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Plant-derived flavone Apigenin: The small-molecule with promising activity against therapeutically resistant prostate cancer

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ABSTRACT

Prostate cancer is the second leading cause of cancer related deaths in men in the United States. Mounting evidences suggest that in the pathophysiology of prostate cancer epigenetic modifications play a considerable role. Histone deacetylases (HDACs) have strong crosstalk with prostate cancer progression as they regulate various genes meant for tumour suppression. HDACs are emerging as striking molecular targets for anticancer drugs and therapy as their aberrant expression has been implicated in several cancers. Histone deacetylase inhibitors (HDACi), the small molecules interfering HDACs are the propitious chemotherapeutic agents as they tune the altered acetylation homeostasis for attenuating disease signalling. More than 20 HDACi have entered into the clinical trials and 4 have crossed the journey by gaining FDA approval for treating distinct haematological malignancies including multiple myeloma. Despite the therapeutic benefits, the synthetic HDACi cause detrimental side effects like atrial fibrillation, raising concerns regarding their applicability. Taking these facts into consideration the current article focused on plant-derived HDAC inhibitor Apigenin and its marvelous role in prostate cancer therapy. Moreover, the article sheds light on Apigenin induced apoptosis in various prostate cancer models. The defined inhibitor provokes apoptotic signaling in these models by multiple mechanisms like restraining HDACs, declining the levels of antiapoptotic proteins. Importantly, Apigenin hampers NF-κB signalling and down-modulates its regulated gene products for bringing therapeutic effect. Furthermore, Apigenin shows synergistic effect in combinatorial therapy and induces apoptosis even in prostate cancer models resistant to conventional therapeutic regimens.

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1. Introduction

It is well-established that aberrant gene functions and altered patterns of gene expression play a considerable role in the biology of cancer [1]. This impaired gene expression is the outcome of epigenetic dysregulation. Gene silencing forms the etiology of myriad of human diseases including cancer and neurodegeneration. Critical processes responsible for epigenetic gene silencing include DNA methylation, post-translational modifications of histones, non-coding RNAs and nucleosome positioning. Post-translational modifications, particularly histone acetylation and deacetylation, occurring on the amino terminal tails of histone proteins are decisive in determining epigenetic regulation [2–4]. Histone acetylation, the dynamic post-translational modification is tightly regulated by antagonistic activity of histone acetyl transferases (HATs) and HDACs [5]. HATs add acetyl moiety to the lysine residues of nucleosomal histones creating the open chromatin topology by enhancing electrostatic repulsion between polyanionic DNA and polycationic histones [5–7]. HDACs erase acetyl group deposited by HATs and thus create closed chromatin conformation by enhancing electrostatic attraction between histones and DNA (Fig. 1). This results in chromatin compaction and subsequent gene silencing [8]. HDACs deacetylate many non-histone targets as well and this discovery has triggered a new wave for further research in this novel arena [9]. HDACs play a key role in regulating distinct cellular processes. Class I HDACs play a substantial role in cell cycle regulation, cellular proliferation and in regulating smooth muscle contractility [10,11]. HDAC6 regulates vital processes like cell migration, cell stress, protein folding and immune synapse formation [12,13]. This HDAC deacetylates alpha-tubulin protein and its aberrant expression has been reported to trigger prostate cancer by stabilizing androgen receptor [14]. Further, HDAC6 and HDAC10 have been found to play a significant role in heat shock protein (Hsp)-mediated vascular endothelial growth factor receptor (VEGFR) regulation [15]. The ability of modulating multiple targets makes HDACs as central regulators of several diseases including cancer. HDAC overactivity has been positively correlated to altered cell cycle regulation, enhanced proliferation and angiogenesis besides induction of various oncogenes. Therapeutic intervention with small molecule HDACi have shown promising results in solid and haematological malignancies, cognitive disorders and ischemic strokes [16,17]. Recent studies have demonstrated that the plant-derived molecules like sulforaphane, chrysin, pomiferin and Apigenin show HDAC inhibitory activity [18–21]. In human epidermal growth factor receptor 2 (HER2/neu)-overexpressing breast cancer cells, Apigenin has been found to induce apoptosis in a dose and time dependent fashion. While Apigenin showed direct inhibitory activity towards phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3 K), it inhibited a serine/threonine kinase (Akt) indirectly. Moreover, Apigenin induced proteasomal degradation of HER2/neu through polyubiquitination [22]. Therapeutic intervention with Apigenin has shown substantial antiproliferative effect against human breast cancer cell models (MDA-MB-453) human breast cancer cells in a concentration and time dependent manner. Apigenin-induced apoptosis in these cells has been found to involve both intrinsic and extrinsic mechanisms as evidenced by the activation of caspases of both pathways [23]. Apigenin in combination with 5-Fluorouracil has been reported to have antiproliferative effect in breast cancer cell model resistant to latter. These cells (MDA-MB-453) overexpress ErbB2 (HER2) whose levels remain unchanged on singlet therapy involving 5-Fluorouracil [24]. The combined therapeutic regimen showed marked reduction in ErbB2 levels. Moreover, inhibition of Akt expression has been seen on combined treatment emphasizing that 5-Fluorouracil acts synergistically with Apigenin restraining cell growth and inducing apoptosis by down-modulating ErbB2 expression and Akt signalling [24]. Apigenin has been found to induce DR5 expression through p53 independent mechanism. This inhibitor in combination with TRAIL synergistically enhances the apoptosis induced by latter in human malignant tumor cells. These findings clearly suggest that the combination of these inhibitors may prove as a promising therapeutic strategy for cancers having inactivated p53 [25]. Therapeutic intervention with Apigenin inhibited growth and increased apoptosis in pancreatic cancer cell models (BxPC-3, MiaPaCa-2). This effect was found to be dose and time dependent. Moreover, p53 post-translational modifications, its nuclear translocation, DNA binding, p21 and p53 upregulated modulator of apoptosis (PUMA) upregulation were all enhanced on Apigenin based pharmacological intervention, in both these p53 mutated models [26]. Apigenin inhibited proteasomal chymotrypsin-like activity resulting in induction of apoptosis in MDA-MB-231 cell and xenograft models. Despite, the antibreast tumour activity, Apigenin showed no overt toxicity to the tested animals which determines its safety and clinical relevance [27]. Keeping in view the aforementioned facts the current article focuses on plant derived HDAC inhibitor Apigenin and its promising role in prostate cancer therapy along with the underlying signalling mechanism being involved. Importantly, the article provides extensive details regarding the therapeutic strategy that can be used for circumventing therapeutically challenging cases and for enhancing the therapeutic efficacy of this promising small molecule in the forthcoming future.

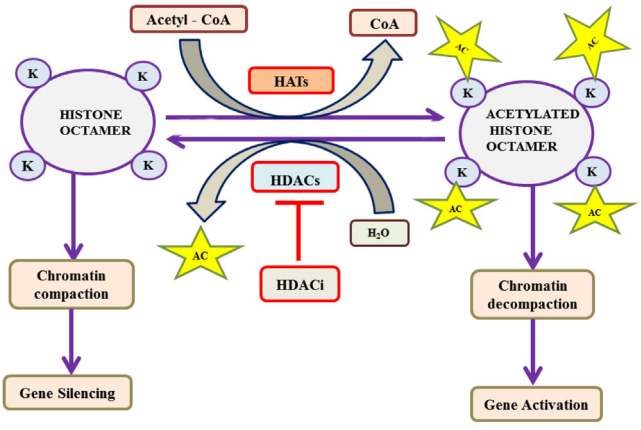

Fig. 1. Mechanism of action of HATs and HDACs. While HATs add acetyl moiety(Ac) to the lysine (K) residues of nucleosomal histones, using acetyl coenzyme A as cofactor and result in gene activation, classical HDACs act antagonistically, erase the acetyl group deposited by HATs culminating in gene silencing. HDACi, the small molecules interfering HDACs augment the acetylation status of histones facilitating transcriptional activation.

2. Distinct classes of HDACs

2.1. Classification based on similarity to yeast HDACs

HDACs are emerging as promising targets in cancer therapy and neurodegeneration. HDACs, the conjugated protein enzymes are