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Abstract & References

Andrographis paniculata Diterpenoids Protect against Radiation-Induced Transformation in BALB/3T3 Cells

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One of the most concerning side effects of exposure to radiation are the carcinogenic risks. To reduce the negative effects of radiation, both cytoprotective and radioprotective agents have been developed. However, little is known regarding their potential for suppressing carcinogenesis. *Andrographis paniculata*, a plant, with multiple medicinal uses that is commonly used in traditional medicine, has three major constituents known to have cellular antioxidant activity: andrographolide (AP1); 14-deoxy-11,12-didehydroandrographolide (AP3); and neoandrographolide (AP4). In our study, we tested these elements for their radioprotective properties as well as their anti-neoplastic effects on transformation using the BALB/3T3 cell model. All three compounds were able to reduce radiation-induced DNA damage. However, AP4 appeared to have superior radioprotective properties compared to the other two compounds, presumably by protecting mitochondrial function. The compound was able to suppress radiation-induced cellular transformation through inhibition of STAT3. Treatment with AP4 also reduced expressions of MMP-2 and MMP-9. These results suggest that AP4 could be further studied and developed into an anti-transformation/carcinogenic drug as well as a radioprotective agent.

REFERENCES

1. Lim JC, Chan TK, Ng DS, Sagineedu SR, Stanslas J, Wong WS. Andrographolide and its analogues: versatile bioactive molecules for combating inflammation and cancer. Clin Exp Pharmacol Physiol 2012; 39:300–10. Crossref, PubMed, Google Scholar

2. Kulyal P, Tiwari UK, Shukla A, Gaur AK. Chemical constituents isolated from *Andrographis paniculata*. Ind J Chem 2010; 49B:356–9. Google Scholar

3. Raghavan R, Cheriyamundath S, Madassery J. 14-Deoxy-11,12-didehydroandrographolide inhibits proliferation and induces GSH-dependent cell death of human promonocytic leukemic cells. J Nat Med 2014; 68:387–94. Crossref, PubMed, Google Scholar

4. Suriyo T, Pholphana N, Rangkadilok N, Thiantanawat A, Watcharasit P, Satayavivad J. *Andrographis paniculata* extracts and major constituent diterpenoids inhibit growth of intrahepatic cholangiocarcinoma cells by inducing cell cycle arrest and apoptosis. Planta Med 2014; 80:533–43. Crossref, PubMed, Google Scholar

5. Pfisterer PH, Rollinger JM, Schyschka L, Rudy A, Vollmar AM, Stuppner H. Neoandrographolide from *Andrographis paniculata* as a potential natural chemosensitizer. Planta Med 2010; 76:1698–700.

Crossref, PubMed, Google Scholar

6. Guan SP, Kong LR, Cheng C, Lim JC, Wong WS. Protective role of 14-deoxy-11,12-didehydroandrographolide, a noncytotoxic analogue of andrographolide, in allergic airway inflammation. J Nat Prod 2011; 74:1484–90. Crossref, PubMed, Google Scholar

7. Lee MJ, Rao YK, Chen K, Lee YC, Chung YS, Tzeng YM. Andrographolide and 14-deoxy-11,12-didehydroandrographolide from *Andrographis paniculata* attenuate high glucose-induced fibrosis and apoptosis in murine renal mesangeal cell lines. J Ethnopharmacol 2010; 132:497–505. Crossref, PubMed, Google Scholar

8. Liu J, Wang ZT, Ji LL. In vivo and in vitro anti-inflammatory activities of neoandrographolide. Am J Chin Med 2007; 35:317–28. Crossref, PubMed, Google Scholar

9. Seed TM. Radiation protectants: current status and future prospects. Health Phys 2005; 89:531–45. Crossref, PubMed, Google Scholar

10. Grdina DJ, Shigematsu N, Dale P, Newton GL, Aguilera JA, Fahey RC. Thiol and disulfide metabolites of the radiation protector and potential chemopreventive agent WR-2721 are linked to both its anti-cytotoxic and anti-mutagenic mechanisms of action. Carcinogenesis 1995; 16:767–74. Crossref, PubMed, Google Scholar

11. Rades D, Fehlauer F, Bajrovic A, Mahlmann B, Richter E, Alberti W. Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 2004; 70:261–4. Crossref, PubMed, Google Scholar

12. Jagetia GC. Radioprotective potential of plants and herbs against the effects of ionizing radiation. J Clin Biochem Nutr 2007; 40:74–81. Crossref, PubMed, Google Scholar

13. Tripathi R, Kamat JP. Free radical induced damages to rat liver subcellular organelles: inhibition by *Andrographis paniculata* extract. Indian J Exp Biol 2007; 45:959–67. PubMed, Google Scholar

14. Creton S, Aardema MJ, Carmichael PL, Harvey JS, Martin FL, Newbold RF, et al. Cell transformation assays for prediction of carcinogenic potential: state of the science and future research needs. Mutagenesis 2012; 27:93–101. Crossref, PubMed, Google Scholar

15. Mascolo MG, Perdichizzi S, Rotondo F, Morandi E, Guerrini A, Silingardi P, et al. BALB/c 3T3 cell transformation assay for the prediction of carcinogenic potential of chemicals and environmental mixtures. Toxicol In Vitro 2010; 24:1292–300. Crossref, PubMed, Google Scholar

16. Pholphana N, Rangkadilok N, Thongnest S, Ruchirawat S, Ruchirawat M, Satayavivad J. Determination and variation of three active diterpenoids in *Andrographis paniculata* (Burm.f.) Nees. Phytochem Anal 2004; 15:365–71. Crossref, PubMed, Google Scholar

17. Reznikoff CA, Bertram JS, Brankow DW, Heidelberger C. Quantitative and qualitative studies of chemical transformation of cloned C3H mouse embryo cells sensitive to postconfluence inhibition of cell division. Cancer Res 1973; 33:3239–49. PubMed, Google Scholar

18. Sasaki K, Bohnenberger S, Hayashi K, Kunkelmann T, Muramatsu D, Poth A, et al. Photo catalogue for the classification of foci in the BALB/c 3T3 cell transformation assay. Mutat Res 2012; 744:42–53. Crossref, PubMed, Google Scholar

19. Zhou X, Chen M, Zeng X, Yang J, Deng H, Yi L, et al. Resveratrol regulates mitochondrial reactive oxygen species homeostasis through Sirt3 signaling pathway in human vascular endothelial cells. Cell Death Dis 2014; 5:e1576. Crossref, PubMed, Google Scholar

20. Fenech M, Morley AA. Measurement of micronuclei in lymphocytes. Mutat Res 1985; 147:29–36. Crossref, PubMed, Google Scholar

21. Fenech M, Morley AA. The effect of donor age on spontaneous and induced micronuclei. Mutat Res 1985; 148:99–105. Crossref, PubMed, Google Scholar

22. Krithika R, Verma RJ, Shrivastav PS. Antioxidative and cytoprotective effects of andrographolide against CCl4-induced hepatotoxicity in HepG2 cells. Hum Exp Toxicol 2012; 32:530–43. Crossref, PubMed, Google Scholar

23. Kamdem RE, Sang S, Ho CT. Mechanism of the superoxide scavenging activity of neoandrographolide - a natural product from *Andrographis paniculata* Nees. J Agric Food Chem 2002; 50:4662–5. Crossref, PubMed, Google Scholar

24. Chen W, Feng L, Nie H, Zheng X. Andrographolide induces autophagic cell death in human liver cancer cells through cyclophilin D-mediated mitochondrial permeability transition pore. Carcinogenesis 2012; 33:2190–8. Crossref, PubMed, Google Scholar

25. Zhou J, Lu GD, Ong CS, Ong CN, Shen HM. Andrographolide sensitizes cancer cells to TRAIL-induced apoptosis via p53-mediated death receptor 4 up-regulation. Mol Cancer Ther 2008; 7:2170–80. Crossref, PubMed, Google Scholar

26. Cheung HY, Cheung SH, Li J, Cheung CS, Lai WP, Fong WF, et al. Andrographolide isolated from *Andrographis paniculata* induces cell cycle arrest and mitochondrial-mediated apoptosis in human leukemic HL-60 cells. Planta Med 2005; 71:1106–11. Crossref, PubMed, Google Scholar

27. Murley JS, Kataoka Y, Weydert CJ, Oberley LW, Grdina DJ. Delayed radioprotection by nuclear transcription factor kappaB-mediated induction of manganese superoxide dismutase in human microvascular endothelial cells after exposure to the free radical scavenger WR1065. Free Radic Biol Med 2006; 40:1004–16. Crossref, PubMed, Google Scholar

28. Murley JS, Nantajit D, Baker KL, Kataoka Y, Li JJ, Grdina DJ. Maintenance of manganese superoxide dismutase (SOD2)-mediated delayed radioprotection induced by repeated administration of the free thiol form of amifostine. Radiat Res 2008; 169:495–505. BioOne, Google Scholar

29. Chen YY, Hsieh CY, Jayakumar T, Lin KH, Chou DS, Lu WJ, et al. Andrographolide induces vascular smooth muscle cell apoptosis through a SHP-1-PP2A-p38MAPK-p53 cascade. Sci Rep 2014; 4:5651. Crossref, PubMed, Google Scholar

30. Frezza C, Gottlieb E. Mitochondria in cancer: not just innocent bystanders. Semin Cancer Biol 2009; 19:4–11. Crossref, PubMed, Google Scholar

31. Shen YC, Chen CF, Chiou WF. Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol 2002; 135:399–406. Crossref, PubMed, Google Scholar

32. Bromberg JF, Horvath CM, Besser D, Lathem WW, Darnell JE, Jr. Stat3 activation is required for cellular transformation by v-src. Mol Cell Biol 1998; 18:2553–8. Crossref, PubMed, Google Scholar

33. Iida K, Itoh K, Maher JM, Kumagai Y, Oyasu R, Mori Y, et al. Nrf2 and p53 cooperatively protect against BBN-induced urinary bladder carcinogenesis. Carcinogenesis 2007; 28:2398–403. Crossref, PubMed, Google Scholar

34. Lee LA, Dolde C, Barrett J, Wu CS, Dang CV. A link between c-Myc-mediated transcriptional repression and neoplastic transformation. J Clin Invest 1996; 97:1687–95. Crossref, PubMed, Google Scholar

35. Baruch RR, Melinscak H, Lo J, Liu Y, Yeung O, Hurta RA. Altered matrix metalloproteinase expression associated with oncogene-mediated cellular transformation and metastasis formation. Cell Biol Int 2001; 25:411–20. Crossref, PubMed, Google Scholar

36. Paul RK, Irudayaraj V, Johnson M, Patric RD. Phytochemical and anti-bacterial activity of epidermal glands extract of Christella parasitica (L.) H. Lev. Asian Pac J Trop Biomed 2011; 1:8–11. Crossref, PubMed, Google Scholar

37. Low M, Khoo CS, Munch G, Govindaraghavan S, Sucher NJ. An in vitro study of anti-inflammatory activity of standardised *Andrographis paniculata* extracts and pure andrographolide. BMC Complement Altern Med 2015; 15:18. Crossref, PubMed, Google Scholar

38. Hung SK, Hung LC, Kuo CD, Lee KY, Lee MS, Lin HY, et al. Andrographolide sensitizes Ras-transformed cells to radiation in vitro and in vivo. Int J Radiat Oncol Biol Phys 2010; 77:1232–9. Crossref, PubMed, Google Scholar

39. Ding M, Zhang E, He R, Wang X. Newly developed strategies for improving sensitivity to radiation by targeting signal pathways in cancer therapy. Cancer Sci 2013; 104:1401–10. Crossref, PubMed, Google Scholar

40. Wang ZM, Kang YH, Yang X, Wang JF, Zhang Q, Yang BX, et al. Andrographolide radiosensitizes human esophageal cancer cell line ECA109 to radiation in vitro. Dis Esophagus 2016; 29:54–61. Crossref, PubMed, Google Scholar

41. Yuan H, Sun B, Gao F, Lan M. Synergistic anticancer effects of andrographolide and paclitaxel against A549 NSCLC cells. Pharm Biol 2016; 54:2629–35. Crossref, PubMed, Google Scholar

42. Zhang C, Qiu X. Andrographolide radiosensitizes human ovarian cancer SKOV3 xenografts due to an enhanced apoptosis and autophagy. Tumour Biol 2015; 36:8359–65. Crossref, PubMed, Google Scholar

43. Lu CL, Qin L, Liu HC, Candas D, Fan M, Li JJ. Tumor cells switch to mitochondrial oxidative

phosphorylation under radiation via mTOR-mediated hexokinase II inhibition–a Warburg-reversing effect. PLoS One 2015; 10:e0121046. PubMed, Google Scholar

44. Nantajit D, Fan M, Duru N, Wen Y, Reed JC, Li JJ. Cyclin B1/Cdk1 phosphorylation of mitochondrial p53 induces anti-apoptotic response. PLoS One 2010; 5:e12341. Crossref, PubMed, Google Scholar

45. Yamamori T, Yasui H, Yamazumi M, Wada Y, Nakamura Y, Nakamura H, et al. Ionizing radiation induces mitochondrial reactive oxygen species production accompanied by upregulation of mitochondrial electron transport chain function and mitochondrial content under control of the cell cycle checkpoint. Free Radic Biol Med 2012; 53:260–70. Crossref, PubMed, Google Scholar

46. Hamanaka RB, Chandel NS. Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. Trends Biochem Sci 2010; 35:505–13. Crossref, PubMed, Google Scholar

47. Turkson J, Bowman T, Garcia R, Caldenhoven E, De Groot RP, Jove R. Stat3 activation by Src induces specific gene regulation and is required for cell transformation. Mol Cell Biol 1998; 18:2545–52. Crossref, PubMed, Google Scholar

48. Wei D, Le X, Zheng L, Wang L, Frey JA, Gao AC, et al. Stat3 activation regulates the expression of vascular endothelial growth factor and human pancreatic cancer angiogenesis and metastasis. Oncogene 2003; 22:319–29. Crossref, PubMed, Google Scholar

49. Subbaramaiah K, Telang N, Ramonetti JT, Araki R, DeVito B, Weksler BB, et al. Transcription of cyclooxygenase-2 is enhanced in transformed mammary epithelial cells. Cancer Res 1996; 56:4424–9. PubMed, Google Scholar

50. Pellikainen JM, Ropponen KM, Kataja VV, Kellokoski JK, Eskelinen MJ, Kosma VM. Expression of matrix metalloproteinase (MMP)-2 and MMP-9 in breast cancer with a special reference to activator protein-2, HER2, and prognosis. Clin Cancer Res 2004; 10:7621–8. Crossref, PubMed, Google Scholar

51. Batkhuu J, Hattori K, Takano F, Fushiya S, Oshiman K, Fujimiya Y. Suppression of NO production in activated macrophages in vitro and ex vivo by neoandrographolide isolated from *Andrographis paniculata*. Biol Pharm Bull 2002; 25:1169–74. Crossref, PubMed, Google Scholar

52. Painuli S, Kumar N. Prospects in the development of natural radioprotective therapeutics with anti-cancer properties from the plants of Uttarakhand region of India. J Ayurveda Integr Med 2016; 7:62–8. Crossref, PubMed, Google Scholar