Chapter

Ohioensins: A Potential Therapeutic Drug for Curing Diseases

Satish Chandra, Dinesh Chandra and Arun Kumar Khajuria

Abstract

Benzonaphthoxanthenones are a class of flavanoids which are absent in the liverworts and hornworts and present only in the mosses. Ohioensins are benzonaphthoxanthenones which are isolated from various moss species. First compound of this series was isolated from the *Polytrichum ohioense* Renauld & Cardot. and hence named as Ohioensin A. Together with Ohioensin A, there are 10 other Ohioensins (B–H) and their derivatives have been extracted from different species of mosses. These compounds are pharmaceutically very important and various studies have shown their usefulness as antioxidant, in Atherosclerosis and cytotoxic activities against various human tumor cell lines. In this chapter, synthesis of Ohioensins, their structure and potential medicinal uses are discussed.

Keywords: atherosclerosis, cancer, cytotoxic activity, moss, Polytrichum

1. Introduction

Bryophytes are tinny nonvascular plants on the earth. They are classified into three phyla Bryophyta (mosses), Marchantiophyta (liverworts) and Anthocerotophyta (hornworts) and represented by 14,000, 6000 and 300 species respectively. Various compounds have been isolated from different species of bryophytes which show antifungal, antiviral, antibacterial, allergic contact dermatitis, anti-HIV, plant growth regulatory, cytotoxic, insecticidal, nitric oxide (NO) production, superoxide anion radical release inhibitory, neurotrophic, muscle relaxing, antiobesity, piscicidal, and nematocidal activities [1].

Among the bryophytes liverworts species possess cellular oil bodies. These are single unit membrane-bound cell organelles that contain ethereal terpenoids and aromatic oils suspended in proteinaceous matrix. Oil bodies are useful in taxonomy and chemosystematics of the liverworts. However, their origin, development and function in the plant is poorly understood. More than 1000 secondary metabolites have been reported from oil bodies and which are considered to be useful in medicine and various other activities. However, these organelles have not been reported in the species of mosses and hornworts [1, 2]. Due to absence of the oil bodies mosses possess comparatively less secondary metabolites. Though, various compounds: monoterpenoids, diterpenoids, triterpenoids, steroids, carotenoids, aromatic compounds (cinnamic acid, benzoic acid, flavones, isoflavones, biflavones, aurones, anthocyanins, benzonaphthoxanthenones) and their

derivatives, alkanes and related compounds, fatty acids (propionic, butylic, valeric, caproic, isovaleric, phenylacetic, cyclohexanecarboxylic acid, palmitic acid, eicosatetraenoic acid and octadecadienoic acid etc.), plant hormones (isopentenyl) adenine (2iP), indole acetic acid) pheophytins and phytochelatins have been isolated from different species of the mosses [3].

Flavonoids are common aromatic compounds present in the mosses and nearly 73 flavonoids and their glycosides have been isolated from different moss species [1]. Benzonaphthoxanthenones are a class of flavanoids only present in the mosses and have been isolated from various moss species [4]. Among Ohioensins, Ohioensin A was first compound isolated from the *Polytrichum ohioense* Renauld & Cardot. and hence named as Ohioensin A [5].

2. Ohioensins

Ohioensins compounds are isolated from various moss species. Chemical formula and source of the compounds are summarized in **Table 1** and their structures are mentioned in **Figure 1**.

S. No.	Compound	Formula	Source	References
1	Ohioensin A	$C_{23}H_{16}O_5$	*Polytrichum ohioense* Renauld & Cardot.	[5, 6]
2	Ohioensin B	$C_{24}H_{18}O_5$	*Polytrichum ohioense* Renauld & Cardot.	[6]
3	Ohioensin C	$C_{23}H_{16}O_5$	*Polytrichum ohioense* Renauld & Cardot.	[6]
4.	Ohioensin D	$C_{24}H_{18}O_6$	*Polytrichum ohioense* Renauld & Cardot.	[6]
5.	Ohioensin E	$C_{25}H_{20}O_6$	*Polytrichum ohioense* Renauld & Cardot.	[6]
6.	Ohioensin F	$C_{23}H_{16}O_6$	*Polytrichastrum alpinum* (Hedw.) G.L. Sm.	[7]
7.	Ohioensin G	$C_{23}H_{16}O_6$	*Polytrichastrum alpinum* (Hedw.) G.L. Sm.	[7]
8.	Ohioensin H	$C_{23}H_{16}O_5$	*Polytrichum commune* Hedw.	[8]
9.	1-O-Methylohioensin B	$C_{25}H_{20}O_5$	*Polytrichum pallidiserum* Funck	[9]
10.	1-O-Methyldihydroohioensin B	$C_{25}H_{22}O_5$	*Polytrichum pallidiserum* Funck	[9]
11.	1,14-Di-O-Methyldihydroohioensin B	$C_{26}H_{24}O_5$	*Polytrichum pallidiserum* Funck	[9]

Table 1.
Source and formula of Ohioensins and their derivatives.

3. Synthesis of Ohioensins

Zheng et al. [6] proposed synthesis pathway of Ohioensins. They suggested that these compounds are synthesized from the condensation of o-hydroxycinnamate and hydroxylated bibenzyls. Their synthetic pathway is summarized in **Figure 2**.

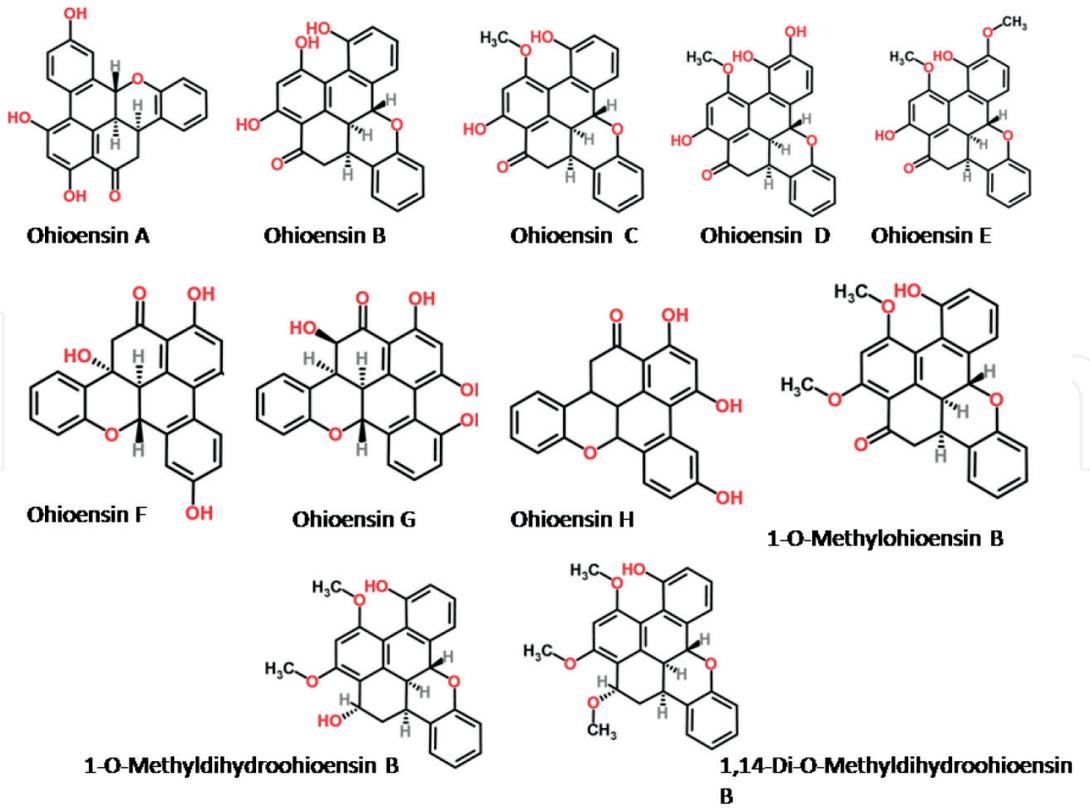

Figure 1.
Structure of Ohioensins and their derivatives.

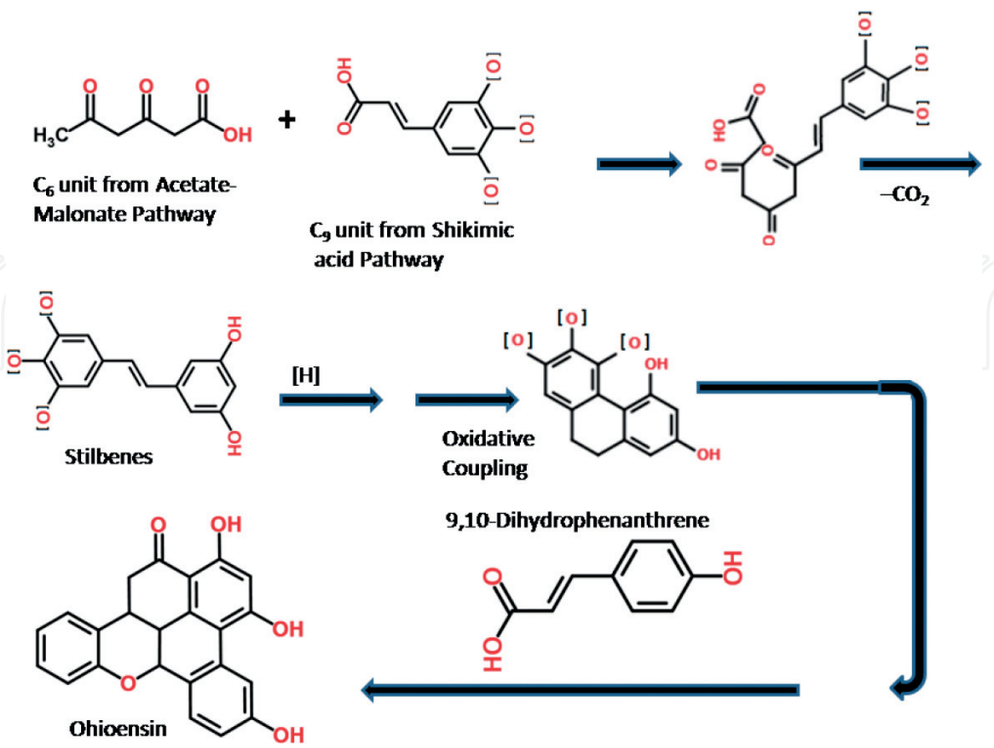

Figure 2.
Synthesis of Ohioensins.

4. Pharmaceutical properties

4.1 Cytotoxic activity

Compounds extracted from different species of bryophytes have shown cytotoxic activity against various cancer cell lines as: P-388 murine leukemia tumor, squamous carcinoma (KB), lung carcinoma (A549), breast ductal carcinoma (MDA-MB-435), liver hepatoblastoma (HEP-G2), and colon adenocarcinoma (LOVO) cell lines, glioma A172 cells, U87 glioma, T98G, osteosarcoma U2OS, leukemia HL-60, K562, MDR K562/A02 and MCF-7 breast cancer etc. These compounds induce apoptosis and necrosis through activation of caspases (a family of cysteine aspartic proteases), DNA fragmentation, activation of p38 (mitogen-activated protein kinase), nuclear condensation, proteolysis of poly (ADP-ribose) polymerase (PARP) and inhibition of antiapoptotic nuclear transcriptional factor-kappa B, etc. These mechanisms play important role in the maintenance of the cell population size and apoptosis of cell in vivo [10]. Ohioensins also show cytotoxic activities against various cancer lines.

- Ohioensin A exhibits cytotoxicity against murine leukemia (PS) cell line and breast cancer cell line (MCF-7) in culture at ED_{50} (Effective Dose) 1.0 and 9.0 pg./mL, respectively [5].

- Ohioensin B show inhibitory activity against Mouse leukemia (9PS) [11] Ohioensin B also show cytotoxic activity against MCF-7 human breast adenocarcinoma, HT-29, human colon adenocarcinoma [6].

- Ohioensin C, Ohioensin D and Ohioensin E show activities against 9PS, murine P388 leukemia [6].

- 1-O-methylohoensin B show activity against HT-29, human colon adenocarcinoma, human melanoma RPMI-7951 and mild activity against human glioblastoma multiforme U-251 MG [9].

- l-O-methyldihydroohioensin B inhibit human glioblastoma multiforme U-251 MG and 1,14-di-O-methyldihydroohioensin B inhibit human lung carcinoma A549 and human melanoma RPMI-7951 cell lines [9].

- Ohioensin H exhibit cytotoxic activities against human T cell leukemia (6 T-CEM), human lung carcinoma (A549), human bowel carcinoma (LOVO), human breast adenocarcinoma (MDA-MB-435) and human hepatoma carcinoma (HepG2) in concentration dependent manner [8].

4.2 Protein inhibitory activity

Ohioensin A (IC50 4.3 ± 0.3 μM), Ohioensin C (IC50 7.6 ± 0.7 l μM), Ohioensin F (IC50 3.5 ± 0.2 μM), Ohioensin G (IC50 5.6 ± 0.7 μM) compounds inhibits the activity of Protein tyrosine phosphatase 1B (PTP1B) in a dose-dependent manner [7].

4.3 In the treatment of atherosclerosis

Atherosclerosis disease is characterized by the disrupted balance and abnormal accumulation of lipids, inflammatory cells, matrix deposits and smooth muscle cell

proliferation in the wall of medium- and large caliber arteries [12]. Arteries are composed of an outer layer (also known as adventitia), a tunica media (made up of layers of smooth muscle cells) and interior layer (also called tunica intima) lined with endothelium. During normal conditions balance between the concentrations of nitrogen oxide (NO, act as vasodilator), and Endothelin-1 (ET-1, act as vasoconstrictor) in the arteries is maintained and the endothelium is shielded from inflammation, injury and thrombosis. Moreover, in such conditions leukocytes could not bind to the endothelium, smooth muscle cells (SMCs) not proliferate and platelet aggregation is minimized. However, during atherosclerosis NO production is inhibited and protection conferred on the endothelial cells is removed [13]. Subsequently endothelium is exposed to leukocytes and SMCs begins to proliferate. Excessive fat in the diet or genetic disorders cause increase in cholesterol and saturated fat in the blood. The low density lipoprotein (LDL) assembles on the proteoglycan of the endothelium and bind together to form aggregates. LDL become highly susceptible for chemical modification and oxidation after aggregation. Oxidation is usually brought by lipoxygenases of infiltrating leukocytes (monocytes and T-lymphocytes), NADH/NADPH oxidases of vascular cells. Procoagulant properties are increased and anticoagulant properties are inhibited when LDL oxidized. Oxidized LDL also increase adhesiveness of leukocyte to the endothelium. When atherosclerosis set in endothelium expresses intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and P-selectins as leukocyte adhesion molecules. Furthermore, tumor necrosis factor α (TNF-α) a cytokine, induces expression of ICAM-1 and VCAM-1 on vascular cells [14]. Hence for curing the atherosclerosis, expression of ICAM-1 and VCAM-1 needs to be down regulate or block for inhibiting interaction between leukocytes and vascular cells [15].

Ohioensin F, prevents TNF-α-stimulated expression of VCAM-1 and ICAM-1 and subsequently reduces monocyte adhesion to Vascular smooth muscle cells (VSMCs). Effects of Ohioensin F also suppress ROS production, MAPK pathways, Nuclear factor-κB (NF-κB) and Protein kinase B (Akt) activation. Thus, Ohioensin F inhibits expression of adhesion molecules which may provide a new therapeutic strategy for the treatment of atherosclerosis [16]. This property of the compound already has been patented [17].

4.4 Antioxidant activity

Ohioensin F and Ohioensin G isolated from the methanolic extract of *Polytrichum alpinum* showed potent antiradical activities against 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS•$^{+}$) and 2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl (DPPH) free radicals. The compounds (ohioensin F and ohioensin G) and the crude methanolic extract converted DPPH into DPPH-H by donating a hydrogen atom and inhibited the production of the chromogen cation of ABTS. Ohioensin F, ohioensin G and methanolic extract showed Fe^{3+} to Fe^{2+} reducing capacity and also show moderate activity against free radical nitric oxide (NO) in dose-dependent manner [18].

5. Conclusions

Nearly all Ohioensins show cytotoxic activities against various cell lines, thus these can be used in the treatment of the various Cancer. Though, more research is needed in this aspect of the Ohioensins. Ohioensin F play important role in the

treatment of atherosclerosis and act as strong antioxidant. However, further investigation for therapeutic potential of these compounds is warranted.

Conflict of interest

Authors show no conflict of interest.

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