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Natural Small-Molecules Obtained From Lichens as a Novel Source of Anti-Angiogenic Agents

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Introduction

Herbal remedies of practitioners have been used for thousands of years in a wide range of cancer treatments [1]. Lichens are structurally complex and self-supporting symbiotic organisms consisted of fungus and algae and/or cyanobacteria. To date, over 1000 lichen secondary compounds derived from fungal metabolism have been discovered which presence in lichens as depisides, depsidones, dibenzofurans, pulvinic acid, anthraquinones, xanthones and shikimic acid derivatives mostly having low molecular weight [2-5]. Most of these small-molecules are exclusively present in lichens, and major of which present a wide variety of biological influences including antiviral, antimicrobial, antiprotozoal, anti-inflammatory, anti-pyretic, analgesic, photoprotective, enzyme inhibitory, antiproliferative, antitumor and anti-angiogenic properties [4,6-10]. Thus, lichens still remain a quite significant source of biologically active compounds and attracted great attention of researchers in drug search industry. However, there are very few studies about the effects of these unique acids on angiogenesis which is an important target in fighting with cancer and the other angiogenesis-dependent diseases [11].

Angiogenesis, sprouting of new blood vessel from existing vasculature, is an obligation for tumor development, growth and metastasis. Newly generated vessels play a crucial role for tumor cells by supplying oxygen and nutrients, removing waste products and providing a migration channel opening into the circulatory system [12,13]. Angiogenesis is therefore manipulated by tumor cells themselves thorough the topical accumulation of pro-angiogenic factors able to draw and prompt endothelial cells in the peritumoral microenvironment [14]. The activated endothelial cells proliferate, migrate and organize to form new capillary networks [15]. Thus, angiogenesis is a strategic target in inhibition of development, invasion and metastasis of tumors.

To the best of our knowledge, the first study about anti-angiogenic activity of a small-molecule derived from lichen was performed against tube-like formation of rat adipose tissue endothelial cells (RATEC) and published by Koparal et al. (2010). Discovery of anti-angiogenic substances usually begins with in vitro endothelial tube formation researches due to endothelial cells form blood vessels, and these experiments are cheap and fast experiments [16]. They reported that olivetoric acid, a depside derivative which is isolated from the acetone extract of the lichen *Pseudevernia furfuracea* (var. ceratea) had inhibited the proliferation of RATEC cells and disrupted the formation of tube-like structure of the serum starved RATEC cells by influence on the organization of actin cytoskeleton [6,17]. Usnic acid is a dibenzofuran derivative and one of the major small-molecules in lichens [18]. Song had studied anti-angiogenic potential of 98% pure usnic acid obtained from Sigma-Aldrich (St. Louis, MO), by using in vivo vascular endothelial growth factor-induced mouse corneal angiogenesis model and chick embryo chorioallantoic membrane assay, and in vitro endothelial tube formation and migration assays. They found that usnic acid inhibits the angiogenesis by blocking vascular endothelial growth factor receptor 2 (VEGFR-2) mediated AKT and ERK1/2 signaling pathways [7]. (S)-(-) - usnic acid, one of the chiral forms of usnic acid, had also been found as anti-angiogenic lichen compounds by Koparal (2015). Additionally, Koparal (2015) reported that vulpinic acid, a pulvinic acid derivative, have a great potential to be an anti-angiogenic agent with low cytotoxic but significant anti-angiogenic activities on the tube-like structure formation of human umbilical vein endothelial cells (HUVEC) (Koparal 2015). Emodin is an anthraquinone derivative that inhibits vascular endothelial growth factor-A-induced angiogenesis by suppressing the phosphorylation of receptor-2 (KDR/Flk-1), and suppresses cancer cell migration thorough inhibition of the phosphatidylinositol 3-kinase-Cdc42/Rac1 pathway [19,20]. However, emodin is not exclusively presents in lichens but also presents in roots and barks of numerous plants, and molds [21-23]. Similarly, a well-known mycotoxin, secalonic acid-D is not exclusively presents in lichens [24,25]. Guru et al. (2015) reported that secalonic acid-D inhibits hypoxia-inducible factor 1-alpha (HIF1α) and vascular endothelial growth factor (VEGF)-mediated angiogenesis with no significant toxicity by regulating Akt/mTOR/p70S6K signaling cascade [25].

Consequently, there are limited but qualified studies about anti-angiogenic potentials of lichen derived secondary metabolites in the literature, and published papers revealed that these small-molecules have a great potential to be anti-angiogenic agents with low toxicities and significant inhibition of angiogenesis and angiogenesis-related cellular migration. We therefore would like to draw your attention to the small-molecules isolated from lichens as attractive source of anti-angiogenic agents for cancer therapy and treatment of angiogenesis-related diseases.

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