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Perspective

# Potentiating Andrographolide's Antineoplastic Characters for Evading Malignant Transformation of Stem Cells

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**Abstract**

Stem cells are differentially modulated and fated by the influence of their microenvironment, commonly known as 'stem cell niche'. Studies of stem cell niche transformation leading to its malignancy and signaling molecules involved therein, is greatly limited by the fading boundaries of distinction between the existing cancerous cells and the de-novo transformed cells of the stem cell niche. The potent question being addressed in this communication focuses on developing new strategies to limit the malignant transformation of stem cells using andrographolide (a plant derived compound), which has been extensively used in Indian and Chinese traditional medicine. In this study we try to extend the inhibiting effect of andrographolide on Interleukin-6 (IL-6) expression (both mRNA and protein) leading to the onset of a wide range of anti-cancerous and chemo-protective biological functions.

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**Keywords**

- Andrographolide
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- Reactive oxygen species (ROS)
- Apoptosis
- Angiogenesis
- Cell cycle
- Immunomodulation
- Stem cell niche

## INTRODUCTION

The stem cell niche has critical importance in deciding the stemmness and proliferative potential of the cells as well as determining the induction of differentiation to attain a fate [1-12]. However in context of growing evidences of malignancy in cells due to external carcinogenic factors like toxic radiations (e.g. UV); heavy metals (e.g. arsenic, lead etc.); DNA damage etc. [2,3,6]. Several external factors leading to carcinogenesis are known to induce the expression of oncogenes or activation of proto-oncogenes either in a randomly spontaneous manner or inform of a series of accumulated mutations [1,3]. These transforming cells can be either the cells of the stem cell niche or the cells neighboring the niche, which would ultimately result in transformed niche and affect the properties of the residing stem cells. IL-6 has been as the key cytokine involved in signaling of and between such transformed cells [1,3-5]. IL-6 mediated signaling has been implicated for its dual role in both tumor progression and suppression [6]. Therefore, selectively targeting the IL-6 expression is a promising strategy to evade such neoplastic transformations. Screening of large number of potential plant-derived compounds has highlighted 'andrographolide', as a key compound for multifaceted biological functions like anticancerous, proapoptotic, anti-angiogenic and cell cycle arrest [13,14,15,18,22]. Andrographolide ($C_{20}H_{30}O_5$), a diterpenoid lactone derived from *Andrographolide paniculata Nees* has an added advantage of being extensively studied for their physio-chemical properties like structure, bond properties and stereochemistry [10,18,20]. This compound has been extensively used in herbal medicines of India and China for the liver disorder, cardiovascular problems, fever, diarrohea and herpes etc [8,9,13] (Figure 1).

Apart from andrographolide, several other natural products that can be competitive natural analogues are under clinical trials [15,17,21]. The chemical analogues of andrographolide that have identified by Jada et al. are 3,19-isopropylideneandrographolide;14-acetyl-3,19-isopropylideneandrographolide;14-acetylandr- ographolide; 3,19-(2-bromobenzylidene) andrographolide and 3,19-(3-chloro-4-fluorobenzylidene)and- rographolide [ 27].

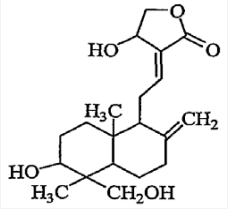


**Figure 1** Structure of Andrographolide.

## PROSPECTIVE METHOD

The proposed strategy utilizes the drug, andrographolide in preventing normal stem cell carcinogenesis. Arsenic transformed malignant cells are known to be potential xenobiotic source for inducing cancer due to events like active mutagenesis following heavy metal contamination. Arsenic transformed malignant cells are shown to have a role in converting normal stem cells into cancer stem cells, when cultured non contiguously. This contact is conducted by the release of IL-6 during contiguous cell culture. The mechanism of secretion of the interleukin-6 by the MECs even though is not completely understood. In this study we would like to check whether andrographolide, an interleukin-6 inhibitor could prevent or limit the potency of arsenic induced MECs to convert normal stem cells to cancerous stem cells when arsenic transformed malignant cells pretreated with the drug are co-cultured non contiguously with normal stem cells as well as treating the co-culture with andrographolide without any pretreatment when co-cultured non-continuously (Figure 3).

## DISCUSSION

### IL-6 Inhibition

IL-6, a pleotropic cytokine has specific IL-6 receptors (IL-6R), with its alpha subunit binding to IL-6 and the signal transducer unit, i.e. gp-130. Three of these subunits form a hexameric complex with two molecules of each subunit [18]. The IL-6R responds to both intrinsic constitutive and extrinsic administered IL-6 levels. In most human cancers usage of andrographolide has significantly limited the subsequent IL-6 levels both at mRNA and protein level [16]. In case of human prostrate cancer, andrographolide inhibits both autocrine and paracrine mediated IL-6 signaling and is independent of the cell type [23,24]. The level of IL-6 and its receptor expression has been consistently related to the progressing stages of cancer and is most significant at benign hyperplasia and metastasis. Furthermore with the increasing tumor mass the IL-6 levels become significantly high and thus can be targeted for anti cancerous drug designing [30,31,32]. In case of human prostrate cancer cells the binding of IL-6 to androgen receptors (AR) is signaled by Stat3, which overexpresses AR in an androgen deprivation therapy [23,25]. Stat3Tyr705 has been identified as an important signaling moiety for IL-6 signaling and is strongly limited for phosphorylation in presence of andrographolide. Along with Stat3 pathway, MAPK, Akt (Ser473) and Erk pathway induced cell proliferation is inhibited by andrographolide treatment [28,29]. Even, the v-src induced Erk1/2 phosphorylation and Akt phosphorylation is inhibited.

### Synergistic cancer evasion

In addition to the IL-6 inhibition and subsequent signaling alteration, andrographolide also initiates a wide range of biological pathways that promote anticancerous hallmarks (cell cycle arrest, cytotoxicity of cancer cells) and down regulate pro-cancerous hallmarks (angiogenesis, Immunomodulation and apoptosis evasion). Apart from its effect on cancerous cells, andrographolide is also known to have a protective potential of healthy cells and also selectively eliminate the cancerous cells (Figure 2).

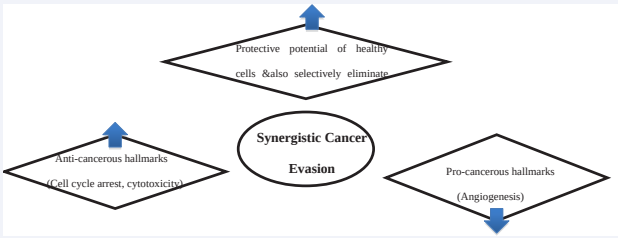


**Figure 2** Wide-range of Cancer inhibiting actions of andrographolide up regulating the anti-cancerous hallmarks and the Protective potential and down regulating the pro-cancerous hallmarks.

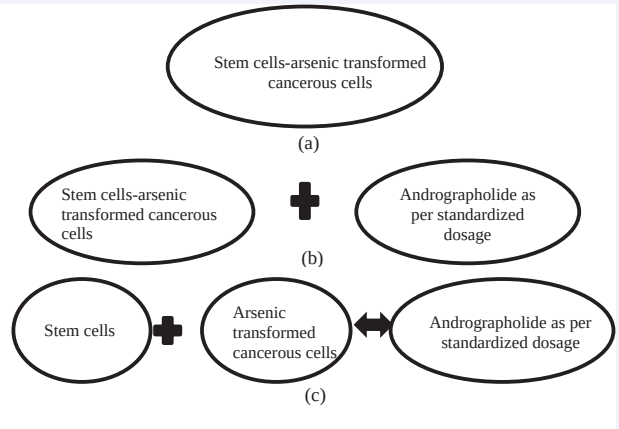


**Figure 3** Effect of andrographolide on evading malignant transformation of stem cells. (a) To check the transformational ability of cancerous cell for the co-cultured stem cell. (b)To check the transformational ability of cancerous cell for the co cultured stem cell with administration of andrographolide without any pretreatment. (c) To check the transformational ability of andrographolide pretreated cancerous cell for the co cultured stem cell.

Also there is a significant lowering of expression of proteins like Cyclin-D, Cyclin-A, CDK-4, CDK-2 (important for progression of cell cycle into synthetic and mitotic phases) and overexpression of CDK Inhibitors (cyclin dependent kinases), cyclin inhibitors like p16, p21, p27 ultimately leading to arrest of cell cycle at G0/G1 phase [26]. In cases of lymphocytic leukemia and human epidermoid leukemia it has been known that alcoholic extract of andrographolide is effective in inducing cytotoxicity of cancerous cells.

Andrographolide is also known to increase the apoptosis and necrosis of cancerous cells [17]. Apoptosis promotion occurs in a strategic manner by up regulation of extrinsic ligands for the ligand-receptor based induction of apoptosis. There is a subsequent overexpression of both activator caspase (caspase8) and effector caspases (caspase3/7/9) along with subsequent amplication of the mitochondrial signal in form of cytochrome c via the pro-apoptotic Bcl-2 family of protein upregulation [20]. Further the TNF-alpha ligand expression is elevated in presence of andrographolide that helps in induction of apoptosis via TRAIL pathway (TNF-alpha related apoptosis inducing ligand). This plant-derived lactone is also known to reduce the levels of NF-κB and IFN-v along with the levels of ROS (reactive oxygen species)

and RNS (reactive nitrogen synthase) and thereby limiting the overall cell-proliferation ability [31,32]. IL-2 level also rises subsequent to the treatment of andrographolide that helps in cytotoxicity of cancerous cells [12,16,21]. Angiogenesis promoting factors like VEGF (Vascular epithelial Growth factor), NO (nitric oxide), VCAM (vesicular cell adhesion molecule) are lowered along with upregulation of inhibitor of metalloproteinases in presence of andrographolide [25].

Andrographolide is now a day's being effectively used in combination therapy along with chemotherapy in order to escalate the effectiveness of chemotherapy along with elimination of undesired side effects. In case of healthy cells, andrographolide extends its friendly characteristics by protecting the cells from chemicals like cyclophosphamide, hydrocortisone, hepatotoxins etc. [23].

## CONCLUSION

It had been shown that andrographolide plays an important role in the inhibition of Janus tyrosine kinases-signal transduction pathways, Phosphatidylinositol 3-kinase (PI-3K) and NF-κB signaling pathways and the induction of tumour suppressor proteins p53 and p21. All theses leading to inhibition of cancer cell proliferation, survival, metastasis and angiogenesis. So understanding the effect of andrographolide will play an important role in developing novel drugs against cancer treatment and stem cell homeostasis. In future days the major question to address for andrographolide research will be to translate the invitro experiments into animal models and to understand their biological significance.

## REFERENCES

1. Xu Y, Tokar EJ, Sun Y, Waalkes MP. Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype. Environ Health Perspect. 2012; 120: 865-871.
2. Jayakumar T, Hsieh CY, Lee JJ, Sheu JR. Experimental and Clinical Pharmacology of Andrographis paniculata and Its Major Bioactive Phytoconstituent Andrographolide. Evid Based Complement Alternat Med. 2013; 2013: 846740.
3. Kumar RA, Sridevi K, Kumar NV, Nanduri S, Rajagopal S. Anticancer and immunostimulatory compounds from Andrographis paniculata. J Ethnopharmacol. 2004; 92: 291-295.
4. Xu Y, Tokar EJ, Sun Y, Waalkes MP. Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype. Environ Health Perspect. 2012; 120: 865-871.
5. Chabner BA, Roberts TG Jr. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer. 2005; 5: 65-72.
6. Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. J Ethnopharmacol. 2005; 100: 72-79.
7. Mans DR, da Rocha AB, Schwartsmann G. Anti-cancer drug discovery and development in Brazil: targeted plant collection as a rational strategy to acquire candidate anti-cancer compounds. Oncologist. 2000; 5: 185-198.
8. da Rocha AB, Lopes RM, Schwartsmann G. Natural products in anticancer therapy. Curr Opin Pharmacol. 2001; 1: 364-369.
9. Warber SL, Seymour M, Kaufman PB, Kirakosyan A, Cseke LJ. Modes of action at target sites. In: Cseke LJ, Kirakosyan A, Kaufman PB, Warber SL, Duke JA, Brielmann HL, editors. Natural Products from Plants. Boca Raton, Fla, USA: CRC Press, Taylor and Francis. 2006; 415–440.
10. Butler MS, Newman DJ. Mother Nature's gifts to diseases of man: the impact of natural products on anti-infective, anticholestemics and anticancer drug discovery. Prog Drug Res. 2008; 65: 3-44.
11. Oberlies NH, Kroll DJ. Camptothecin and taxol: historic achievements in natural products research. J Nat Prod. 2004; 67: 129-135.
12. Peterson F, Amstutz R. Progress in Drug Research, Natural Products as Drugs. Basel, Switzerland. Birkhauser. 2008; 66: 427.
13. Ebadi M. Pharmacodynamic Nature of Herbal Medicine. Boca Raton, Fla, USA: CRC Press, Taylor and Francis. 2007.
14. Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional Chinese medicine: a comparative overview. Evid Based Complement Alternat Med. 2005; 2: 465-473.
15. Padmavathi B, Rath PC, Rao AR, Singh RP. Roots of Withania somnifera Inhibit Forestomach and Skin Carcinogenesis in Mice. Evid Based Complement Alternat Med. 2005; 2: 99-105.
16. Olalde Rangel JA, Magarici M, Amendola F, Del Castillo O. The Systemic Theory of Living Systems. Part IV: Systemic Medicine--The Praxis. Evid Based Complement Alternat Med. 2005; 2: 429-439.
17. Konkimalla VB, Efferth T. Anti-cancer natural product library from traditional chinese medicine. Comb Chem High Throughput Screen. 2008; 11: 7-15.
18. Sabu KK, Padmesh P, Seeni S. Intraspecific variation in active principle content and isozymes of Andrographis paniculata Nees (Kalmegh): a traditional hepatoprotective medicinal herb. Journal of Medicinal and Aromatic Plant Sciences. 2000; 23: 637–647.
19. Woo AYH, Waye MMY, Tsui SKW, Yeung STW, Cheng CHK. Andrographolide up-regulates cellular-reduced glutathione level and protects cardiomyocytes against hypoxia/reoxygenation injury. Journal of Pharmacology and Experimental Therapeutics. 2008; 325: 226–235.
20. Li W1, Xu X, Zhang H, Ma C, Fong H, van Breemen R, et al. Secondary metabolites from Andrographis paniculata. Chem Pharm Bull (Tokyo). 2007; 55: 455-458.
21. Rajani M, Shrivastava N, Ravishankara MN. A rapid method for isolation of andrographolide from andrographis paniculata nees (kalmegh). Pharm Biol. 2000; 38: 204-209.
22. Lomlim L, Jirayupong N, Plubrukarn A. Heat-accelerated degradation of solid-state andrographolide. Chem Pharm Bull (Tokyo). 2003; 51: 24-26.
23. Smith AB, Toder BH, Carroll PJ, Donohue J. Andrographolide: an X-ray crystallographic analysis. Journal of Crystallographic and Spectroscopic Research. 1982; 12: 309–319.
24. Yu BC, Hung CR, Chen WC, Cheng JT. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med. 2003; 69: 1075-1079.
25. 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.
26. Liu IM, Cheng JT. Mediation of Endogenous Î²-Endorphin in the Plasma Glucose-Lowering Action of Herbal Products Observed in Type 1-Like Diabetic Rats. Evid Based Complement Alternat Med. 2011; 2011: 987876.
27. Jada SR, Subur GS, Matthews C, Hamzah AS, Lajis NH, Saad MS, et al. Semisynthesis and in vitro anticancer activities of andrographolide analogues. Phytochemistry. 2007; 68: 904-912.

28. Siripong P, Konkathip B, Preechanukool K, Picha P, Tunsuwan K, et al. Cytotoxic diterpenoid constituents from Andrographis paniculata Nees. Leaves. Journal of the Science Society of Thailand. 1992; 18: 187–194.

29. Geethangili M, Rao YK, Fang SH, Tzeng YM. Cytotoxic constituents from Andrographis paniculata induce cell cycle arrest in jurkat cells. Phytother Res. 2008; 22: 1336-1341.

30. Cheung HY, Cheung SH, Li J, Cheung CS, Lai WP, 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: 1106-1111.

31. Wang S. The promise of cancer therapeutics targeting the TNF-related apoptosis-inducing ligand and TRAIL receptor pathway. Oncogene. 2008; 27: 6207-6215.

32. Chiou WF, Chen CF, Lin JJ. Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells by andrographolide. Br J Pharmacol. 2000; 129: 1553-1560.

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