Tumor suppressor protein p53 activating natural scaffolds as anticancer agents

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Abstract:

The tumor suppressor protein p53 has been extensively studied in the area of cancer research. The unbelievable findings of ayurveda or phytochemical studies have provided another opportunity to target p53 protein for treatment of cancer or related conditions. Almost every anticancer agent, including natural products, activates p53 directly or indirectly to induce arrest of cell cycle and apoptotic death in cancer cells. However, there are various underlying pathways involved in the activation of p53. Several phytoconstituents and their derivative have been reported as potential anticancer agents and some are being used clinically such as resveratrol, dulxanthone A, silibinin, camptothecin, paclitaxel, ellipticine etc. These agents activate p53 by phosphorylation *via* acting on different anticancer targets such as DNA damage, topoisomerases, kinases etc. Here, we provide the mechanistic detail on activation of p53 by these agents to induce death of cancer cells.

Keywords: p53, resveratrol, dulxanthone A, silibinin, camptothecin, paclitaxel, ellipticine.

Introduction:

Tumor suppressor p53 is a homotetrameric transcription factor that plays important role in maintaining the cellular homeostasis through the cell cycle arrest, senescence and apoptosis [1]. Anyway, p53 is involved in the induction of apoptotic cell death in cancer cells either through transcription pathways or through non-transcroptional pathways [2]. The various phytoconstituents and their derivatives have been developed for treatment of different types of cancer as a single agent or in combination with other anticancer agents [3]. Some of these agents are resveratrol, dulxanthone A, silibinin, camptothecin, paclitaxel and ellipticine which induce the activation of p53 for their anticancer activities (**Fig. 1**). One of significance of these natural scaffolds is activation of both wild-type as well as mutant p53 proteins [4]. The activation of p53 involved its phosphorylation after DNA damage which in turn transcriptionally activates different apoptotic factors to initiate cell cycle arrest and death of cancer cells [5]. Although, p53 itself induced apoptosis by activating downstream caspases through intrinsic and extrinsic pathways [6]. Here, we provided an updation on induction of p53-mediated apoptosis in cancer cells by six natural scaffolds. Additionally, their structures and IC_{50} values included for comparative characterisation of features and anticancer potencies.

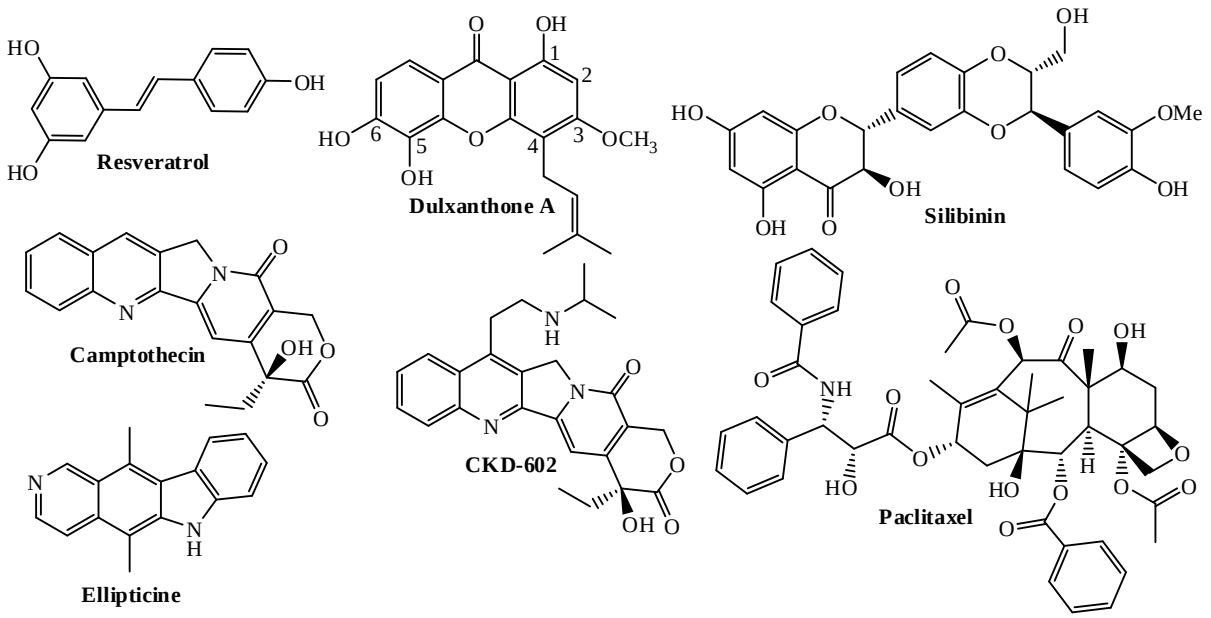

Fig. 1: Structures of phytoconstituents as activators of p53.

1. Resveratrol

Resveratrol is a phyto-atexin which is present in more than 72 plant species, dominantly in skin of grapes [7-9]. It has been found to be one of the most potential, effective and promising cancer chemopreventive agents. In mammary and skin cancer models, it has been shown anti-carcinogenic activity with higher potency [10]. Additionally, resveratrol has been found to be associated with antitumor activities in different types of tumors in a concentration and duration dependent manner [11-13]. Resveratrol inhibits formation of tumor by inducing inhibitory effects at different stages of tumor such as initiation stage, promotion stage and progression stage. However, the exact molecular mechanism and pathways of anti-cancer activities of resveratrol are still not well defined. This indicates involvement of multiple targets in the anti-cancer effect of resveratrol. In a study, Lin *et al.* have been reported that resveratrol induces p53 activation through the mitogen activated protein kinase (MAPK) mediated phosphorylation of p53 at amino acid residue Ser15 [14]. Then activated p53 binds to oligonucleotide segment of DNA specified for p53 binding in DU145 prostate cancer cell lines to induce arrest of cell cycle and apoptotic cell death. Later, Haider *et al.* have been reported that phosphorylation of amino acid residue (Ser15) in p53 by resveratrol which in turn promotes interaction between p53 and p300 (a cAMP response element-binding protein). The overall effect of this interaction resulted in the stabilization as well as activation of p53 to enhance its transcriptional activity [15]. These events finally lead to initiation of cell cycle arrest and apoptotic death in cancer cells through multiple mediators.

2. Dulxanthone A

Dulxanthone A (1, 5, 6-trihydroxy-3-methoxy-4-(3-methyl-2-buten-1-yl)-9H-xanthen-9-one) is a 4-prenylated xanthone and present in the Garcinia plant species [16, 17]. Earlier, dulxanthone A has been reported to induce cell cycle arrest and apoptotic death in human liver cancer cell line (HepG2) though upregulation of level of p53 at the concentration ranging between 20-40 μg/ml. The *in vitro* study showed that dulxanthone A treatment upregulate mitochondrial apoptotic proteins PUMA, Apaf-1, cytochrome C, procaspase-9 and activation of caspases to induce apoptosis. While, cell cycle related proteins p27/21, cdc-2, and cyclin A/B/E were found to be

downregulated [18]. Xia *et al.* have also been reported that different xenthones, including dulxanthone A, from extract of *G. cowa* induce arrest of cell cycle and apoptotic cell death in the different types cancer cell lines with higher selectivity as compared to normal cells [19]. Kaennakam *et al.* reported the cytotoxic effect of dulxanthone A and other xanthones from bark of *G. schomburgkiana* in HepG2, HeLa, HT29, MCF7 KB, and S3 cell lines [20]. However, dulxanthone A showed less potency (IC_{50} = 34.69-65.65.26 µM) as compared with some other xanthones (IC_{50} = 1.45-9.46 µM). Further, structure activity relationship study indicated that presence of 1, 1-dimethylallyl and -OH groups at position-4 and 5/6 enhanced the cytotoxic activity.

3. Silibinin

Several studies have been shown that phosphorylation at different amino acid residues, including Ser15, of p53 increase the accumulation as well as activation of p53 in different cell lines depending on DNA damage or type of apoptotic stimuli. The Ser15 phosphorylation of p53 leads to the translocation of active p53 to the mitochondria to initiate the intrinsic pathway of apoptosis in cancer cells [21]. However, the activation of p53 will lead to intrinsic or extrinsic pathway of apoptosis is mainly dependent on the types of cell and apoptotic stimuli.

Silibinin is a phytoconstituent with three aryl ring systems in which two terminal aromatic ring systems attached to the central ring are oriented *Trans* from each other. This agent belongs to the flavonolignan category of phytoconstituents. It has been found to induce arrest of cell cycle, cell growth and apoptosis in human bladder cancer cells in a concentration dependent manner in both *in vitro* and *in vivo* models. Similar to resveratrol, the exact molecular mechanism of anti-cancer activity of silibinin is still remains to be explored. However, studies suggested that silibinin induce anticancer effect by acting on multiple targets in the cancer cell lines. In a study, Tyagi *et al.* identified that silibinin also induces phosphorylation of Ser15 amino acid residue of p53 through the activation of ATM-CHK2 kinase pathway. Further data indicated that phosphorylated p53 (active form of p53), in turn, induces activation of caspases (especially caspase 2) *via* activation of c-Jun N-terminal kinases 1 and 2 (JNK1/2). The activation of caspase 2 initiates stimulation of caspase-cascade for intrinsic (mitochondrial) apoptosis pathway in human bladder cancer cells [22]. Moreover, active p53 translocates and binds with DNA in the nucleus to induce transcription of variety of factors involved in apoptosis and arrest of cell cycle. Additionally, it also downregulate the factors involved in grown and division of cell by suppressing their transcription.

4. Camptothecin

Camptothecin is an alkaloid consisting of pyrano-indolizino-quinoline fused ring system and obtained from stem and back of a Chinese tree, *Camptotheca acuminate* (also known as happy tree). The (S)-(+)-camptothecin and its derivatives have found to be associated with promising anti-cancer activity in clinical trials for treatment of various cancers such as lung cancer, cervical cancer and other malignancies [23-26]. These compounds exhibit high stereospecificity and selectivity for topoisomerase I (topo I) for reversible binding at interface of DNA-topo I complex to prevent the religation step [27] and this resulted in DNA fragmentation. The damage of DNA activates ATM kinases which in turn phosphorylates different targets to induce cell cycle arrest and apoptosis.

Carson et al. have been reported that captothecin at the concentration of 10 μM induces apoptosis in HeLa cells with increased expression of p53 and significance modification in p53-regulated genes [28]. The phosphorylation of p53 stabilizes it and activates several apoptosis related genes depending of cell types. Camptothecin induces phosphorylation at Ser15, Ser392, Thr387, mediated by ATM, CHK1/2, in different cancer cell line [29-31]. The camptothecin induced activation of p53 may be mediated by NF-κB [32] and calpains [33]. Ray *et al.* reported that camptothecin does not induce the apoptosis in the cell lacking p53 [34]. Lee *et al.* reported that camptothecin analogue, CKD-602, induces activation of p53 through the phosphorylation at Ser15 in both *in vitro* and *in vivo* cervical cancer model [35]. The results indicated that CKD-602 (IC_{50} = 30-150 ng/ml) enhances the expression of cyclin B1, p53/$p53^{p}$, PARP/cleaved-PARP (DNA repairing enzyme) and BAX (death inducer protein) to induce cell cycle arrest and apoptosis.

5. Paclitaxel

Chemically, paclitaxel belongs to the tetracyclic diterpenoid class of phytoconstituents and was obtained from bark of Taxus brevifolia (a native tree of Pacific regions of America). It is widely used successful anticancer drug for treatment of various types of cancers such ovarian, breast, lung, head and neck cancers [36]. It has also been shown effectiveness in the anaplastic thyroid cancer and other malignancies [37, 38]. The anticancer mechanism of paclitaxel is well explored as it targets microtubules in proliferating cancer cells to induce microtubular hyperpolymerization and stabilization. The hyperpolymerized and stabilized microtubules induce several un-repairable defects cell cycle that lead to cell death [39-41]. Previous studies have been indicated that paclitaxel induces phosphorylation of p53 at Ser20 through the activation of hCHK2, an event necessary for p53 stabilization and thus, increase in p53 level [42-46]. However, the detailed of molecular mechanisms of its anticancer activity on the machinery of cell cycle is still remains unclear. Paclitaxel has also been shown effectiveness as cytotoxic agent in p53 deficient cells [47]. Pushkarev *et al.* [48] reported that low doses (25 nM) of paclitaxel promotes G1/S transition by inducing Pin1, thus exhibiting mitogen-like effect. This effect found to contribute to apoptosis through the p53 induced transcriptional activation of p73 as a lead mechanism for anticancer activity of paclitaxel. In contrast to apoptosis, paclitaxel also induces necrosis-like cell death at higher doses (100-1000 nM) and decreases expression levels of Pin1 which may be contribute as a major reason for arrest of cells in G2/M cell cycle.

6. Ellipticine

Ellipticine is an alkaloid consisting of tetracyclic pyridocarbazole system and first time extracted from the *Ochrosia elliptica* Labill tree (a native of north-eastern Australia) of Apocynaceae family in 1959 [49]. Woodward *et al.* have been reported the first chemical synthesis of ellipticine and subsequently various strategies for its synthesis have been uncovered along with its derivatives [50-55]. Ellipticine and its derivatives have been shown potent anti-cancer activities limited side effects [56-59]. They act primarily through the inhibition of topoisomerase II and DNA-intercalation [60, 61]. Earlier, Kuo *et al.* have been shown that ellipticine induces apoptotic cell death in a dose and duration dependent manner (IC_{50} = 4.1 μM) in HepG2 cell line through p53-mediated pathway [62]. It induces cell death through autophagy and apoptosis through p53 activation in cooperation with Akt and induces apoptosis in mutant p53 cells along with restoration of its transcriptional

functions [63, 64]. The ellipticine derivative, NSC176327, has been reported to induce arrest of cell growth, cell cycle and apoptosis with high potency (IC_{50} = 0.5-1 μM) through non-genotoxic activation of p73 in p53-dfficient HCT116 cells [65]. Recent study by Gębarowski has also been shown that ellipticine restores the functional activation of mutant p53 and induces cell cycle arrest and apoptosis in CCRF/CEM cell line at the concentration range 0.1-1.0 μM [66]. In a molecular docking study, Omar and Tuszynski have been shown that ellipticine and its (9-OH)-ellipticine binds with mutant p53 by interacting with Cys124 backbone. The (9-OH)-ellipticine also showed arene-H interaction to Cys124 side chain. This study also suggested rescue of mutant p53 by ellipticine through the conformational changes in the protein structure [67]. However, from above studies, it may be concluded that ellipticine acts by affecting multiple targets to induce anticancer activity in different cancer cells.

Conclusion

Natural product containing phytoconstiuents act by activation of p53 through different mechanisms and pathways to induce cell cycle arrest and apoptosis. This activation involved phosphorylation of p53 at different amino acid residues by kinases. However, activation of mutant-p53 undergoes conformational changes after direct interaction with anticancer agents. P53 activation is mediated by up or downregulation of different factor depending on cell types, concentration and duration of treatment.

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