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**Meeting Report**

# Profiling natural compounds: focus on cancer

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**Abstract**

Natural sources such as plants, insects and microorganisms have provided humans with therapeutic agents for thousands of years, and technological advances have allowed the modification of such natural compounds to generate better drugs. At cancer conferences worldwide, there is a constant flow of data on potent anticancer and/or chemopreventive agents isolated from natural sources. Likewise, nature provides molecules with novel mechanisms of action, which could be exploited to suppress processes implicated in cancer. Resveratrol, silibinin, ellagic acid, MK-615, curcumin, EGCG, erucin and licofelone are just several of the natural compounds that were discussed at the 65th Annual Meeting of the Japanese Cancer Association and the 5th Annual International Conference on Frontiers in Cancer Prevention Research. Findings and presentations at both conferences provided a clear message that natural products will continue to be of great interest as potential drugs, and further investigation of the world's biodiversity is expected to replenish pipelines with novel molecules.

## Introduction

Compounds derived from natural sources continue to attract interest at cancer conferences worldwide, promising potent anticancer and/or chemopreventive activity and novel mechanisms of action. The 65th Annual Meeting of the Japanese Cancer Association held in Yokohoma in September 2006 and the 5th Annual International Conference on Frontiers in Cancer Prevention Research held in Boston in November 2006 provided platforms for the presentation and discussion of novel findings surrounding natural compounds and cancer treatment and prevention. The structures of the compounds discussed below are shown in Figure 1.

## Natural compounds for cancer

The insect-derived antibacterial agent **5-S-GAD** (**1**) was shown to have an inhibitory effect on tumor-associated angiogenic processes *in vivo*. Unlike some antiangiogenic agents that act on signaling pathways associated with pericytes, 5-S-GAD was found to directly affect endothelial cells (1). Korean scientists have discovered that an active compound called **verrucosidin** (**2**), a pyrone-type polyketide, isolated from *Penicillium verrucosum* var. *cyclopium*, concentration-dependently suppressed the expression of the molecular chaperone GRP78 ($IC_{50}$ = 50 nM), which is associated with glucose deprivation-induced stress signaling pathways in poorly vascularized tumors. Verrucosidin was strictly selective for the hypoglycemic state, killing glucose-deprived human colon cancer cells (2). **Epoxyquinol B** (**3**), a fungal metabolite with antiangiogenic activity, suppressed vascular endothelial growth factor (VEGF)-induced activation of VEGFR2/PLCγ/ERK1/2 signaling, inhibited the migration of human umbilical vein endothelial cells (HUVEC) and exhibited antitumor properties (3). **Cucurbitacin E** (**4**), a triterpenoid derived from cucurbitaceous plants, potentiated doxorubicin's effect in various tumors (4), while an active component of *Angelica keiskei*, designated **xanthoangelol** (**5**), was suggested to induce apoptosis in cancer cells by increasing p53 expression without changing the levels of Bcl-2 and Bax (5). A metabolite derived from actinomycetes, **lysocellin** (**6**), induced G1 cell cycle arrest by increasing p21 and reducing cyclin D1 expression. Additionally, pretreatment with lysocellin reduced unwanted toxicity and alopecia associated with etoposide treatment in rats (6).

**MK-615**, an antineoplastic agent extracted from the Japanese apricot, demonstrated antitumor activity, inducing apoptosis, arresting cancer cells in the G2/M phase of the cell cycle and inhibiting Aurora A kinase activity (7). Incubation of breast cancer cell lines with MK-615 resulted in concentration-dependent apoptosis (8). An ingredient found in vegetables, **arctigenin** (**7**), was found not only to suppress the activation of the arylhydrocarbon (AhR) receptor but also to inhibit AhR-mediated signaling (9). Lung mutagenesis caused by NNK (4-[methylnitrosamino])-1-[3-pyridyl]-1-butanone) was prevented in mice given **nobiletin** (**8**), a flavonoid commonly found in citric fruits (10), and **pomegranate fruit juice** (3% or

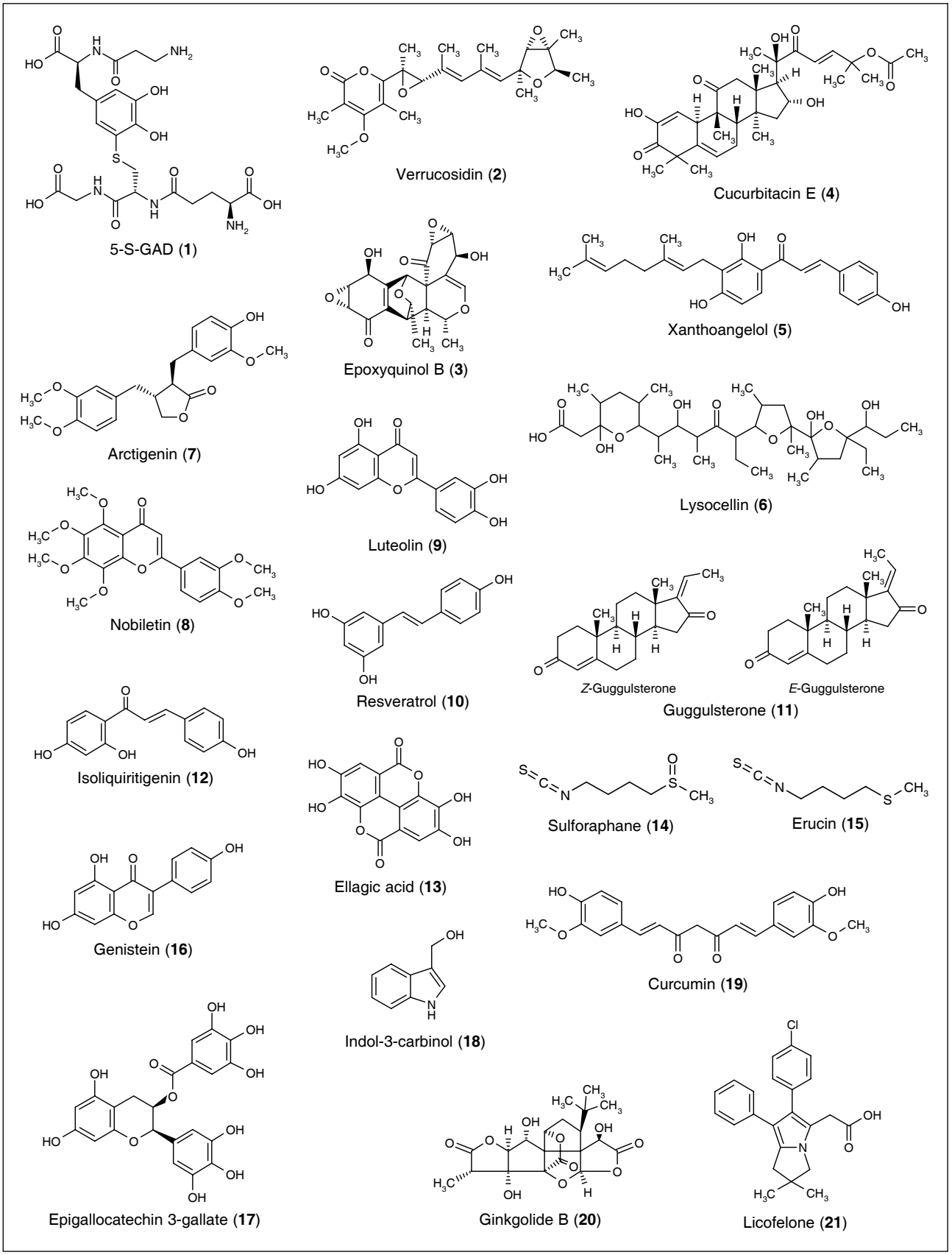


Fig. 1. Structures of natural compounds with potential in the treatment or prevention of cancer.

higher concentration) induced apoptosis in prostate cancer cells (11).

***Ganoderma lucidum*** was found to have potential not only for the prevention and treatment of cancer, but also for protecting against toxicity from chemotherapy and for potentiating immunity (12). Combination of TRAIL (TNF-related apoptosis-inducing ligand) and **luteolin** (**9**), a flavonoid that activates death receptor 5 (DR5), sharply increased the level of apoptosis in cancer cells when compared to treatment with either agent alone (13). A component of the Chinese herbal medicine "saibokuto", called ***Scutellaria baicalensis***, suppressed proliferation and induced apoptosis in an estrogen-responsive B-1F cell line; however, "saibokuto" was found to stimulate proliferation of these cells (14).

**Resveratrol** (**10**), an active ingredient in grapes and red wine currently in phase I/II development, was found to suppress growth and induce apoptosis in androgen-dependent and -independent prostate cancer cells, upregulating the expression of p53, Bax, Bak, PUMA, Noxa and Bim, and downregulating Bcl-2 and Bcl-$X_L$. It also inhibited the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and increased the level of histone H3 and H4 acetylation. The authors suggested that sensitivity to resveratrol depends on the interaction among p53, Akt and the caspase-mediated apoptotic pathway, and that it could potentially be used as a chemopreventive agent (15). Another study reported that the antiproliferative activity of resveratrol in the ABC-type lymphoma cell line is the result of its inhibitory effect on STAT3/Myc signaling to glycolysis. Disruption of this signaling represents a novel strategy for treating ABC-type lymphoma, a disease that has only a 35% 5-year survival rate (16).

An extract of *Commiphora mukul* contains a compound called **guggulsterone** (**11**), which is used in traditional Indian medicine and has shown anticancer activity in acute myeloid leukemia (AML), prostate and lung cancers. Scientists from the University of Pittsburgh reported that guggulsterone inhibits the proliferation of head and neck squamous cell carcinoma (HNSCC) cell lines and concentration-dependently reduces the levels of phoshorylated and total STAT3, an oncogenic transcription factor often constitutively active in HNSCC (17).

**Silymarin** and **silibinin** are extracts of milk thistle (*Silybum marianum)* widely used as nonprescription dietary supplements for their hepatoprotective properties. There are eight primary compounds, called flavonolignans, in milk thistle: silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin and taxifolin. These compounds were found to be cytotoxic and/or growth-suppressive in tumor cells lacking p53 or p21, with isosilybin B being the most potent and selective for tumor cells. Milk thistle compounds, especially silybin A, silybin B, isosilybin A and isosilybin B, induced IGFBP-3 (insulin-like growth factor binding protein-3) protein and suppressed the expression of AMACR ($\alpha$-methylacyl-CoA racemase), a prostate cancer biomarker, suggesting that they might be preferable to silymarin or silibinin as chemopreventive agents (18, 19).

The dried roots and stolons of *Glycyrrhiza glabra* L., commonly known as licorice, are comprised of 1-1.5% flavonoids, such as **isoliquiritigenin** (**12**), which have potent antioxidant properties. A study from Ohio State University offered evidence on the ability of isoliquiritigenin to increase mRNA expression of downregulated tumor suppressor genes, as well as to prevent 1,2-dimethylhydrazine (DMH)-induced formation of lung and colon tumors in mice. Further evaluation of this botanical as a chemopreventive agent is warranted (20).

**Ellagic acid** (**13**), a phenolic compound abundant in fruits, possesses anticancer and chemopreventive properties. A study from the New York University School of Medicine recently demonstrated that ellagic acid decreases the expression of epidermal growth factor receptor (EGFR) in human cervical carcinoma (Caki) and lung cancer (A-549) cells via a p53-independent mechanism (21). **Sulforaphane** (**14**), an isothiocyanate present in broccoli and cruciferous vegetables, is a potent inducer of enzymes such as glutathione *S*-transferases, glucuronyltransferases and quinone reductases, which are responsible for carcinogen elimination. It is thus being considered as a potential chemopreventive agent. Scientists from the State University of New Jersey have found that concentrations of sulforaphane used for intestinal perfusion of rat ileum segments affected the level of intestinal disposition and sulforaphane's ability to modulate gene expression. Taking into account the altered pharmacokinetic parameters reported in this study would facilitate the proper design of prevention strategies with sulforaphane (22). Meanwhile, a study from the University of California at Santa Barbara reported that sulforaphane and its sulfide analogue **erucin** (**15**) blocked the proliferation of human breast cancer MCF7 cells ($IC_{50}$ = 11 and 19 $\mu$M, respectively) by arresting them in the G2/M phase, disrupting mitotic spindle formation and proper chromosome segregation and inducing apoptosis. High concentrations of either compound were also toxic to normal human mammary epithelial cells, but did not cause an apparent block in mitosis (23).

According to results from several studies, **genistein, epigallocatechin 3-gallate (EGCG), indol-3-carbinol (I3C), curcumin, ginkgolide B** and **licofelone** (**16-21**) continue to be investigated as promising chemopreventive agents. All six agents are currently undergoing clinical development. Diet supplemented with curcumin, which is in phase II/III trials as an oncolytic agent at various organizations, including Hadassah Medical Organization, Johns Hopkins University, M.D. Anderson Cancer Center and Tel-Aviv Sourasky Medical Center, was found to prevent hematogenous breast cancer metastases in immunodeficient mice (24), as well as to enhance the apoptosis-inducing potential of TRAIL and sensitize TRAIL-resistant prostate cancer cells (25). Additionally, liposomal curcumin was also effective in blocking the proliferation of human prostate cancer cells (26). The addition of genistein (phase II; National Cancer Institute) to prostate cancer LNCaP cells enhanced the apoptotic effect of $\gamma$-tocotrienol (27), and two reports dis-

cussed the mechanisms underlying the chemopreventive properties of EGCG (phase II; National Cancer Institute) (28, 29). A study from Dongeui University and the University of Maryland suggested that I3C (phase II; National Cancer Institute) inhibits cancer progression and metastasis by restoring tight junctions in prostate cancer (30). Licofelone, a potent cyclooxygenase (COX) and lipoxygenase (LOX) inhibitor that is currently in phase III development for osteoarthritis by EuroAlliance, induced apoptosis and suppressed the growth of cells derived from human benign prostatic hyperplasia (BPH). Incubation of metastatic prostate cancer 59R cells with licofelone markedly reduced the protein and mRNA levels of prostaglandin $E_2$ ($PGE_2$), COX-2, LOX-5 and vascular endothelial growth factor (VEGF), suggesting that its potent activity against prostate cancer cells involves its ability to abrogate the function of enzymes involved in arachidonic acid metabolism (31). Modulation of platelet-activating factor (PAF) and its receptor PAFR by gingkolide B was reported as a potentially useful therapeutic and/or chemopreventive approach to manage ovarian cancer, since PAFR is overexpressed in various ovarian cancer cell lines and tissues (32).

## References


1. Akiyama, N., Kunimasa, K., Oikawa, T. et al. *Inhibition of angiogenesis by 5-S-GAD, an insect-derived antibacterial substance.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1153.

2. Park, H.R., Ryoo, I.J., Choo, S.J., Hwang, J.H., Kim, J.Y., Cha, M.R., Yoo, I.D. *Cytotoxic activity of verrucosidin as a GRP78 down-regulator against HT-29 human colon carcinoma cells at low glucose concentration.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst O-073.

3. Kamiyama, H., Kakeya, H., Miyazaka, O., Nishikawa, K. *Anti-angiogenic effects by epoxyquinol B.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1158.

4. Nagamine, M., Sadzuka, Y. *Effect of cucurubitacin E on anti-tumor activity of doxorubicin.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst O-230.

5. Motani, K., Tabata, K., Kimura, Y., Akihisa, T., Suzuki, T. *Xanthoangelol, a constituent of Angelica keiskei, induces p53-mediated apoptosis in neuroblastoma.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst O-074.

6. Takahara, Y., Yogosawa, S., Kamiyama, J. et al. *Lysocellin, a metabolite of the novel drug 'alopestatin', induces G1 arrest and prevents cytotoxicity induced by etoposide.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-332.

7. Sawada, T., Okada, T., Nakagawa, A., Mori, S., Ohsawa, T., Adachi, M., Kubota, K. *New anti-neoplastic agent, MK615 inhibits various types of human cancer.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1043.

8. Nakagawa, A., Sawada, T., Okada, T., Ohsawa, R., Adachi, S., Kubota, K. *New anti-neoplastic agent, MK615 from Japanese apricot inhibits growth of breast cancer cells in vitro.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1044.

9. Sekimoto, M., Umehara, K., Remoto, K., Degawa, M. *Inhibitory effect of arctigenin on arylhydrocarbon receptor (AhR)-mediated biological reaction.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-010.

10. Ikeda, M., Masumura, K., Matsui, K., Kohno, H., Sakuma, K., Tanaka, T., Nohmi, T. *Chemopreventive effect of nobiletin on NNK-induced mutagenesis in the lung of gpt delta transgenic mouse.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-009.

11. Asamoto, M., Tang, M., Kanda, C., Naike, A., Hokaiwado, N., Shirai, T. *Effects of pomegranate fruit juice for apoptosis in prostate cancer.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst O-301.

12. Sakazaki, T., Kuramoto, F., Itokawa, Y., Gu, Y. *Anti-cancer and immunological enhancement effect by Ganoderma lucidum.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1046.

13. Horinaka, M., Yoshida, T., Shiraishi, T., Nakata, S., Nishino, H., Sakai, T. *Combination-oriented molecular-targeting prevention in cancer – Combination with TRAIL and DR5 inducer, luteolin.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst O-302.

14. Murashima, T., Nishizawa, Y., Yamasaki, M., Nishizawa, Y. *Effects of Scutellaria baicalensis on the proliferation of estrogen-responsive cell line B-1F.* 65th Annu Meet Jpn Cancer Assoc (Sept 28-30, Yokohama) 2006, Abst P-1047.

15. Srivastava, R., Shankar, S. *Resveratrol regulates Bcl-2 family members, phosphatidylinositol 3'-kinase/AKT, mitochondrial p53 and apoptosis in prostate cancer cells.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A37.

16. Faber, A.C., Chiles, T.C. *Disruption of constitutively active Stat3 signaling and myc-mediated glycolysis with the polyphenolic compound resveratrol inhibits proliferation and induces apoptosis in activated B-cell (ABC)-type lymphoma.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A101.

17. Leeman, R.J., Singh, S.V., Grandis, J.R. *Guggulsterone and chemoprevention of head and neck squamous cell carcinoma.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst PR-02.

18. Pappa, A., Agarwal, R., Milikowsky, M.J., Wani, C.M., Oberlies, H.N., Kroll, J.D. *Flavonolignans from extracts of milk thistle (Silybum marianum) suppress biomarkers of prostate oncogenesis and colon carcinoma cell proliferation independently of p53 or p21.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B89.

19. Graft, N.T., Kroll, J.D., Agarwal, R., Wani, C.M., Oberlies, H.N. *Preparation of large-scale samples of the major bioactive constituents in milk thistle (Silybum marianum) for preclinical investigations of prostate cancer chemoprevention.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B90.

20. Liu, Y., Chin, Y.W., Nines, R., Casto, B., Kinghorn, D.A., Pereira, A.M. *Prevention of mouse colon and lung tumors and modulation of mRNA expression of genes by isoliquiritigenin.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B109.

21. Narayanan, R., Hickey, C., Nargi, D. et al. *EGFR expression in human cancer cells is down-regulated by the phenolic anti-oxidant ellagic acid.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A88.

22. Agrawal, S., Xu, Y., Desiderio, J., Cook, J.T. *Intestinal disposition of sulforaphane in rat ileum and its concentration dependent effects on gene expression of metabolizing enzymes and transporters.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B106.

23. Azarenko, O., Jordan, A.M., Wilson, L. *Effects of the isothiocyanates sulforaphane and erucin on breast cancer and normal human mammary epithelial cells.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B158.

24. Bachmeier, B.E., Nerlich, A.G., Iancu, C.M. et al. *The chemopreventive polyphenol curcumin prevents hematogenous breast cancer metastases in immunodeficient mice.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A67.

25. Shanakr, S., Siddiqui, I., Srivastava, R. *Curcumin enhances the apoptosis-inducing potential of TRAIL in prostate cancer.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B85.

26. Thangapazham, L.R., Tele, C.S., Passi, N., Puri, A., Blumenthal, R., Maheshwari, K.R. *Liposomal curcumin inhibits the proliferation of human prostate cancer cells in vitro.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B95.

27. Vraka, S.P., Constantinou, I.A. *Equol and genistein enhance the apoptotic effects of gamma-tocotrienol in prostate cancer LNCaP cells.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B80.

28. Kuzuhara, T., Sei, Y., Yamaguchi, K., Tanabe, T., Suganuma, M., Fujiki, H. *New aspects of cancer prevention with green tea catechin.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A96.

29. Dong, Z. *Molecular targets for cancer prevention by tea polyphenols.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A85.

30. Kim, O.S., Eddington, N., Choi, H.Y., Lee, J.I. *Effects of indol-3-carbinol (I3C) on tight junction activity in prostate cancer cells- LNCAP, PC3 and DU145.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst B115.

31. Narayanan, N.K., Hickey, C.H., Nargi, D., Narayanan, B.A. et al. *Licofelone down-regulates lipoxygenases LOX-5, LOX-12, and vasculoendothelial growth factor (VEGF) in metastatic prostate cancer cells.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A87.

32. Aponte, M.M., Kwong, J., Mok, S.C., Berkowitz, R.S., Cramer, D.W., Ye, B. *Gingkolide may prevent ovarian cancer through the platelet activating factor receptor (PAFR) pathway.* 5th Annu Int Conf Front Cancer Prev Res (Nov 12-15, Boston) 2006, Abst A106.