Medicinal Chemistry Research (2019) 28:1039–1048
https://doi.org/10.1007/s00044-019-02358-w

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Viridicatol and viridicatin isolated from a shark-gill-derived fungus *Penicillium polonicum* AP2T1 as MMP-2 and MMP-9 inhibitors in HT1080 cells by MAPKs signaling pathway and docking studies

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Received: 18 February 2019 / Accepted: 8 May 2019 / Published online: 23 May 2019

Abstract

Matrix metalloproteinases (MMPs), the key enzymes in extracellular matrix degradation, seemed to increase in tumorigenesis, which has a relationship with metastasis and invasions. In this study, we investigated the MMP inhibitory effect of viridicatol and viridicatin, two compounds extracted from shark-gill-derived fungus *Penicillium polonicum* AP2T1, on MMP-2 and -9 in vitro and in silico. The MTT assay showed that viridicatol and viridicatin had no cytotoxicity at a concentration of 50 μM on HT1080 human fibrosarcoma cells. In addition, the studies by gelatin zymography and Western blot analysis confirmed that the two compounds effectively inhibited the protein activities and expressions of MMP-2 and -9. Moreover, molecular docking studies simulated and clarified the interaction between compounds and MMPs, respectively. Furthermore, the effect of those two compounds on mitogen activated protein kinases (MAPKs) was also assessed by Western blot analysis. Collectively, these results suggested that viridicatol and viridicatin could be potential inhibitors of MMPs and *P. polonicum* may be a rich source of bioactive compounds with MMP inhibitory property.

Keywords Shark gills · Viridicatol · Viridicatin · MMPs · MAPKs

Introduction

Marine organism can produce a large number of natural products with a novel structure and a unique active mechanism. The development of marine research and the innovation of technology draw more attention toward discovering various compounds. Among them, marine fungi act as a representative (Blunt et al. 2014; Chen et al. 2014; Schueffler and Anke 2014). The secondary metabolites derived from marine fungi and possess diverse structures with rich biological activities and yields. According to their structures, those metabolites are classified into protein, alkaloids, terpenoids, carbohydrates, lipids, nitrogen, heterocyclic compounds, and more (Pietra 1997). This often shows pharmaceutically relevant bioactivities such as anti-tumor, anti-bacterial, anti-viral, anti-inflammation, and other effects (Bugni and Ireland 2014; Moore 2005; Saleem et al. 2007). The metabolic products of marine *Penicillium* are rich and various. It has been well documented that they showed diverse bioactivities including anti-cancer, anti-tumor, and anti-inflammatory effects (Pietra 1997).

Sharks extract their oxygen through gills filter seawaters and this progress provides an opportunity for various marine microbes like fungi to attach to shark sponge-like gills. However, there are a few reports about the fungi derived from sharks gills and the potential biological activities of compounds which are isolated from those fungi (Zhang et al. 2016). Quinolinones, which are typical metabolites produced by *Penicillium*, exhibit a wide range of biological activities such as antioxidant, anti-osteoporosis, anti-influenza, and anti-cancer activities. Some quinonoid

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compounds have been applied for tumor treatment (El-Shafiy and Shebl 2018; Gao et al. 2012). In our early research, two quinolinone compounds were isolated from shark-gill-derived fungi *Penicillium polonicum* AP2T1 such as viridicatol and viridicatin and they had the anti-microbial and anti-proliferative activities (Zhang et al. 2017) Other studies have shown that the two compounds have been found in *Penicillium* in other marine organisms and have anti-inflammatory and other activities (Birkinshaw et al. 1963; Cunningham and Freeman 1953; Ko et al. 2015).

Cancer is one of the most serious threats to human health and life. Many scientists are devoted toward exploring newer, more effective, and low toxicity anti-tumor drugs. Characterized by its ability to degrade the extracellular matrix (ECM) components and metal-dependence, matrix metalloproteinases (MMPs) are a group of endopeptidases (Cortesreynosa et al. 2008) playing essential roles in tumor progression, fibrosis, chronic inflammation, and vascular diseases (Cai et al. 2013). MMP-2 and MMP-9 are known to be involved in processes such as tumor invasion and metastasis (Kim et al. 2010). MMP-2 is a zinc-dependent endopeptidase deemed to be the most direct and important MMP (Gouda et al. 2014) such as human breast cancer (Nguyen et al. 2013). The activation of MMP-2 can degrade the ECM and matrix proteins in tissues such as collagen and fibrin. MMP-9 is similar in this case (Bauvois 2012; Lee et al. 2008). Many experimental results indicated that MMP-2 was overexpressed in brain cancer, breast cancer, lung tumors, melanoma, ovarian cancer, and other types of cancer. It was also closely related to tumor cell migration (Chatzizacharias et al. 2008). Moreover, MMP-9 was thought to play a major role in tumor growth and metastasis because it has a unique ability to degrade type IV collagen (Nguyen et al. 2013)

Mitogen activated protein kinases (MAPKs) provide an important post-translational modification for a number of cellular processes such as cell growth, differentiation, migration, survival, and apoptosis (Zwergel et al. 2017). MAPKs, which are an evolutionarily conserved and common signal transduction superfamily, participates in malignant tumor genesis, invasion, and metastasis (Zhao et al. 2015). Persistent activation of extracellular regulated protein kinases (ERK) in cancer cells can cause an increase induction of MMPs along with an ECM and basement-membrane degradation, which contributes to the cancer cells in terms of invading surrounding tissues (Zhao et al. 2015). Recent studies have shown that the role of the p38 MAPK signaling pathway can induce cell migration of UMUC-3 cells. c-Jun amino-terminal kinases (JNK) is one of the members of the MAPKs family and controls cell cycle, apoptosis, survival, nuclear hormone receptors, and MMPs (Gweon and Kim. 2013).

In addition, as a highly metastatic model, HT1080 fibrosarcoma cell is used to study tumor invasion and metastasis (Selvey et al. 2004). In this study, we investigated the inhibitory effects of viridicatol and viridicatin on MMP-2 and MMP-9.

Materials and methods

Materials

The viridicatol and viridicatin isolated from the marine fungus, *P. polonicum* AP2T1 were obtained according to our previous experiment (Zhang et al. 2017); by interpretation of MS and NMR data as well as by comparison with other references (Wei et al. 2011).

Human fibrosarcoma cells HT1080 were acquired from the Cell Bank of Chinese Academy of Sciences (Shanghai, China). Cell culture media Dulbecco's Modified Eagle's Minimal Essential Medium (DMEM), penicillin/streptomycin, fetal bovine serum, horse serum, and other materials required for culturing cells were purchased from Gibco BRL, Life Technologies (Grand Island, NY). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), gelatin zymography reagents, gelatin A, Triton-100, phorbol-12-myristate-13-acetate (PMA), and other reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA). Antibodies against phospho-ERK1/2 (sc-81492), ERK1 (sc-94), phospho-p38 (sc-166182), p38 (sc-535), phospho-JNK (sc-6254), JNK (sc-345), MMP-2 (sc-6838), MMP-9 (sc-6840), and β-actin goat anti-rabbit IgG were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Horse anti-mouse IgG were from the Cell Signaling Technology (Beverly, MA, USA) company. Protein markers were supplied by Thermo Fisher Scientific. The stock solution of 100 mM viridicatol and viridicatin was prepared in dimethyl sulfoxide (DMSO) and stored at −20 °C.

Cell culture and vitality

HT1080 cells were maintained in DMEM medium supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 U/ml streptomycin in a humid atmosphere of 5% CO_2 and 95% air at 37 °C. The cytotoxic activity of compounds was evaluated in HT1080 cells using the MTT assay. Cells were cultured in 96-well plates (0.5×10^5 cells/well for cells in 100 µl of medium). 100 µl viridicatin and viridicatol solutions were added to each well at a final concentration of 10–100 µM. The cells were exposed to the drug for 24 h. Afterward, the medium was replaced by medium (200 µl) containing 0.5 mg/ml MTT. After 3 h of incubation, the MTT formazan was dissolved in 150 µl

DMSO and the optical absorbance was measured at 570 nm using a microplate reader (BioTek, USA).

Measurement of MMP-2 and MMP-9 activity by zymography

HT1080 cells were seeded in 24-well plates with a density of 2×10^5 cells/ml and pre-treated with different concentrations of viridicatin and viridicatol (10, 20, and 50 μM) for 1 h. The cells were then stimulated by PMA (100 ng/ml) for another 24 h. Cell conditioned medium was subjected to substrate gel electrophoresis. The conditioned medium was then subjected to zymography on 7.5% SDS-PAGE copolymerized with 0.1% gelatin. The gel was washed in 2.5% Triton-X-100 for 30 min to remove SDS and was then incubated overnight in a reaction buffer (50 mM Tris–HCl pH 7, 4.5 mM $CaCl_2$, and 0.2 M NaCl). After incubation, the gel was stained with 0.5% Coomassie brilliant blue in 30% methanol and 10% glacial acetic acid. The bands were visualized by de-staining the gel with water. The mean density of each band was analyzed using ImageJ software (National Institute of Mental Health, Bethesda, MD, USA).

Western blot analysis

HT1080 cells were treated with different concentrations of viridicatin and viridicatol (10, 20, and 50 μM) for 1 h before being incubated with PMA (10 ng/ml) for 24 h. The adherent cells were subsequently harvested, washed twice with ice-cold PBS, and lysed in RIPA buffer containing proteinase inhibitors (1% cocktail and 1 mM PMSF) at 4 °C for 1 h. After centrifugation for 15 min at 12,000×*g* at 4 °C, the protein concentration in the supernatant was determined with a BCA assay kit, according to the manufacturer's instructions. Equivalent amounts of proteins (100 μg/lane) were separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred to NC membranes. Each membrane was blocked with 5% skim milk in Tris-buffered saline with Tween-20 (TBS-T) saline (20 mM Tris–HCl, pH 7.5, 137 mM NaCl, and 0.1% Tween-20) at room temperature for 4 h and then incubated with the indicated primary anti-bodies against MMP-2, MMP-9, ERK, p-ERK, p38, p-p38, JNK, p-JNK, and β-actin overnight at 4 °C. After being washed with TBS-T, the membranes were incubated with secondary anti-bodies (HRP-conjugated goat anti-rabbit or goat anti-mouse IgG) for 2 h at room temperature and visualized with an enhanced chemi-luminescence (ECL) detection system (Syngene, Cambridge, UK). The mean density of each band was analyzed using ImageJ software (National Institute of Mental Health, Bethesda, MD, USA).

Molecular docking

Docking calculations were carried out using Swiss dock, which is a web service for predicting the molecular interactions that may occur between a target protein and a small molecule (http://www.swissdock.ch/) (Grosdidier et al. 2011). Ligand docking and binding site analysis with free software UCSF Chimera (Pettersen et al. 2004). Docking calculations were carried out on MMP-2 (Protein Data Bank Code: 1CK7) and MMP-9 (Protein Data Bank Code: 1L6J) protein models.

Statistical analysis

The data were presented as mean ± SD ($n = 3$). Data were analyzed using the analysis of variance (ANOVA) procedure of Statistical Analysis System (SAS Institute, Cary, NC, USA). Significant differences between treatment means were determined by using Duncan's multiple range tests. The significance of differences was defined at $P < 0.05$.

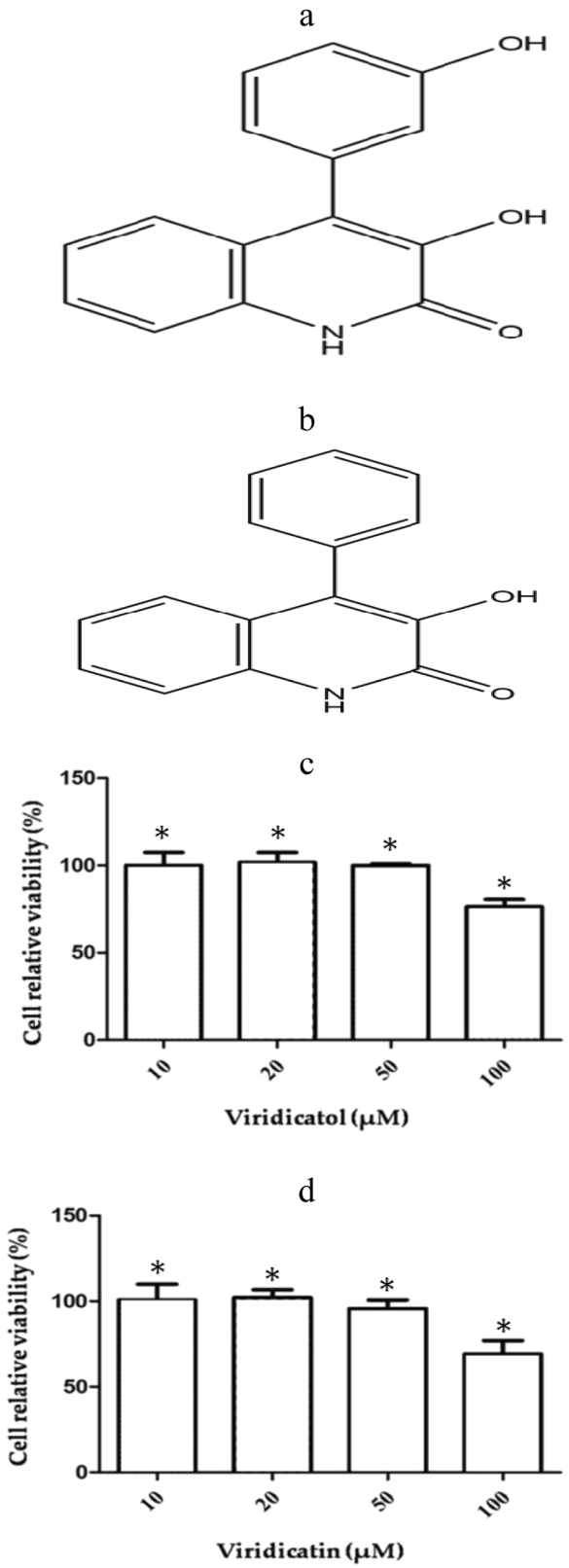
Results

Effect of the viridicatol and viridicatin on cell viability of HT1080

The effect of the viridicatol (Fig. 1a) and viridicatin (Fig. 1b) on cell viability was determined by the MTT assay. This is shown in Fig. 1c, d. The results showed that both compounds had no obvious cytotoxic effect on the cells at concentrations of 10, 20, and 50 μM. In addition, these three concentrations are safe concentrations in subsequent experiments. When the concentration reached 100 μM, both compounds show clear cytotoxicity, which means the subsequent experimental treatment concentrations were set to be 10, 20, and 50 μM.

Determination of MMP-2 and MMP-9 activity by gelatin zymography

The effects of viridicatol and viridicatin on the gelatinase/proteolytic activity of MMP-2 and MMP-9 in HT1080 cells were measured by gelatin zymography. The HT1080 cells were pretreated with different concentrations (10, 20, and 50 μM) of compounds and then stimulated with PMA (10 ng/ml) for 24 h. This is shown in Fig. 2. The cells exposed to PMA (10 ng/ml) enhanced the enzymatic activities of MMP-2 and MMP-9 compared to the untreated group. However, in the presence of viridicatol or viridicatin, the activity of MMP-2 and MMP-9 were decreased in a dose-dependent manner.



◀ **Fig. 1** **a** Chemical structures of the 3-hydroxy-4-(3-hydroxyphenyl) quinolin-2(1H)-one (viridicatol). **b** Chemical structure of the 2,3-dihydroxy-4-phenylquinoline (viridicatin). **c** Effects of viridicatol on HT1080 cells proliferation and survival. The inhibition ratio on cell proliferation was determined by the MTT assay after 24 h of incubation. **d** Effects of viridicatin on HT1080 cells proliferation and survival. The inhibition ratio on cell proliferation was determined by the MTT assay after 24 h of incubation. Data are representative of three independent experiments and expressed as means ± SD. $*P < 0.01$, vs. untreated cells

Effect of the viridicatol and viridicatin on MMP-2 and MMP-9 protein expressions in HT1080 cells

The purpose of this section was to determine whether those two compounds can inhibit the expressions of MMP-2 and -9. As shown in Fig. 3, viridicatol (10, 20, and 50 μM) could significantly inhibit MMP-2 expression in a dose-dependent manner and it was found to be non-effective on the expression of MMP-9. However, corresponding to results obtained from gelatin zymogram, viridicatin (10, 20, and 50 μM) had a clear inhibitory effect on the expressions of MMP-2 and MMP-9 detected by Western blot analysis.

Effect of the viridicatol and viridicatin on MAPKs activation in HT1080 cells

The Western blot analysis was availed to determine whether viridicatol and viridicatin would down-regulate phosphorylation of MAPKs including JNK, ERK, and p38. As shown in Fig. 4, viridicatol (10, 20, and 50 μM) reduced the phosphorylation of p38, JNK, and ERK in a dose-dependent manner. Viridicatin (10, 20, and 50 μM) reduced the phosphorylation of JNK and p38 in a dose-dependent manner. However, ERK was not susceptible to the viridicatin expose. These results suggested that viridicatol reduced MMP-2 and MMP-9 expression by inhibiting phosphorylation of p38, JNK, and ERK. Viridicatin could regulate the phosphorylation of JNK and p38 but not of ERK.

Computational analysis of structure-activity relationships from docking studies

The compounds viridicatin and viridicatol were docked at active sites of the structure of human pro-MMP-2 (gelatinase A-1CK7) and a crystal structure of MMP-9 (gelatinase B-1L6J), respectively. The docking picture obtained from UCSF Chimera in Fig. 5. Viridicatin and viridicatol were docked with MMP-2 and MMP-9, which revealed the lowest estimated energy of binding (−8.82, −7.42, −8.88, and −7.68 kcal/mol) and a greater negative full fitness score

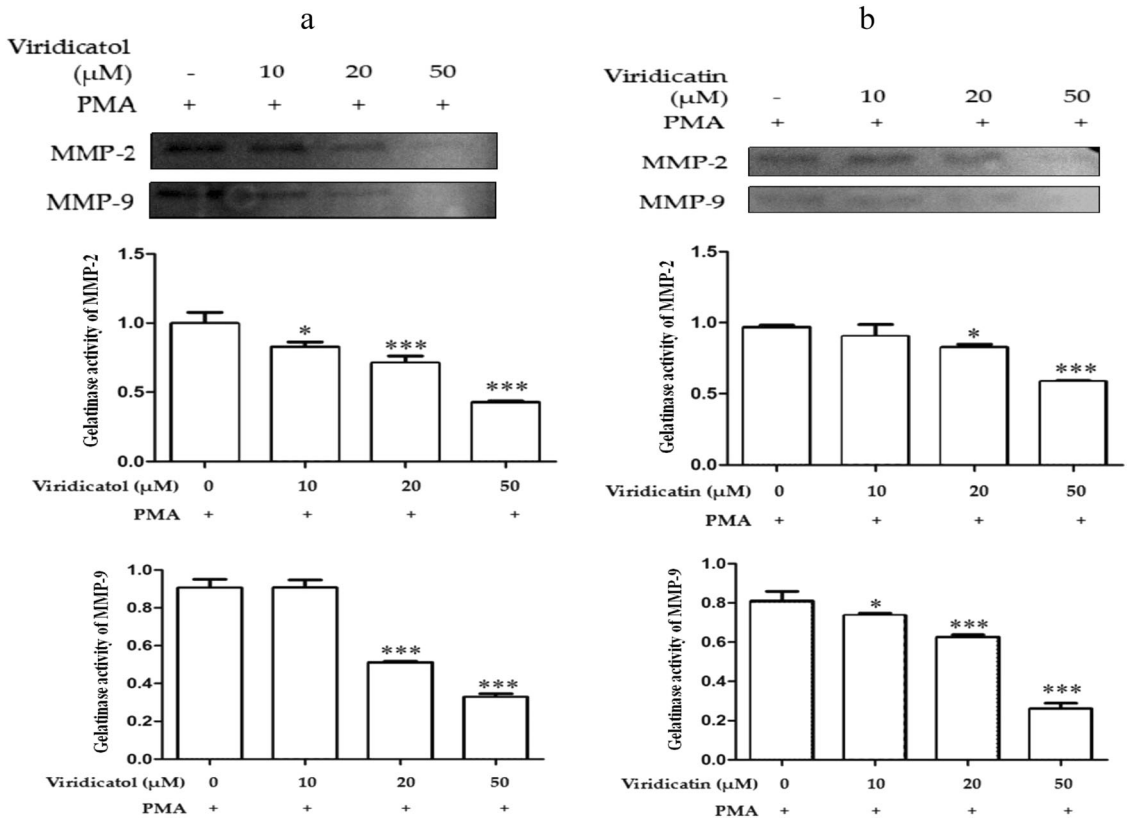


Fig. 2 Effects of viridicatol and viridicatin on activating and expressing MMP-2 and MMP-9 in HT1080 cells. **a** The gelatin zymography for determining MMP-2 and MMP-9 activities in viridicatol-treated HT080 cells. HT1080 cells treated with viridicatol (10, 20, and 50 μM) for 1 h and stimulated by PMA (10 ng/ml) for 24 h. Gelatinolytic activities of MMP-2 and MMP-9 in conditioned media were detected by electrophoresis of a soluble protein on a gelatin containing 10% polyacrylamide gel. **b** Gelatin zymography for the determination of MMP-2 and MMP-9 activities in viridicatin-treated HT080 cells. HT1080 cells treated with viridicatin (10, 20, and 50 μM) for 1 h and stimulated by PMA (10 ng/ml) for 24 h. Gelatinolytic activities of MMP-2 and MMP-9 in conditioned media were detected by electrophoresis of soluble protein on a gelatin containing 10% polyacrylamide gel. Inverting the image used ImageJ. Data are representative of three independent experiments and expressed as means ± SD. $^{*}P < 0.05$, $^{***}P < 0.001$ vs. PMA-stimulated cells

(−3111.72, −1867.33, −3124.23, and −1880.73 kcal/mol). The structures of gelatinase A-1CK7 and gelatinase B-1L6J are bound with viridicatin and viridicatol by hydrogen bonds in Fig. 5b, d, f, g.

Discussion

MMPs are a class of Zn^{2+} endopeptidases involved in many pathological and physiological processes (Sbardella et al. 2012). Under normal conditions, the endogenous inhibitors of MMPs maintain a balance between active and inactive MMPs, but this balance is broken in pathological conditions such as osteoporosis, arthritis, tumor metastasis, cardiovascular disease, and congestive heart failure (Baker et al. 2000; Nikkola et al. 2002; Spinale et al. 1998). Therefore, effective MMP inhibitors that can directly regulate MMP enzyme activity is key for treating tumors (Baker et al. 2000; Edkins et al. 2012). Up to data, many MMPs inhibitors are organic synthesis compounds. However, the odds of making them in clinical applications are very low due to the side effects (Butler et al. 1999). The most representative MMPs inhibitors are Batimastat and Marimastat. As the first generation of inhibitors, Batimastat has the disadvantage of poor solubility, which leads to nausea and vomiting. Marimastat is the second-generation inhibitor and there are obvious adverse reactions such as skeletal muscle pain, inflammation, and severe joint pains (Li et al. 2009). In recent years, the development of MMP inhibitors from natural products has proven to be an effective method. The actual effects of these compounds are determined by their structure. Interestingly, ocean compounds have opened a new perspective for pharmaceutical developments and may fight against multiple tumor types. The discovery of novel natural products to block cancer growth and migration are the key goals of cancer researchers. Consequently, we consider the possibility that both compounds have anticancer effects by inhibition of MMP expression. Our results demonstrate that viridicatol and viridicatin inhibit MMP-2/-9 enzyme activity in HT1080 cells.

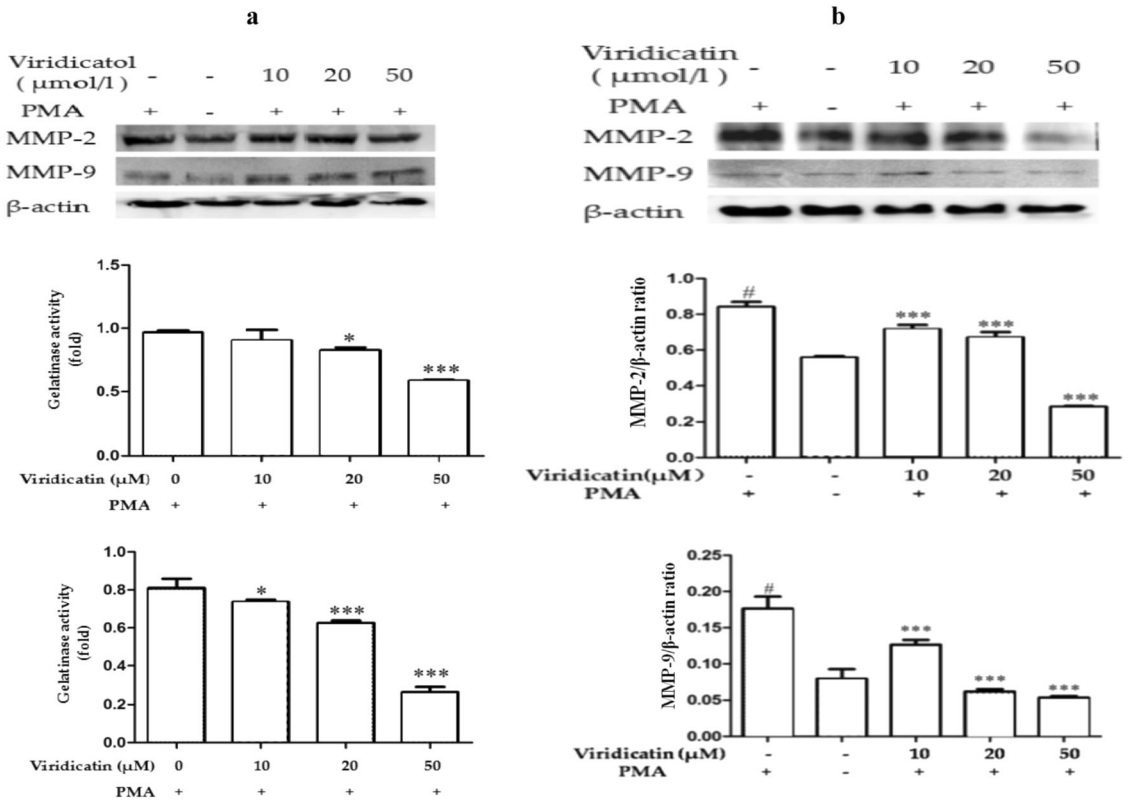


Fig. 3 **a** Inhibitory effect of viridicatol on the protein expressions of MMP-2 and MMP-9 in HT1080 cells. **b** Inhibitory effect of viridicatin on the protein expressions of MMP-2 and MMP-9 in HT1080 cells. Data are representative of three independent experiments and expressed as means ± SD. $^{\#}P < 0.05$ vs. untreated control, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. PMA-stimulated cells

Ocean is rich in natural compounds and it has provided a large number of medical candidates (Kasahara et al. 1992). The ocean area accounts for 71% of the earth's area. Therefore, the ocean is the center of global bio-diversity. There are about 300,000 kinds of marine organisms while a small portion of these may be just marine life. Sharks belong to the cartilaginous fish class and are classified as a type of relatively primitive fishes by modern fish taxonomy. It has a unique historical evolutionary status (Lopez et al. 2013). In the marine ecosystem food chains, sharks are the top predators and play an important role in maintaining the stability of the marine ecosystem (Kong et al. 2008). Until recently, little was known about the fungi found in shark gills and their biomedicinal potential (Zhang et al. 2016). And marine microorganisms are an important source of anti-tumor active substances, such as *Pseudomonas, Agrobacterium, Vibrio, Micrococcus, Bacillus, Enterubacrerium, Alteromonas, Chainiarubra, and Flavobacterium*. Viridicatol and viridicatin from shark gills fungi have been shown to have some biological activities, but the inhibitory activity on MMPs has not been reported (Zhang et al. 2017). Previously, other natural products were reported as MMPs inhibitors such as isorhamnetin 3-O-β-D-glucoside (0.5–10 μM) (Sun et al. 2012), purified abalone oligopeptide (10–100 μM) (Nguyen et al. 2013), and p-hydroxyphenethyl-β-d-glucoside (0–40 μM) (Suojanen et al. 2009). Based on these studies and MTT experiments (Fig. 1), the concentration of 0–50 μM was used for further study. In addition, it has been well documented that PMA can induce the expression of MMP-2 and MMP-9. The expression of MMP-2 and MMP-9 was detected using gelatin zymography combined with Western blot analysis. The results showed that the expression of MMP-2 and MMP-9 decreased in cells pre-treated with viridicatin in a dose-dependent manner (Figs. 2 and 3), but viridicatol could significantly inhibit MMP-2 expression and it was found to be non-effective on the expression of MMP-9. This proves that both compounds different possessed potent anti-metastasis activity for inhibitory effects on cell invasion and migration rather than cytotoxic effects.

To understand the signal pathways involved in the PMA-induced HT1080 cell migration and invasion by activating MMP-2 and MMP-9, we investigated the possible involvement of the MAPKs pathways. The MAPKs signaling cascades including ERK, JNK, and p38 had been shown to be involved in the cell migration of various cancer cell types (Suh et al. 2013). Inhibition of ERK, JNK, and p38 with a specific inhibitor may prevent cell migration in response to a

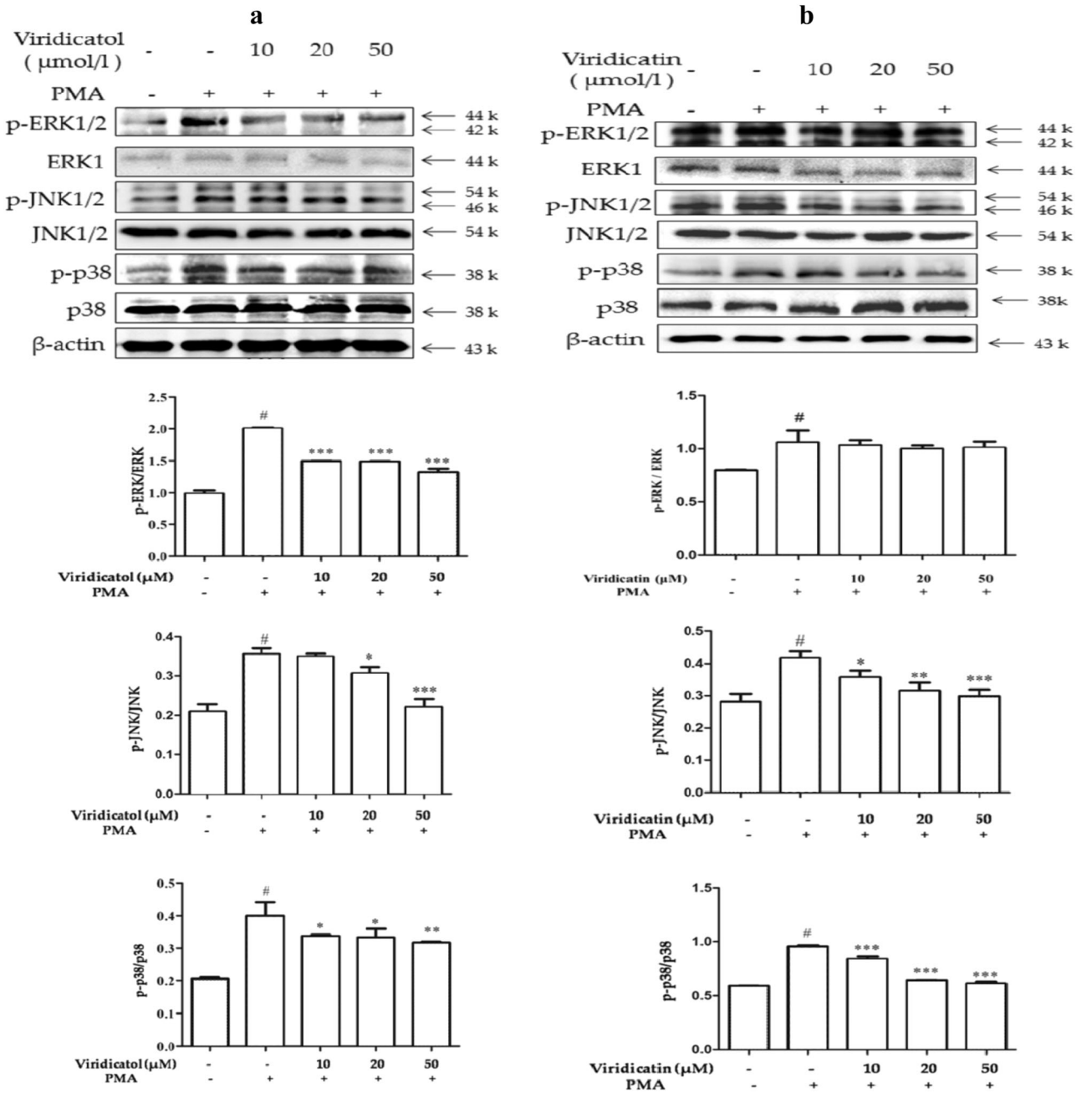


Fig. 4 **a** Effects of viridicatol on the activation of MAPKs. HT1080 cells were treated with various concentrations (10, 20, and 50 μM) of viridicatol for 24 h. The phosphorylation of ERK, JNK, and p38 was analyzed by the Western blotting method. **b** Effects of viridicatin on the activation of MAPKs. HT1080 cells were treated with various concentrations (10, 20, and 50 μM) of viridicatin for 24 h. The phosphorylation of ERK, JNK, and p38 was analyzed by the Western blot analysis. Data are representative of three independent experiments and expressed as means ± SD. $^{\#}P < 0.05$ vs. untreated control, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. PMA-stimulated cells

cellular response stimulator such as fibroblast growth factor or epidermal growth factor (Kong et al. 2008). Our present study showed that viridicatol (10, 20, and 50 μM) reduced the phosphorylation of p38, JNK, and ERK in a dose-dependent manner. Viridicatin (10, 20, and 50 μM) reduced the phosphorylation of JNK and p38 in a dose-dependent manner (Fig. 4). The MMP-2 and MMP-9 expression in HT1080 cells induced by viridicatol and viridicatin correlated with the regulation of the MAPKs pathways. Many inhibitors can inhibit MMPs and MAPKs activity simultaneously. SB203580 decreased the protein expression levels of MMP-2 and MMP-9 concomitantly, indicated that the pharmacological mechanism of silibinin may involve the p38 MAPK signaling pathway (Lu et al. 2017). In previous studies, we have also found that PMA- or TNF-a-induced MMP-9 expression was downregulated by treatment with selective inhibitors of

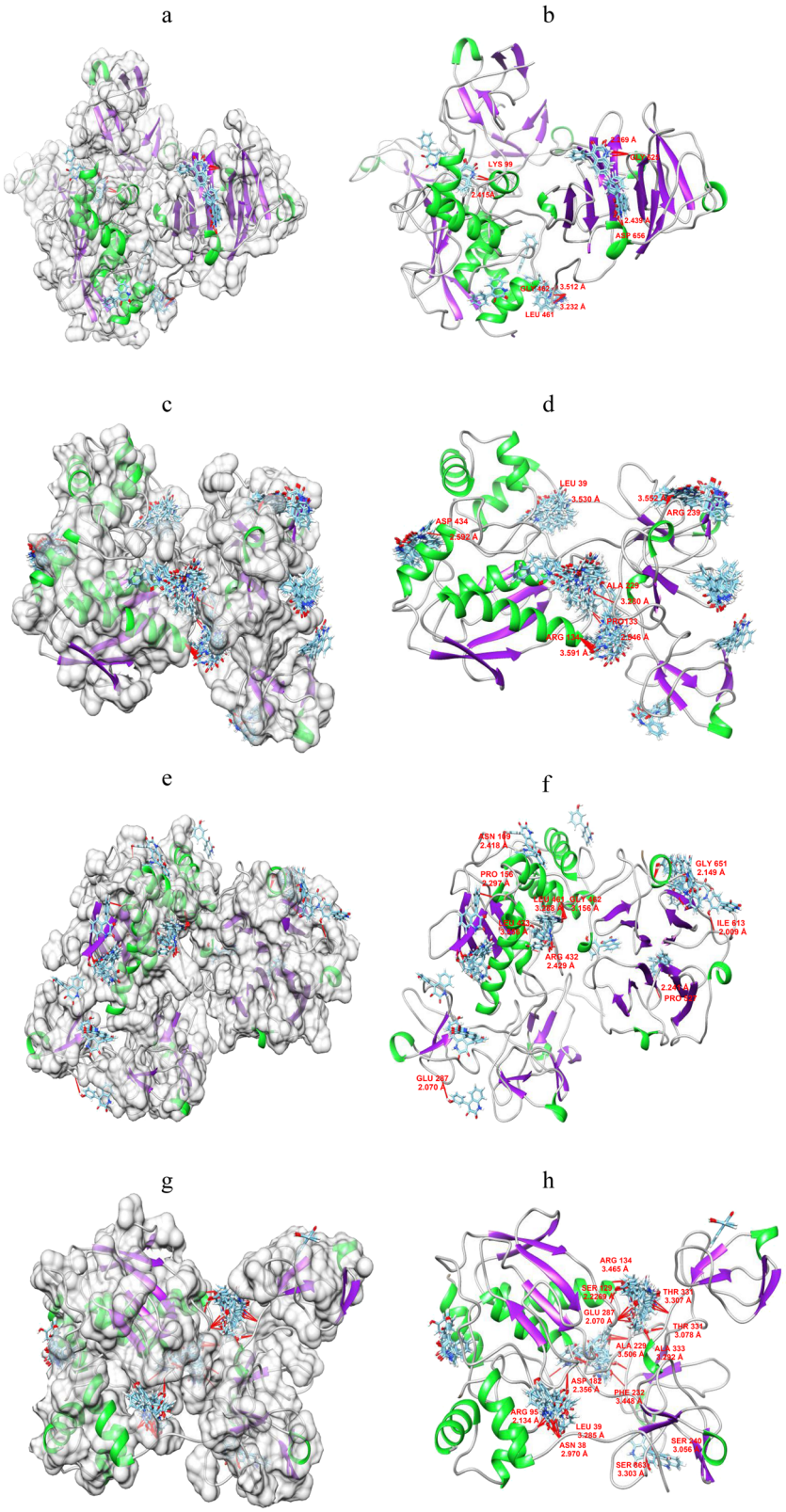


Fig. 5 Docking of viridicatin and viridicatol with MMP-2 and MMP-9 (gelatinase A-1CK7 and gelatinase B-1L6J). **a**, **c**, **e**, **g** The interacting side chains of gelatinase A-1CK7 and gelatinase B-1L6J are displayed in a surface mode. **b**, **d**, **f**, **h** Hydrogen bond interactions of viridicatin and viridicatol with gelatinase A-1CK7 and gelatinase B-1L6J, respectively

the ERK1/2 (U0126), p38 MAPK (SB203580), JNK (SP600125), or Akt (wortmannin) pathways in different cell lines (Jung and Lee 2017). PD98059 significantly attenuated the increased MMP-2 protein induced by propoxur (Hsu et al. 2017). So, we suppose that viridicatol and viridicatin have the same effect as alkaloids.

Quinolinones have structural diversities and many biological activities such as anti-tubercular, antiviral, herbicidal, anti-depression activities, and more. Marine fungi can produce very diverse biologically active compounds including quinolinones (Zhang et al. 2017). Quinolinones, which are the nitrogen-containing alkaloids are well-distinguished for their broad range of anti-tumor, anti-inflammatory, anti-lupus, anti-angiogenic, anti-arthritis, anti-microbial, anti-viral, and anti-fungal properties (El-Shafiy and Shebl 2018). From the molecular docking model, it was also found that both compounds have binding sites with MMP-2 and MMP-9 (Fig. 5), which suggested that two compounds have the possibility to inhibit tumor migration.

In summary, this study investigated the anti-tumor effects of viridicatin and viridicatol on PMA-induced HT1080 cells. The two compounds inhibited the activities and protein expressions of MMP-2 and MMP-9. The present study provides a potential application of these compounds in arresting cancer cell metastasis.

Acknowledgements The study was supported by the Yangfan Scarce Top Talent Project of Guangdong Province and the Program for Scientific Research Start-up Funds of Guangdong Ocean University (201433008 and 201433009). The study was supported by the Basic Research and Free Exploration Grant of Shenzhen Science and Technology Innovative Committee (JCYJ 20170306165013264) and the Department of Science and Technology of Guangdong Province (2013B02100015). The study was supported by Guangdong Tongde Pharmaceutical Co., Ltd. and National Engineering Research Center for Modernization of Traditional Chinese Medicine (Lingnan Medicinal Plant Oil Branch) and funded by Development Project about Marine Economy Demonstration of Zhanjiang City (2017C8B1).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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