Interest

All the authors declare that they have no conflicts of interest regarding funding supports in this manuscript.
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Supplementary Materials

Supplementary data associated with this review is the graphic abstract about bioactive polyynes from O. horridus. (Supplementary Materials)

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