

HS-1793 inhibits cell proliferation in lung cancer by interfering with the interaction between p53 and MDM2

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Abstract. The transcription factor or tumor suppressor protein p53 regulates numerous cellular functions, including cell proliferation, invasion, migration, senescence and apoptosis, in various types of cancer. HS-1793 is an analog of resveratrol, which exhibits anti-cancer effects on various types of cancer, including breast, prostate, colon and renal cancer, and multiple myeloma. However, to the best of our knowledge, the role of HS-1793 in lung cancer remains to be examined. The present study aimed to investigate the anti-cancer effect of HS-1793 on lung cancer and to determine its association with p53. The results revealed that HS-1793 reduced cell proliferation in lung cancer and increased p53 stability, thereby elevating the expression levels of the target genes p21 and mouse double minute 2 homolog (MDM2). When the levels of MDM2, a negative regulator of p53, are increased under normal conditions, MDM2 binds and degrades p53; however, HS-1793 inhibited this binding, confirming that p53 protein stability was increased. In conclusion, the findings of the present study provide new evidence that HS-1793 may inhibit lung cancer proliferation by disrupting the p53-MDM2 interaction.

Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide. Despite great advances in novel treatments over the past few decades, the survival rate is still low

compared to that of other cancers (1,2). Non-small cell lung cancer (NSCLC) is the most common form, accounting for 85% of new diagnoses of lung cancer (3,4).

p53 is closely linked with a variety of transcriptional and non-transcriptional activities that regulate cell proliferation, DNA repair, cell senescence, and cell death (5,6). Mouse double minute 2 homolog (MDM2) is an E3 ligase that negatively regulates p53. When TP53 is abnormally activated, MDM2 promotes poly-ubiquitination and causes proteasomal degradation to downregulate p53, thereby maintaining p53 at a normal level (7,8). Therefore, interference in the interaction between MDM2 and p53 is an important part of the anti-cancer treatment method targeting p53 activation (9).

HS-1793 (4-(6-hydroxy-2-naphthyl)-1,3-benzenediol), a synthetic resveratrol analog, substituted the unstable double bond present in resveratrol with a naphthalene ring (10,11). HS-1793 improved photosensitivity and metabolic instability and is more potent than resveratrol (12,13). It is a well-known drug that causes cell death by inducing apoptosis in several types of cancer, including breast, prostate, colon, and renal cancers and multiple myeloma (14-17). HS-1793 causes mitochondrial-mediated apoptosis in breast cancer and also induces cell cycle arrest by reducing Akt phosphorylation in colon cancer and multiple myeloma (14,17,18). In prostate cancer cells, it inhibits migration by inhibiting the expression of hypoxia-inducible factor-1 α and vascular endothelial growth factor (19). However, the effect of HS-1793 on lung cancer has not yet been elucidated.

In the present study, we report the effect of HS-1793 on A549 and H460 cell lines harboring p53 wild type. HS-1793 inhibits the binding of p53 and MDM2, resulting in increased p53 protein stability and expression of target genes and subsequently inhibiting the proliferation of NSCLC cells. Therefore, HS-1793 acts as a binding inhibitor of p53 and MDM2 and is a potential drug target for lung cancer.

Materials and methods

Chemicals and antibodies. 4-(6-Hydroxy-2-naphthyl)-1,3-benzenediol (HS-1793) was purchased from AOBIOUS Inc. Antibodies against p53 (cat. no. sc-126), GAPDH (cat. no. sc-47724), p21 waf1/Cip1 (cat. no. sc-6246), and

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ubiquitin (cat. no. sc-8017) were purchased from Santa Cruz Biotechnology. MDM2 (cat. no. op46) was purchased from Calbiochem®. Anti-mouse IgG and anti-rabbit IgG were purchased from Sigma-Aldrich; Merck KGaA.

Cell culture. A549 and H460 cell lines were obtained from American Type Culture Collection (ATCC). The cells were cultured in Dulbecco's modified Eagle medium (DMEM; HyClone, GE Healthcare) or RPMI-1640 medium (HyClone) supplemented with 10% fetal bovine serum (FBS; Corning Inc.) and 1% penicillin-streptomycin (Gibco; Invitrogen; Thermo Fisher Scientific, Inc) and then incubated in a 5% CO₂ incubator at 37°C.

Proliferation assay and cell cycle. Cell viability was determined using a cell count kit (CCK)-8 assay kit (Dojindo), according to the manufacturer's instructions. Briefly, lung cancer cells were seeded into a 96-well microplate, and CCK-8 solution (10/100 µl medium) was added to each well of the plate. After incubation of the plate for 1-4 h in a CO₂ incubator at 37°C, the absorbance of each well was measured at 450 nm using a microplate reader (Molecular Devices) with a reference wavelength of 650 nm. Lung cancer cells were treated with HS-1793 at the dose indicated in the figures. Cell cycle distribution was determined by DNA staining with PI. Cells were harvested and fixed in 70% ethanol. Cell pellets were suspended in PI and simultaneously treated with RNase at 37°C for 30 min. The percentage of cells in different phases of the cell cycle was measured using a FACScanto II flow cytometer (BD biosciences).

Clonogenic assay. Cells were plated at equal densities in 6-well plates (1x10³ cells/well) for 24 h and then treated with HS-1793 at the doses and times indicated in Fig. 1. After treatment, the cells were trypsinized, serially diluted, and re-plated. The cells were grown at 37°C with 5% CO₂ for 7 days, and the colonies were fixed and stained with 0.01% crystal violet. Subsequently, the stained dyes were extracted, and the optical density (OD) at 560 nm was measured using a 96-well plate reader (Molecular Devices).

Protein isolation and western blot analysis. Cells were lysed in lysis buffer A [20 mM HEPES (pH 7.5), 150 mM NaCl, 1 mM EDTA, 2 mM EGTA, 1% Triton X-100, 10% glycerol, and protease inhibitor cocktail Set II (Sigma-Aldrich; Merck KGaA)], and the cellular debris was removed by centrifugation at 10,000 x g for 10 min. Proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred onto nitrocellulose membranes, blocked with 5% skim milk in 0.01 M TBS (pH 7.5) containing 0.5% Tween-20, and labelled with the appropriate primary antibodies. Antigen-antibody complexes were detected based on chemiluminescence detection (Abclone). Protein band intensity was measured using the ImageJ software.

Cycloheximide chase assay. Cycloheximide (CHX) chase assay was performed to evaluate the regulation of p53 protein stability by HS-1793. Cells were pre-incubated with or without 5 µM HS-1793 for 2 h. Subsequently, 20 µg/ml CHX was added to inhibit protein synthesis. The cells were collected at 0, 1, 3, 6,

and 9 h following treatment with CHX. Total cell lysates were analyzed using western blot with anti-p53 and anti-GAPDH. The results from western blot analysis were quantified using ImageJ, and the stable p53 protein level was quantified.

RNA isolation and quantitative reverse transcription-quantitative polymerase chain reaction (RT-qPCR). RNA was extracted from A549 and H460 cells using an Accuprep® Universal RNA extraction kit (Bioneer). Briefly, 1 µg RNA was reverse-transcribed with oligo (dT) 12-18 primers using the First-Strand cDNA Synthesis Kit (Fermentas; Thermo Fisher Scientific, Inc.). All reactions were performed in triplicate, and the β-2-microglobulin (B2M) gene was used as control. Using the comparative threshold cycle (Ct) or standard method, relative quantification of p53 gene expression was calculated after normalization against B2M for each sample. The primers for qPCR were designed as follows: p53 primer, forward, 5'-CCT CACCATCATCACACTGG-3' and reverse, 5'-CCTCATTCAGCTCTCGGAAC-3'; B2M primer, forward, 5'-CTCGCT CCGTGGCCTTAG-3' and reverse, 5'-CAAATGCGGCAT CTTCAA-3'.

Immunoprecipitation (IP). For co-IP, A549 and H460 cells were treated with HS-1793 (5 µM) or DMSO for 9 h or 18 h. Cells for endogenous IP were lysed in lysis buffer A. The lysate was immunoprecipitated with antibodies to detect p53, MDM2, or normal immunoglobulin G. Protein A/G sepharose beads (Santa Cruz Biotechnology) were then applied, and the final precipitated proteins were quantified using western blot analysis with the corresponding antibodies.

Statistical analysis. All data are obtained from three replicate experiments and expressed as mean ± standard deviation of three independent experiments. Statistical difference between multiple groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, using SigmaPlot 12.0 software (2013; Systat Software Inc.). P<0.05 was considered to indicate a statistically significant difference.

Results

HS-1793 diminishes cell viability in A549 and H460 cells. HS-1793 affects cell viability in various carcinomas (14-17). The anti-cancer effect was extensively examined in H1299, A549 and H460 lung cancer cells by CCK-8 assay. Results showed that HS-1793 significantly inhibited cell viability in A549 and H460 cells (high dose; 7.5 and 10 µM) but not in H1299 cells, suggesting that A549 and H460 cells were HS-1793 sensitive (Fig. S1). Therefore, we decided to proceed with our studies in A549 and H460 cells. As shown in Fig. 1A, cell viability was determined after treatment of A549 and H460 cells with 0 to 10 µM HS-1793 for 24 h. HS-1793 has a slightly weaker effect on cell viability at concentrations up to 5 µM at the 24 h time point. However, at concentrations of 7.5 and 10 µM, HS-1793 induced a significant loss of viability (Fig. 1A). We made similar observation at the different time points (Fig. S2) We also determined G0-G1 arrest after exposure to low doses of HS-1793 (<7.5 µM); however, the proportion of cells in the G2-M was significantly increased after exposure to 10 µM (S3). In addition, the clonogenic assay demonstrated that HS-1793 diminished colony

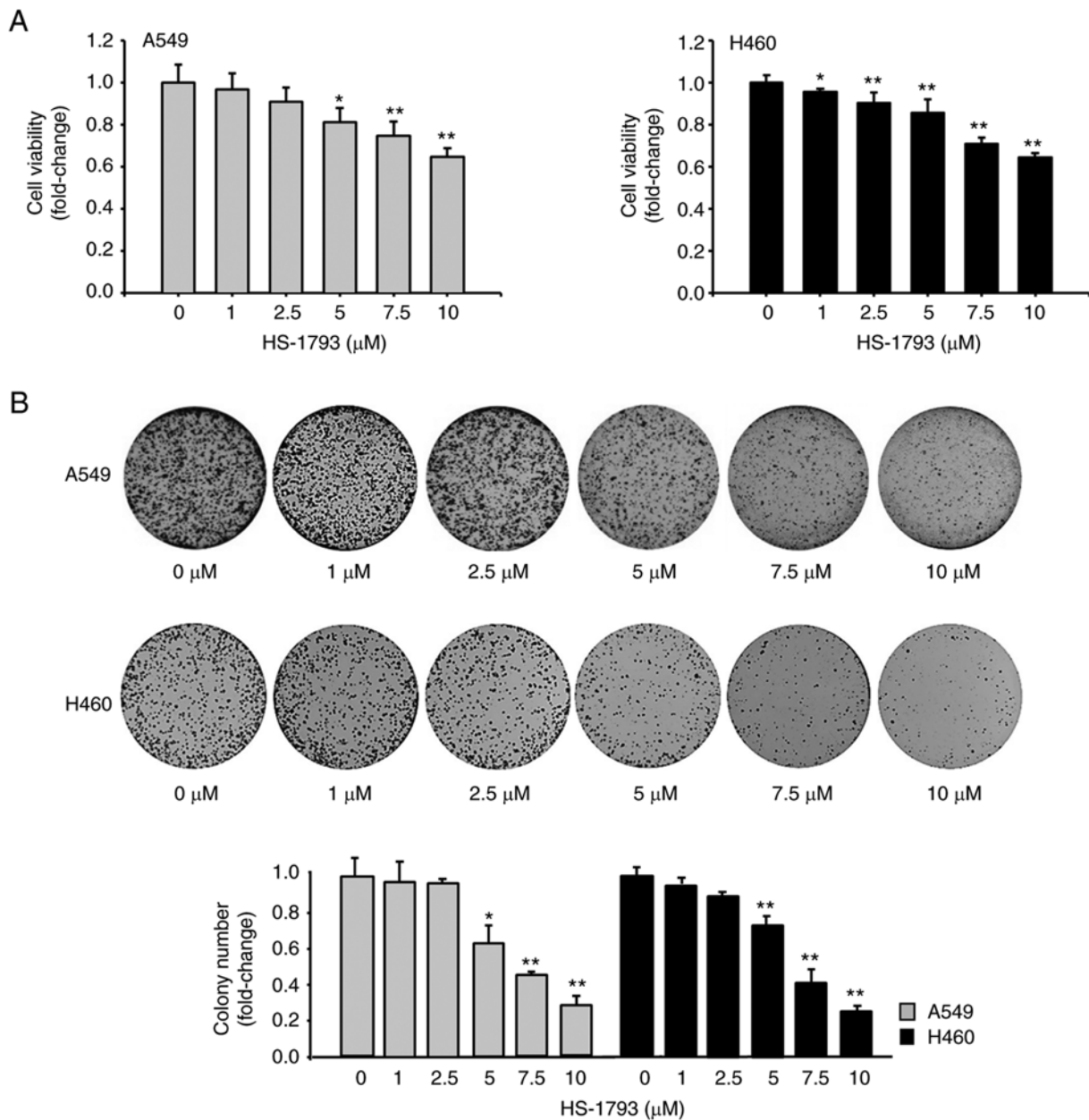


Figure 1. HS-1793 diminishes the viability of A549 and H460 cells. (A) A549 and H460 cells were treated with HS-1793 at different concentrations (0, 1, 2.5, 5, 7.5, and 10 μM) for 24 h, and absorbance was measured at 450 nm after 1 h incubation, using a CCK-8 reagent to confirm cell viability. Results are expressed as fold change. Data indicate the mean ± standard deviation (SD) of three independent experiments. *P<0.05, **P<0.01 vs. control. (B) The clonogenic assay was performed using the same cells as above. After treatment with HS-1793 in a dose-dependent manner, the media was replaced after 24 h. The media was then changed once every 2-3 days; the cells were fixed after 7 days of observation and counted by staining with crystal violet. Results are expressed as fold change. Data indicate the mean ± SD of three independent experiments. *P<0.05, **P<0.01 vs. control. CCK-8, cell counting kit-8.

production in a dose-dependent manner (Fig. 1B). Based on these results, we focused on the effects of HS-1793 at a concentration of 5 μM and a 24 h treatment in subsequent experiments.

HS-1793 increases p53 protein expression and its target genes. Based on the findings of previous breast cancer studies, to confirm the relationship between HS-1793 and p53 in lung cancer, p53 protein level was confirmed using western blotting. We first compared the basal level of p53 protein between A549 and H460 cells. As shown in Fig. S3, the basal level of p53 protein in A549 cells is approximately 50% higher than that in H460 cells (Fig. S4). Next, to evaluate whether HS-1793 regulated p53 protein level, we treated A549 and H460 cells with concentration-dependent

manner. HS-1793 increased the p53 protein level in a concentration-dependent manner (Fig. 2A and B). As shown in Fig. 2C and D, HS-1793 also increased the p53 protein level in a time-dependent manner. Next, we confirmed whether p53 regulates its target genes when upregulated by HS-1793. A549 and H460 cells were treated with HS-1793 at different doses and time durations, cell lysates were prepared, and western blot analysis was performed. As shown in Fig. 3A and B, HS-1793 significantly increased the protein expression of p21 and MDM2 in A549 and H460 cells in a dose- and time-dependent manner. We also evaluated the mRNA levels of p53 target gene (p21) in a time-dependent manner and made a similar observation in A549 and H460 cells in response to HS-1793 treatment (Fig. S5).

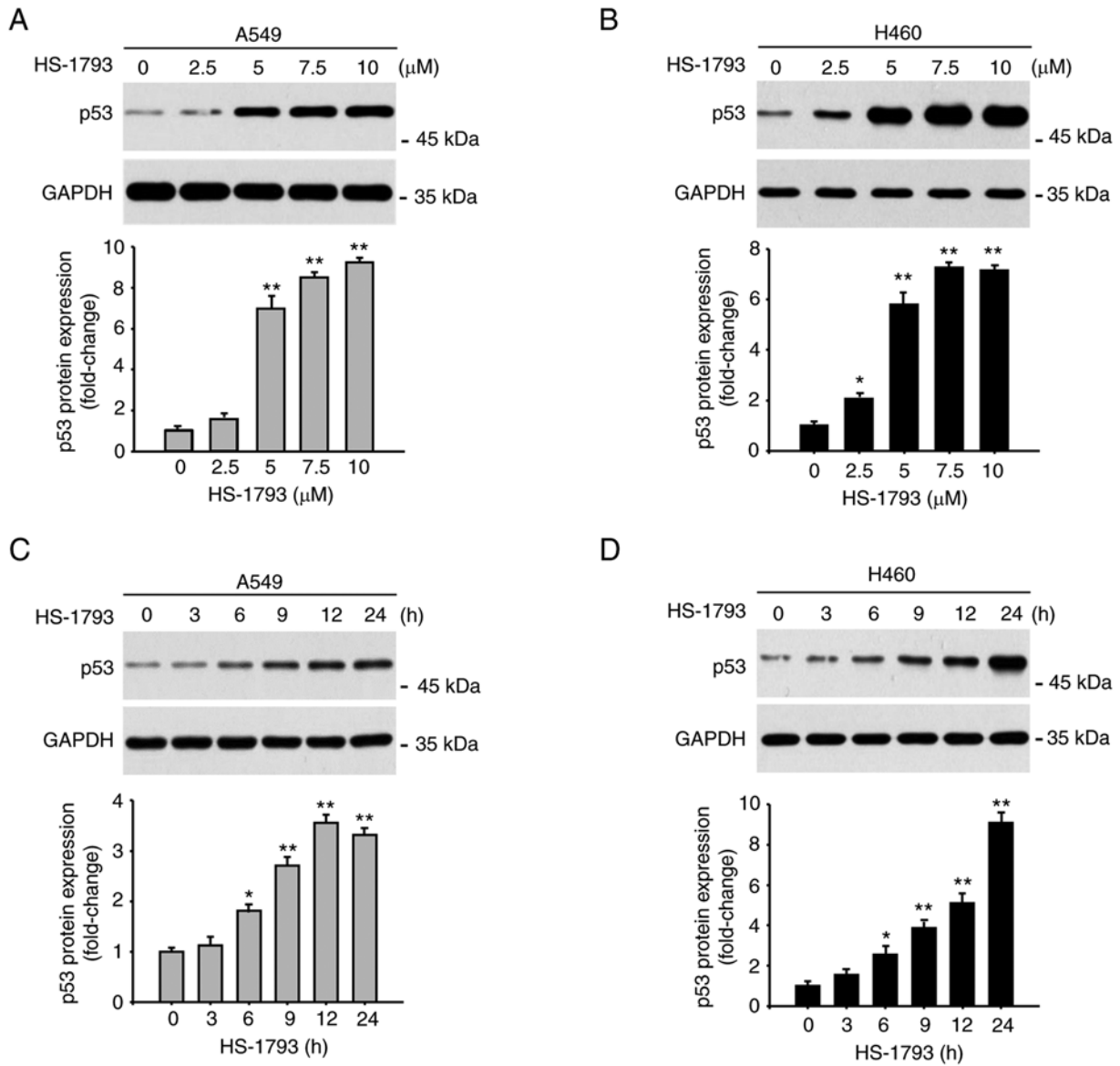


Figure 2. HS-1793 increases p53 protein expression. The protein expression of p53 in (A) A549 and (B) H460 cells was measured by western blot analysis. GAPDH was used as a loading control at each concentration (0, 2.5, 5, 7.5, and 10 μM) for 24 h. The experiment was independently performed twice, quantified through the ImageJ program, normalized with GAPDH, and displayed as a graph. The expression of p53 in (C) A549 and (D) H460 cells was confirmed in a time-dependent manner (0, 3, 6, 9, 12, and 24 h) by selecting 5 μM concentration of HS-1793, which showed a significant increase in the data above. Results are expressed as fold change. Data indicate the mean ± standard deviation of two independent experiments. *P<0.05, **P<0.01 vs. control. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

HS-1793-induced p53 protein expression is mediated by a post-translational mechanism. A CHX chase assay was performed to determine whether the upregulation of p53 expression by HS-1793 was due to transcription upregulation or increased protein stability. A549 (Fig. 4A) and H460 cells (Fig. 4B) were first treated with HS-1793 and then with CHX for the indicated durations. As shown in Fig. 4A and B, p53 half-life increased in the presence of HS-1793. In contrast, the mRNA expression of p53 was not significantly changed in the presence of HS-1793 (Fig. 4C and D).

HS-1793 blocks the interaction between p53 and MDM2. To identify the molecular mechanism underlying p53 stability, we performed an IP assay using antibodies specific for p53 and MDM2. As shown in Fig. 5A and B, p53 and MDM2 were

strongly bound to each other when antibodies for p53 or MDM2 were used. In contrast, HS-1793-treated cells decreased to precipitate either protein, emphasizing that HS-1793 regulates the interaction between p53 and MDM2.

Discussion

Lung cancer is one of the most common carcinomas worldwide and is the primary cause of all cancer-related deaths in both male and female cancer patients. There are four major histological types of lung cancer, including small cell lung cancer (SCLC) and three types of NSCLC (20,21). As NSCLC accounts for over 85% of new lung cancer diagnoses, its treatment is of great importance (22-24). Early detection and multimodal care have selectively shown high

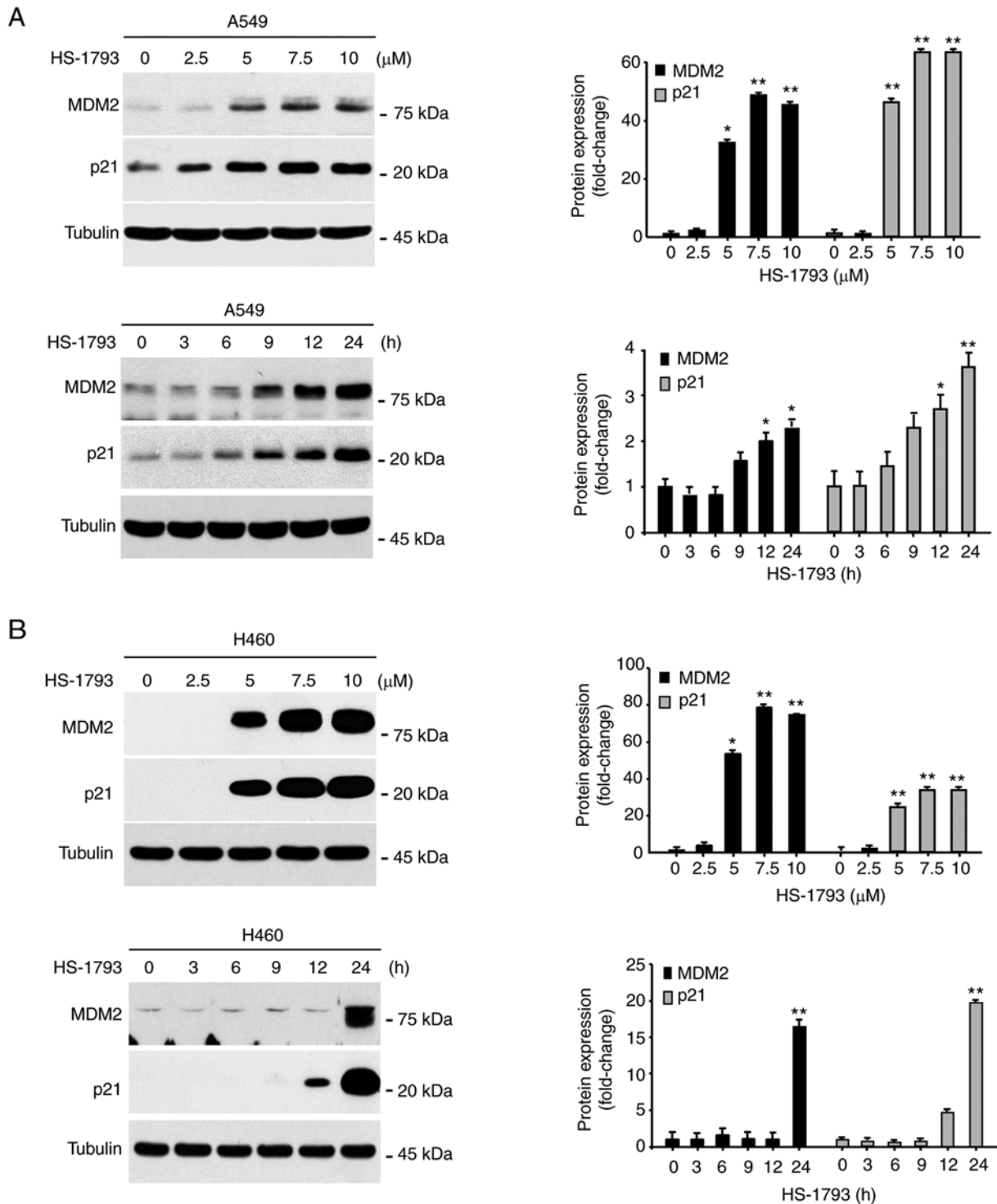


Figure 3. Increased p53 expression by HS-1793 upregulates its target genes *p21* and *MDM2*. (A and B) A549 and H460 cells were treated with HS-1793 (A) in a dose-dependent manner for 24 h and (B) in a time-dependent manner (5 μM). The cells were subjected to western blotting using the indicated antibodies. This experiment was independently performed twice, protein expression was quantified through the ImageJ program, normalized to tubulin expression, and displayed as a graph. Results are expressed as fold change. Data indicate the mean ± standard deviation of two independent experiments. *P<0.05, **P<0.01 vs. control. MDM2, mouse double minute 2 homolog.

patient survival rates (25,26). However, the overall treatment and survival rates for NSCLC are low, and further studies are needed.

Resveratrol has demonstrated potential anti-cancer activity against several types of human cancer, including prostate (27,28), breast (29,30), colorectal (31,32), and skin cancers (33), and has also been used as a chemotherapeutic

drug to treat various lung cancer cells (34-36). Its anti-lung cancer effect has been widely studied, with results suggesting that it could exert potent anti-tumor effects by upregulating microtubule-associated protein 1 light chain 3 (37) and p53 (38), downregulating smad activator 2 and 4 (39), and inhibiting the phosphatidylinositol-3-kinase pathway (40). Although resveratrol has potential therapeutic properties, it

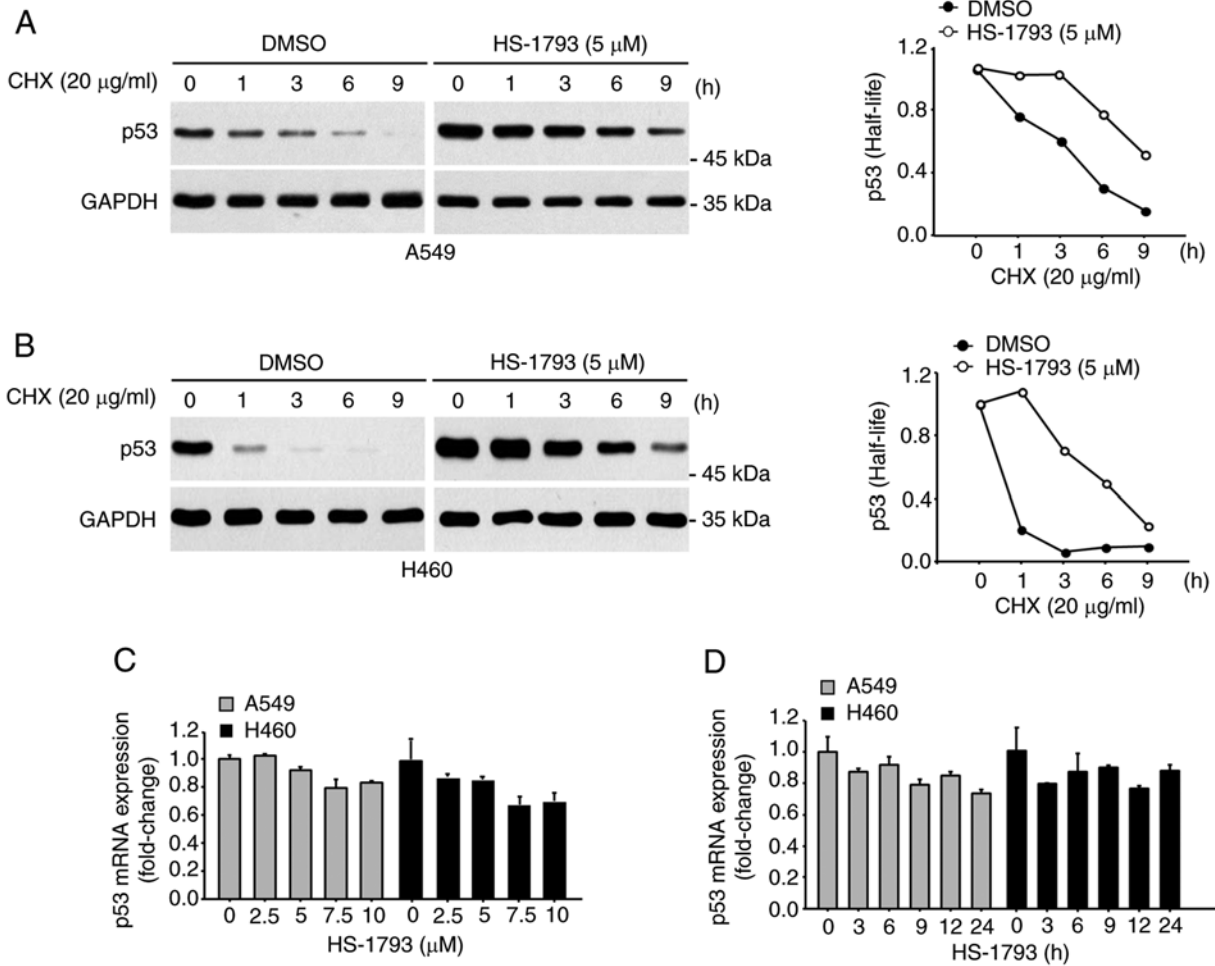


Figure 4. HS-1793 increases protein stability but not p53 transcription. (A) A549 and (B) H460 cells were pre-treated with HS-1793 for 6 h; incubated with CHX (20 μg/ml) for 0, 1, 3, 6, and 9 h; harvested; and analyzed using western blot. Band intensity was quantified by normalizing p53 with GAPDH as a control using the ImageJ program. (C and D) A549 and H460 cells were treated with HS-1793 (C) in a dose-dependent manner for 24 h and (D) in a time-dependent manner (5 μM). mRNA expression of the cells was measured using a quantitative polymerase chain reaction. B2M was used as a control and normalized to obtain a relative quantification graph. Results are expressed as fold change. Data indicate the mean ± standard deviation of independent experiments performed twice. CHX, cycloheximide; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; B2M, beta-2-microglobulin.

has poor pharmacokinetic properties, such as increased photosensitivity and rapid metabolism (41,42). We, therefore, tested the anti-cancer effect of resveratrol in lung cancer using its synthetic analog HS-1793.

HS-1793 has enhanced pharmacokinetic properties, such as reduced photosensitivity and metabolic instability, and is more potent than resveratrol (12,13). HS-1793 exhibits anti-cancer effects such as cell cycle arrest and cell death in various carcinomas (14-18,43), but its effects have not been demonstrated in lung cancer. We have determined the effect of HS-193 on the growth of human lung cancer cells. HS-1793 significantly inhibited the proliferation of both A549 and H460 cells harboring wild-type p53. However, H1299 cells containing p53 null were less affected (Fig. S3), suggesting that the p53 signaling pathway may play a pivotal role in HS-1793 treated cells. Therefore, we decided to proceed with our studies in A549 and H460 cells harboring wild-type p53 allele.

In a previous paper, Kim *et al* identified a relationship between HS-1793 and p53 in breast cancer (18), but the exact mechanism was unclear. In this study, we showed that HS-1793 induced a dose-dependent increase in p53

expression. In addition, we revealed that HS-1793 could significantly increase p53 stability in both A549 and H460 cells. Although a similar effects of HS-1793 observed for both cells, unlike A549 cells, expression of the target genes of p53, including p21 and MDM2, was delayed in H460 cells after HS-1793. While wild-type p53 expression is observed in A549 and H460 cells, the relative protein level is not equal between the cell lines. As shown in Fig. S4, the protein level in A549 cells is approximately 50% higher than that in H460 cells. The differential expression of p53 between these two cancer cell lines may be attributed to the response of the HS-1793-treated cells.

Several reports demonstrated that Akt represses p53 protein stability via Akt-mediated phosphorylation of MDM2 (44-47). Phosphorylation of MDM2 by Akt enhances the nuclear accumulation of MDM2 and consequently augments the destabilization of p53 by MDM2. Therefore, the Akt/MDM2 and MDM2/p53 signaling pathways serve an important role in the regulation of apoptosis and proliferation. We have previously shown that HS-1793 regulates p-Akt activity as an inhibitor of Akt-HSP90 binding (17). Notably, in

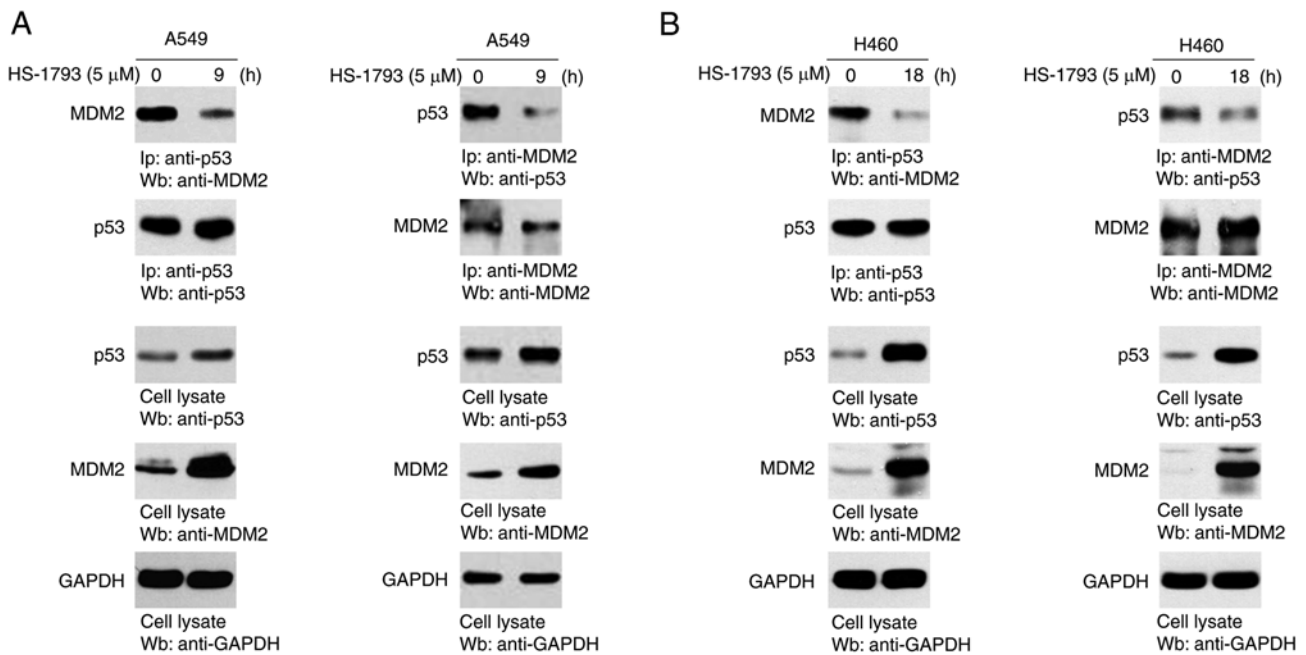


Figure 5. HS-1793 blocks the interaction between p53 and MDM2. The interaction between p53 and MDM2 was confirmed by immunoprecipitation with p53 and MDM2 antibodies. (A) After 9 h treatment with HS-1793 in A549, cells were harvested, and the cell are lysed in lysis buffer A. The lysates (1 mg) was incubated with primary antibodies (2 μg; anti-p53 or 1 μg anti-MDM2) overnight at 4°C. Subsequently, the supernatant was incubated with 50 μl protein A/G sepharose beads for 4 h at 4°C, and the beads were washed with lysis buffer A. A western blot experiment was then performed with the lysate to confirm the interaction. (B) In H460, HS-1793 was treated for 18 h, and the experiment was conducted under the same conditions as above (A). MDM2, mouse double minute 2 homolog.

multiple myeloma, Akt inhibition by HS-1793 results in NF-κB pathway inhibition. We also have analyzed the dose-dependent effect of HS-1793 on the p-Akt level in both A549 and H460 cells. Interestingly, western blot analysis revealed that the p-Akt level was markedly downregulated in response to HS-1793 in A549 cells, whereas a gradual reduction in the p-Akt level was observed in H460 cells (data not shown). Therefore, the subtle difference between the two cell lines for HS-1793 is probably due to p-Akt levels. However, it is also unclear how HS-1793 regulates p53 expression and target genes in lung cancer cells. Therefore, we consider the detailed mechanisms for HS-1793-mediated regulation of p53 target genes by defining a subset of lung tumors for further study.

p53 is a tumor suppressor gene that inhibits tumor development by activating transcription factors related to the cell cycle and apoptosis (48,49). Conversely, MDM2 is a tumor-promoting gene that acts as a negative regulator of p53 (50,51). In various tumors, overexpression of MDM2 inhibits p53 and promotes cell growth (9). Reactivation strategies of wild-type p53, which do not function properly, such as inhibition of E3 ligase activity of MDM2 and using drugs that bind to the p53 pockets of MDM2, are known to be effective chemotherapy methods (52). Thus, we assessed the association between p53 and MDM2 in HS-1793-treated A549 and H460 cells. Our findings revealed that HS-1793 markedly reduced p53-MDM2 interactions. However, further studies are needed to determine whether HS-1793 interferes with the binding of p53 to MDM2 directly or indirectly.

We demonstrated that HS-1793 decreased cell proliferation in lung cancer and increased p53 stability to elevate the expression of its target genes p21 and MDM2. Under normal conditions, MDM2, a negative regulator of p53, binds to and

degrades p53 by acting as an E3 ligase. However, this function is blocked by HS-1793, confirming that p53 protein stability is increased. In summary, the anti-cancer effect of HS-1793 in lung cancer is due to p53 upregulation via blocking the p53-MDM2 interaction.

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Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' contributions

CL and SWJ designed the research. CL, PCWL and SS performed the research. SS and SJ analyzed the data. SS and SWJ wrote the paper. CL, PCWL, SS and SWJ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Mangiameli G, Cioffi U, Alloisio M and Testori A: Lung metastases: Current surgical indications and new perspectives. *Front Surg* 9: 884915, 2022.
- J Saller J and Boyle TA: Molecular pathology of lung cancer. *Cold Spring Harb Perspect Med* 12: a037812, 2022.
- Isaacs J and Stinchcombe TE: Neoadjuvant and adjuvant systemic therapy for early-stage non-small-cell lung cancer. *Drugs* 82: 855-863, 2022.
- Tabbò F, DE Filippis M, Jacobs F and Novello S: Strengths and pitfalls of brigatinib in non-small cell lung cancer patients' management. *Minerva Med* 113: 315-332, 2022.
- Thomas AF, Kelly GL and Strasser A: Of the many cellular responses activated by TP53, which ones are critical for tumour suppression? *Cell Death Differ* 29: 961-971, 2022.
- Koo N, Sharma AK and Narayan S: Therapeutics targeting p53-MDM2 interaction to induce cancer cell death. *Int J Mol Sci* 23: 5005, 2022.
- Wang S and Chen FE: Small-molecule MDM2 inhibitors in clinical trials for cancer therapy. *Eur J Med Chem* 236: 114334, 2022.
- Jiang H, Luo J and Lei H: The roles of mouse double minute 2 (MDM2) oncoprotein in ocular diseases: A review. *Exp Eye Res* 217: 108910, 2022.
- Chène P: Inhibiting the p53-MDM2 interaction: An important target for cancer therapy. *Nat Rev Cancer* 3: 102-109, 2003.
- Jeong MH, Yang K, Lee CG, Jeong DH, Park YS, Choi YJ, Kim JS, Oh SJ, Jeong SK and Jo WS: In vitro genotoxicity assessment of a novel resveratrol analogue, HS-1793. *Toxicol Res* 30: 211-220, 2014.
- Saiko P, Szakmary A, Jaeger W and Szekeres T: Resveratrol and its analogs: Defense against cancer, coronary disease and neurodegenerative maladies or just a fad? *Mutat Res* 658: 68-94, 2008.
- Jeong SH, Jo WS, Song S, Suh H, Seol SY, Leem SH, Kwon TK and Yoo YH: A novel resveratrol derivative, HS1793, overcomes the resistance conferred by Bcl-2 in human leukemic U937 cells. *Biochem Pharmacol* 77: 1337-1347, 2009.
- Jeong SH, Lee JS, Jeong NY, Kim TH, Yoo KS, Song S, Suh H, Kwon TK, Park BS and Yoo YH: A novel resveratrol analogue HS-1793 treatment overcomes the resistance conferred by Bcl-2 and is associated with the formation of mature PML nuclear bodies in renal clear cell carcinoma Caki-1 cells. *Int J Oncol* 35: 1353-1360, 2009.
- Jeong SH, Song IS, Kim HK, Lee SR, Song S, Suh H, Yoon YG, Yoo YH, Kim N, Rhee BD, *et al.*: An analogue of resveratrol HS-1793 exhibits anticancer activity against MCF-7 cells via inhibition of mitochondrial biogenesis gene expression. *Mol Cells* 34: 357-365, 2012.
- Jeong NY, Yoon YG, Rho JH, Lee JS, Lee SY, Yoo KS, Song S, Suh H, Choi YH and Yoo YH: The novel resveratrol analog HS-1793-induced polyploid LNCaP prostate cancer cells are vulnerable to downregulation of Bcl-xL. *Int J Oncol* 38: 1597-1604, 2011.
- Kim DH, Kim MJ, Sung B, Suh H, Jung JH, Chung HY and Kim ND: Resveratrol analogue, HS-1793, induces apoptotic cell death and cell cycle arrest through downregulation of AKT in human colon cancer cells. *Oncol Rep* 37: 281-288, 2017.
- Song IS, Jeong YJ, Jeong SH, Kim HK, Ha NC, Shin M, Ko KS, Rhee BD, Shim S, Jang SW and Han J: Pharmacologic inhibition of AKT leads to cell death in relapsed multiple myeloma. *Cancer Lett* 432: 205-215, 2018.
- Kim JA, Kim DH, Hossain MA, Kim MY, Sung B, Yoon JH, Suh H, Jeong TC, Chung HY and Kim ND: HS-1793, a resveratrol analogue, induces cell cycle arrest and apoptotic cell death in human breast cancer cells. *Int J Oncol* 44: 473-480, 2014.
- Kim DH, Hossain MA, Kim MY, Kim JA, Yoon JH, Suh HS, Kim GY, Choi YH, Chung HY and Kim ND: A novel resveratrol analogue, HS-1793, inhibits hypoxia-induced HIF-1 α and VEGF expression, and migration in human prostate cancer cells. *Int J Oncol* 43: 1915-1924, 2013.
- Minna JD, Roth JA and Gazdar AF: Focus on lung cancer. *Cancer Cell* 1: 49-52, 2002.
- Lemjabbar-Alaoui H, Hassan OU, Yang YW and Buchanan P: Lung cancer: Biology and treatment options. *Biochim Biophys Acta* 1856: 189-210, 2015.
- Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, Petrella F, Spaggiari L and Rosell R: Non-small-cell lung cancer. *Nat Rev Dis Primers* 1: 15009, 2015.
- Zappa C and Mousa SA: Non-small cell lung cancer: Current treatment and future advances. *Transl Lung Cancer Res* 5: 288-300, 2016.
- Hoffman PC, Mauer AM and Vokes EE: Lung cancer. *Lancet* 355: 479-485, 2000.
- Herbst RS, Morgensztern D and Boshoff C: The biology and management of non-small cell lung cancer. *Nature* 553: 446-454, 2018.
- Yang K, Wang YJ, Chen XR and Chen HN: Effectiveness and safety of bevacizumab for unresectable non-small-cell lung cancer: A meta-analysis. *Clin Drug Investig* 30: 229-241, 2010.
- Silk N, Reich J, Sinha R, Chawla S, Geary K and Zhang D: The effects of resveratrol on prostate cancer through targeting the tumor microenvironment. *J Xenobiot* 11: 16-32, 2021.
- Zaffaroni N and Beretta GL: Resveratrol and prostate cancer: The power of phytochemicals. *Curr Med Chem* 28: 4845-4862, 2021.
- Medina-Aguilar R, Marchat LA, Arechaga Ocampo E, Gariglio P, García Mena J, Villegas Sepúlveda N, Martínez Castillo M and López-Camarillo C: Resveratrol inhibits cell cycle progression by targeting Aurora kinase A and Polo-like kinase 1 in breast cancer cells. *Oncol Rep* 35: 3696-3704, 2016.
- Alamolhodaei NS, Tsatsakis AM, Ramezani M, Hayes AW and Karimi G: Resveratrol as MDR reversion molecule in breast cancer: An overview. *Food Chem Toxicol* 103: 223-232, 2017.
- Schneider Y, Vincent F, Duranton B, Badolo L, Gossé F, Bergmann C, Seiler N and Raul F: Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. *Cancer Lett* 158: 85-91, 2000.
- Tessitore L, Davit A, Sarotto I and Caderni G: Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21(CIP) expression. *Carcinogenesis* 21: 1619-1622, 2000.
- Fabbrocini G, Kisslinger A, Iannelli P, Vitale N, Procaccini C, Sparaneo G, Chieffi P, Ayala F, Mancini FP and Tramontano D: Resveratrol regulates p66Shc activation in HaCaT cells. *Exp Dermatol* 19: 895-903, 2010.
- Feng Y, Zhou J and Jiang Y: Resveratrol in lung cancer-a systematic review. *J BUON* 21: 950-953, 2016.
- Rasheduzzaman M, Jeong JK and Park SY: Resveratrol sensitizes lung cancer cell to TRAIL by p53 independent and suppression of Akt/NF- κ B signaling. *Life Sci* 208: 208-220, 2018.
- Kong F, Zhang R, Zhao X, Zheng G, Wang Z and Wang P: Resveratrol raises in vitro anticancer effects of paclitaxel in NSCLC cell line A549 through COX-2 expression. *Korean J Physiol Pharmacol* 21: 465-474, 2017.
- Ohshiro K, Rayala SK, Kondo S, Gaur A, Vadlamudi RK, El-Naggar AK and Kumar R: Identifying the estrogen receptor coactivator PELP1 in autophagosomes. *Cancer Res* 67: 8164-8171, 2007.
- Luo H, Yang A, Schulte BA, Wargovich MJ and Wang GY: Resveratrol induces premature senescence in lung cancer cells via ROS-mediated DNA damage. *PLoS One* 8: e60065, 2013.
- Whyte L, Huang YY, Torres K and Mehta RG: Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. *Cancer Res* 67: 12007-12017, 2007.
- Ebi H, Tomida S, Takeuchi T, Arima C, Sato T, Mitsudomi T, Yatabe Y, Osada H and Takahashi T: Relationship of deregulated signaling converging onto mTOR with prognosis and classification of lung adenocarcinoma shown by two independent in silico analyses. *Cancer Res* 69: 4027-4035, 2009.
- Shaito A, Posadino AM, Younes N, Hasan H, Halabi S, Alhababi D, Al-Mohannadi A, Abdel-Rahman WM, Eid AH, Nasrallah GK and Pintus G: Potential adverse effects of resveratrol: A literature review. *Int J Mol Sci* 21: 2084, 2020.
- Neves AR, Lucio M, Lima JL and Reis S: Resveratrol in medicinal chemistry: A critical review of its pharmacokinetics, drug-delivery, and membrane interactions. *Curr Med Chem* 19: 1663-1681, 2012.
- Kim DH, Hossain MA, Kim MY, Kim JA, Yoon JH, Suh HS, Kim GY, Choi YH, Chung HY and Kim ND: A novel resveratrol analogue, HS-1793, inhibits hypoxia-induced HIF-1 α and VEGF expression, and migration in human prostate cancer cells. *Int J Oncol* 43: 1915-1924, 2013.

44. Chen Y, Li H, Zhang W, Qi W, Lu C, Huang H, Yang Z, Liu B and Zhang L: Sesamin suppresses NSCLC cell proliferation and induces apoptosis via Akt/p53 pathway. *Toxicol Appl Pharmacol* 387: 114848, 2020.
45. Chibaya L, Karim B, Zhang H and Jones SN: Mdm2 phosphorylation by Akt regulates the p53 response to oxidative stress to promote cell proliferation and tumorigenesis. *Proc Natl Acad Sci USA*: Jan 26, 2021 (Epub ahead of print).
46. Zhao Y, Cai J, Shi K, Li H, Du J, Hu D, Liu Z and Wang W: Germacrone induces lung cancer cell apoptosis and cell cycle arrest via the Akt/MDM2/p53 signaling pathway. *Mol Med Rep* 23: 452, 2021.
47. Liu L, Xu Z, Yu B, Tao L and Cao Y: Berbamine inhibits cell proliferation and migration and induces cell death of lung cancer cells via regulating c-Maf, PI3K/Akt, and MDM2-P53 pathways. *Evid Based Complement Alternat Med* 2021: 5517143, 2021.
48. Aubrey BJ, Kelly GL, Janic A, Herold MJ and Strasser A: How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? *Cell Death Differ* 25: 104-113, 2018.
49. Ozaki T and Nakagawara A: Role of p53 in cell death and human cancers. *Cancers (Basel)* 3: 994-1013, 2011.
50. Shi D and Gu W: Dual roles of MDM2 in the regulation of p53: Ubiquitination dependent and ubiquitination independent mechanisms of MDM2 repression of p53 activity. *Genes Cancer* 3: 240-248, 2012.
51. Klein AM, de Queiroz RM, Venkatesh D and Prives C: The roles and regulation of MDM2 and MDMX: It is not just about p53. *Genes Dev* 35: 575-601, 2021.
52. Athar M, Elmets CA and Kopelovich L: Pharmacological activation of p53 in cancer cells. *Curr Pharm Des* 17: 631-639, 2011.



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