An Insight on Prodigiosin Mediated Apoptosis

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Abstract

The medications used for cancer treatment is of pivotal importance, so it is very much necessary to search for and to design nontoxic and safe drug formulations. In recent years the natural products are becoming popular as they are efficient in the suppression of the metastasis. Prodigiosin is a red pigment a secondary metabolite with a tripyrrole ring synthesized by microorganisms. The prodigiosin group includes prodigiosin, undecyl prodigiosin and cycloprodigiosin hydrochloride have the ability to induce apoptosis of cancer cells. The presence of pyrrole ring and the C-6 methoxy substituent is responsible for the cytotoxic activity of the prodigiosin. Prodigiosin has proapoptotic activity against cancer cells that are resistant to many drugs. Hence in recent years the pigment prodigiosin appear to be an attractive drug that have been under the focus of extensive research.

Keywords*: Prodigiosin, apoptosis, pigments, anticancer, in vitro cytotoxicity*

1. Introduction

Synthetic colorants have harmful and carcinogenic effects that have been slowly replaced by the natural pigments [1]. The pigments derived from the natural sources are gaining popularity in recent years all over the world [2]. Natural pigments have wide applications in various industrial sectors, including food, cosmetics and health [3]. Microbial pigments are of much interest due to its less generation time and ease of cultivation [4]. Various factors such as temperature, pH, aeration and the composition of the media influence the pigment production in microorganisms.

2. Prodigiosin

The bioactive compound, prodigiosin (2-methyl-3-pentyl-6-methoxyprodigiosin) is found to be produced by bacteria such as *Streptomyces sps*. and Serratia marcescens [5]. Actinomycetes are Gram positive and filamentous having the high G+C content (>55%) in their DNA [6]. Actinomycetes produce red, orange, yellow, brown or black and violet pigments that has been linked to the UV protection, defence and respiratory mechanism [7]. The red tripyrrole pigment, prodigiosin is characterized by a pyrrolyl dipyrromethene skeleton with 4-methoxy, 2-2 bipyrrole ring system [8] has found to have more therapeutic values [9]. There are different classes of prodigiosin including cycloprodigiosin, undecylprodigiosn and metacycloprodigiosin.

3. Cancer

Cancer is a deadly disease of all age group but increases with age. It accounts for 25% of all human all over the world. Cancer is characterized by uncontrolled proliferation of cells that invade and destruct the adjacent tissues and sometimes also spread through blood or lymph to other locations in the body. These properties of cancers differentiate malignancy from self-limited benign tumors, that do not invade or metastasis. Except some cancers like leukemia that do not form tumor, most of the cancers gives rise to a tumor. Although novel therapeutic drugs have been developed for some cancers, still cancer is the second leading cause of death around the world [10].

4. Possible mechanisms of cancer cell apoptosis

Even though the researches showed that prodigiosin can induce cell death on different types of cancer cells, the mechanism of apoptosis is not yet clear. The cellular effects of apoptosis might be cleavage of DNA [11,12], promotes the movement of proton and chloride ion, by the acidification and disruption of the pH gradient in various cellular compartments and DNA intercalation cell cycle arrest in late G1 and capase activation [13,14,15]. *In vitro* study suggested another possible mechanism of apoptosis, the inhibition of protein phosphatase activity [16, 17] (Fig. 1).

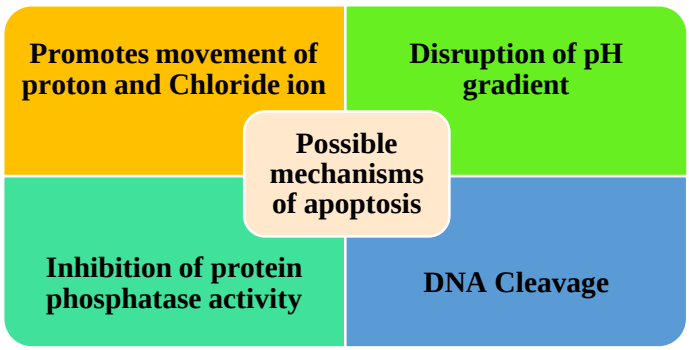

Figure 1: Mechanisms of apoptosis

5. Apoptotic pathways

Apoptosis is a normal process of auto destruction of cells in which the fragmentation of DNA is initiated with the single stranded breaks that produce double-stranded (ds) fragments, which upon cleavage produce olignucleosomal ladders.

The malfunctions of apoptosis lead to cancer an uncontrolled cell growth and multiplication. The process of apoptosis can be studied by the morphological and biochemical changes. The morphological changes of cells during the apoptosis are the nuclear chromatin becomes compact, the cytoplasm becomes condensed, margination and partition of nucleus and cytoplasm into vesicles bound by membranes and may contain nuclear fragments [18].

The two pathways involved in chromatin processing includes capase-dependent and the capase independent pathways (Fig.2). The former involves capase activated DNase (CAD) and the later involves apoptosis-inducing factor (AIF) for the largescale DNA fragmentation and peripheral chromatin condensation [19].

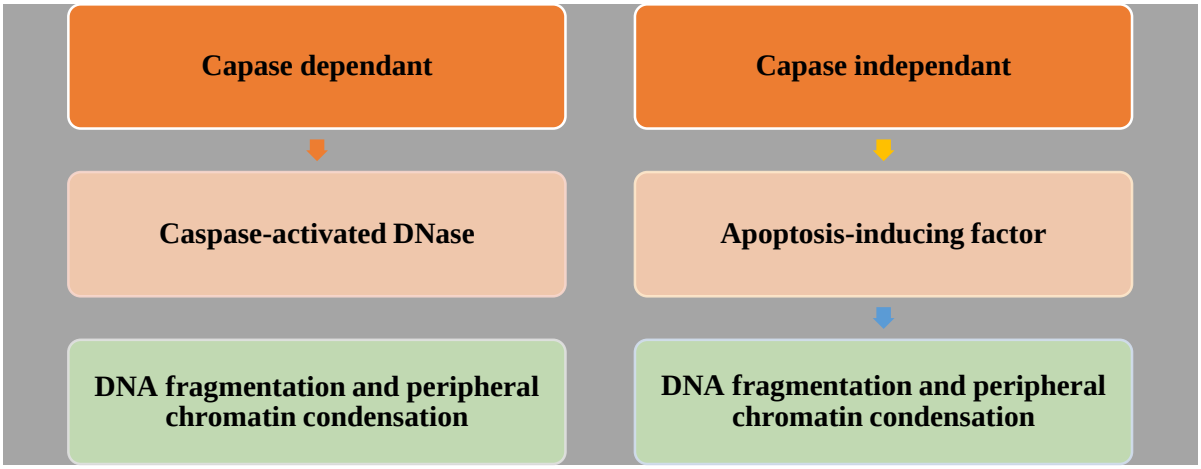

Figure 2: Pathways of apoptosis

6. Autophagy the cellular process

Researches suggested that prodigiosin causes cell death by a cellular process known as autophagy. Autophagy causes vesicles in the cell called autophagosomes that digest damaged organelles or proteins [20] due to this, autophagy might regulate apoptosis in cancers [21]. It has been shown that prodigiosin treatment induced the death of glioblastoma cells and reduced neurosphere growth [22] due to increased autophagy in the cancer cells. Studies also shown the colorectal cancer cells treated with a common chemotherapeutic drug 5-fluorouracil showed increased apoptosis in the presence of prodigiosin [23]. Prodigiosin promoted apoptosis in the cancer cells synergistically with 5- fluorouracil by impairing the autophagic flux.

In another study the combination of the drug PU-H71 and prodigiosin for triple negative breast cancer induced apoptosis and killed cancer cells effectively in metastatic breast cancer cell line [24].

7. Combination therapy

This suggested the combination therapy for cancer treatment in recent years [25]. As prodigiosin works synergistically with the commercially available cancer drugs, it can be used for cancer therapy either in combinations or in single. It is unknown, nevertheless, if this activity can truly lead to a cancer patient's being treated.

The prodigiosin has proapoptotic effect on cancer cells via the regulation of apoptotic and antiapoptotic genes 20 which is regardless of p53 status. The *in vitro* and *in vivo* studies with human choriocarcinoma (JEG3) and prostate cancer cell lines (PC3) showed that prodigiosin induces apoptosis in both the cells with the higher expression of protein makers such as P53 and Bax/Bc1-2 than in the untreated control groups [26].

8. In vitro cytotoxic effect on cell lines

Recent studies revealed that prodigiosin kills human cancer cell lines in vitro. Researches revealed prodigiosin can induce apoptosis and has anticancer effects on haematopoietic cancer cells [27], human lung cancer cells [28], B cells and T cells in chronic lymphocytic leukemia [29], gastric cancer cells [30], multidrug resistant breast cancer cells [31], colorectal cancer cells [32] and glioblastoma multiforme cancer cells [33].

In vitro studies showed prodigiosin has cytotoxic effect on cancer cell lines such as A549, HepG2, MCF-7 and WiDr cells with IC_{50} = 0.006, 0.04. 0.04 and 0.2 µg mL^{-1}, respectively. It was found to be 2.75 fold, 1,67 fold and3.25 fold more efficient IC_{50} value of mitomycin C, a well- known anticancer drug [34]. Further studies also showed the anticancer effect of prodigiosin on MDR, BCRP or MRP2 [35] and has less effect on normal cells. The anticancer activity of prodigiosin in more than 60 different cancer cell lines showed the average IC_{50} value of 2.1 µg/mL. Prodigiosin from the actinomycetes showed IC_{50} value of 62.50 µg/ml on HeLa cell lines by the MTT assay. This shows that actinomycetes pigment prodigiosin had a potent apoptosis in a dose dependent manner against HeLa cells [36]. This proves prodigiosin to be a powerful proapoptotic agent against various cancer cell lines.

The *in vivo* study in mice by Fullan et al., in 1977, showed the antitumor activity of prodigiosin, this specify the cytotoxic properties of prodigiosin have been known for many years [37]. The prodigiosin reacts with a specific target cancer cell to undergo apoptosis [38].

It effectively causes apoptosis in hematopoietic cancer cells, breast cancer [39], digestive cancer cell line HGT-1 [31], large intestinal cancer cells [18] and respiratory cancer cells [40]. However, no toxicity shown on non-malignant cells [28].

9. Clinical trials of prodigiosin

Breast cancer is a malignancy that occurs in the lobules, the glands for milk production or in the ducts that connects the lobules to the nipple [41]. Breast cancer is divided into four subgroups, e.g., ER- positive luminal type, basal type, HER2 enriched and normal-like. Triple-negative breast cancer (TNBC) lack ER, PR & Her2/neu receptors on their cells, which makes them difficult for targeted therapy [44]. Hence it is focused towards the engineered therapy to target the receptors with novel approaches [43].

Wnt/β- catenin signalling pathway plays an important role in the homeostasis tissue. Wnt pathway gets activated by the mutations or the epigenetic changes that contributes to the initiation and development of cancers [44-47]. In phase I and phase II clinical trials of cancer patients, the obatoclax, analogue of prodigiosin [48] has been used [49-50]. However, the results of these clinical trials have not confirmed whether prodigiosin is useful for cancer therapy.

10. Conclusion

To understand the detailed mechanism of apoptosis or cytotoxicity of prodigiosin, researches have to be carried out at the molecular level. With the studies so far made and the positive results obtained, it has been identified that the prodigiosin from microorganism possessed strong and high promising anticancer property against cancer cell lines. It is concluded that prodigiosin could be used to treat cancer with multi drug resistant phenotypes or defects in apoptotic pathways with no adverse effects on normal cells.

11. Conflicts of interest

The authors report no conflict of interest

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