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Phloroglucinol, a drug from marine algae could stimulate apoptosis through fas in oral squamous cell carcinoma

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Abstract

Background: Common cloning strategies depend on the enzymatic digestion of the insert. In addition, the enzymatic digestion of PCR product ends by restriction enzymes is of low efficiency. These limitations are related to the need for enzymatic digestion to produce sticky ends in the insert sequence. Hence, in the present study, we aimed to present a new generation of microRNA gene cloning method without using restriction enzymes for constructing the insert, microRNA gene.

Methods and results: In this strategy, by engineering an expression vector's sequence and designing two intelligent primer sets for two consecutive PCR reactions, the microRNA gene sequence with appropriate restriction sites related to the expression vector was produced, without restriction enzymes. The recombinant expression vector was transfected into HEK293 cells, and microRNA-21 expression was assayed in these cells by real-time PCR, confirming the high efficacy of the presented cloning method.

Conclusion: The present method is an inexpensive and reliable method for microRNA gene cloning by providing a high-performance protocol.

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Introduction

Oral squamous cell carcinoma (OSCC) is aggressive cancer resulting in significant morbidity and mortality. According to the Global cancer statistics records of 2018, approximately 18.1 million new cases and 9.6 million deaths occurred due to cancer, among which OSCC accounts for 354,864 cases and 177,384 deaths [1,2]. The pathogenesis of OSCC involves multiple genetic and epigenetic alterations like loss of heterozygosity, allelic loss, hypermethylation, cytogenetic alteration, oncogenes, and tumor suppressor gene alteration [3,4]. The other causative agent may be the prolonged action of a combination of risk factors. The risk factors associated with OSCC involve intrinsic and extrinsic factors like age, gender, race, history of upper aerodigestive tract cancers, tobacco, alcohol, and viruses [5]. The diagnostic techniques of OSCC include vital staining, light-based detection system, histological methods, cytological techniques, molecular analyses, and imaging techniques. Still, several approaches are being experimented with to establish early detection of oral cancer [6]. The treatment for OSCC ranges from early surgical intervention to present next-generation sequencing. Various new approaches are studied to develop an ideal strategy to treat oral cancer. Some are nanotechnology-based approaches, photodynamic therapy, compound-based approaches, and biomaterial-mediated approaches. These approaches have their limitations, opening the gate for an efficient strategy [7].

Recent studies on several marine drugs highlighted their anti-tumor properties against OSCC, including Pardaxin [8], Fucoxanthin, and Ilimaquinone [9]. These compounds target cell proliferation, growth, DNA damage, apoptosis, oxidative stress, and autophagy. Following the above statement, phloroglucinol, a polyphenolic agent derived from brown algae, was studied for its potential anti-tumor and anti-oxidant properties against different cancer types. Cell cycle arrest, apoptosis induction, metastasis inhibition, and angiogenesis make phloroglucinol a significant anti-tumor compound. The other biological activity of phloroglucinol and its derivatives includes antimicrobial [8], anti-oxidant [9], anticoagulant, anti-proliferative [10], anti-inflammatory [11], anti-viral [12], anti-MMP [13], anti-diabetic [14] and Anti-photoaging [15]. Further, the anti-cancer property of phloroglucinol was studied in different cancer types like colon cancer [16], breast cancer [8,17] and liver cell line [18].

In 2017, Eduarda et al. investigated the anti-cancer effect of fucoxanthin and phloroglucinol against colon cells, both alone and in combination with the commercially available compound 5-fluorouracil. As the 5-fluorouracil-based colon cancer therapy became ineffective recently, the search for a new therapeutic compound turned the focus on fucoxanthin and phloroglucinol for their anti-oxidant anti-cancer properties. The human colorectal cancer cell lines (HCT116 and HT29) and normal colon cell lines (CCD-18Co) were used to conduct on to analyze the effect of compounds on cell viability, induction of DNA damage, and cell death using techniques like MTT assay, comet assay, nuclear condensation assay, and Western blot. The result showed that the fucoxanthin and phloroglucinol alone could induce cell death in cancer cell lines without affecting normal cell lines. Similarly, when combined with 5-fluorouracil, these compounds efficiently increased the cytotoxicity of 5-fluorouracil only in cancer cells [16]. Later in 2021, Petchi Iyappan et al. studied the anti-cancer property of fucoxanthin against OSCC. The effect of fucoxanthin on cell proliferation, apoptosis, and oxidative stress in OSCC was assessed using MTT assay, DCFH-DA, Rhodamine-123, and DAPI, and dual staining techniques. The result showed the potential of fucoxanthin to act against OSCC through apoptosis via increased oxidative stress, cytotoxic effect and decreased MMP [19].

Phloroglucinol could diminish cell viability by inducing apoptosis and suppressing cell cycle progression. The process involves several growth factors and signaling pathways, including PI3K/Akt/mTOR, Ras/ERK-MAPK signaling, insulin-like growth factor 1 receptor (IGF-1R) signaling, and apoptotic pathways. Resulting in induced apoptosis and cell cycle arrest via Fas-induced signaling pathways, downregulated IGF-1R protein, and downstream protein involved in mTOR, PI3K, and ERK-MAPK signaling pathways in colon cancer cells (Figure 1) [20]. To evaluate if Fas-mediated apoptosis impacted IGF-1R signalling pathways, a pan-caspase inhibitor was used to treat HT-29 cells, reducing caspase activation and decreasing PI3K and Akt expression levels. As a result, phloroglucinol targets IGF-1R signaling and induces apoptosis with sustained cell cycle arrest [20].

Further, Inhibition of KRAS and its downstream pathways (PI3K/AKT and RAF-1/ERK signaling) helps suppress breast cancer relapse, as reported in the study in Breast Cancer Stem-like Cells (BCSCs) (Kim, 2015). In addition, hypoxia-induced resistance of OSCC to certain drugs prevails to the problem of concern. One of the widely used chemotherapeutic agents, 5-fluorouracil (5-FU), targets cells in the late G1 and S phases and becomes ineffective under hypoxic conditions [21]. Hypoxia suppresses cell proliferation and introduces it to a G1 phase cell cycle arrest. Drug targeting cells at this phase now become ineffective in their activity due to suppressed growth rate and G1 phase accumulation. Recently the cytotoxicity-inducing effect of phloroglucinol on 5-Fluorouracil was reported in colon cancer cells [16]. The inducing mechanism of phloroglucinol on drug differs based on cell line dependence; for example, japonicin A (dimeric phloroglucinol) in combination with chemotherapy drug paclitaxel expressed a synergistic effect in decreasing cellular proliferation of the OVCAR-3 line [22].

Interestingly, there are no studies using phloroglucinol on OSCC to date, but it has shown superior results against other cancer cell lines with good efficacy. With these earlier reports of phloroglucinol on other cancer studies, we hypothesize that targeting cellular metabolism with phloroglucinol would be a novel therapeutic approach to treat OSCC and prevent disease relapse. The study may focus on the cytotoxic effect of phloroglucinol by analyzing the cell viability pre- and post-treatment, DNA damage, Bax expression, measurement of ROS, MMP, lipid peroxide (LPO), anti-oxidant enzymes level, and apoptosis. Also, investigating the potential of phloroglucinol to act as an inhibitor of the essential relapsing pathway could prevent reversions. Hence phloroglucinol can be a potential compound in oral cancer therapeutics. Phloroglucinol enhances the cytotoxicity of 5-Fluorouracil against hypoxia-induced resistant OSCC and could be a novel approach to increase this agent's efficacy and clinical importance. It can be further developed by investigating other commercially available chemotherapeutic agents with similar properties as 5-Fluorouracil to enhance drug activity against cancer or drug-resistant cells. Thus, more studies evaluating the anti-cancer and cytotoxicity enhancing efficacy of phloroglucinol on oral cancer must be encouraged to achieve a new therapeutic strategy to treat OSCC soon.

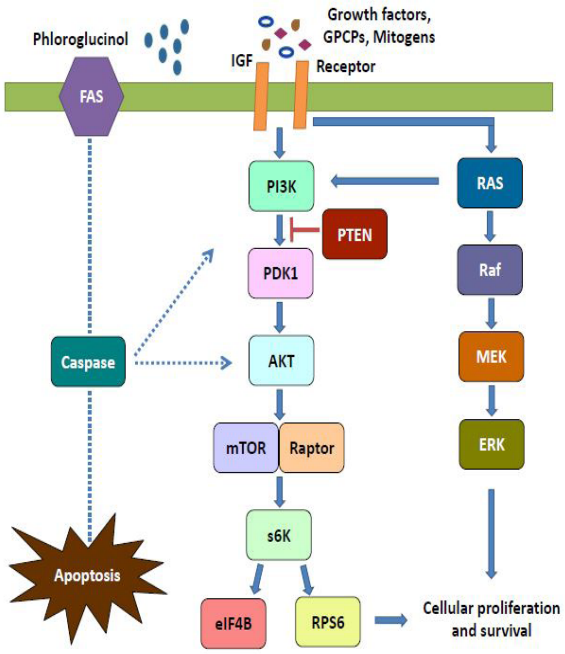

Figure 1: Mechanism of phloroglucinol mediated inhibition of IGF-1R signaling via Fas-induced signaling pathways. Phloroglucinol reduces the expression of IGF-1R and downstream regulatory pathways, namely PI3K/Akt and Ras/ERK-MAPK signaling. It resulted in the inhibition of cancer via increased apoptosis and cell growth suppression.

Declarations

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Conflict of interest statement: The authors declare that there are no conflicts of interest.

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