Title
Natural products and transforming growth factor-beta (TGF-β) signaling in cancer development and progression.

Journal
Current Cancer Drug Targets, 13(5)

ISSN
1568-0096

Authors
Lee, Chung
Zhang, Qiang
Kozlowski, James
et al.

Publication Date
2013-06-01

DOI
10.2174/15680096113139990034

Peer reviewed

Natural Products and Transforming Growth Factor-beta (TGF-β) Signaling in Cancer Development and Progression

Chung Lee[1,2,*], Qiang Zhan[1], James Kozlowski[1], Charles Brendler[3], Marcelo B. Soares[4], Atrya Dash[5], Michael McClelland[6], Michael McClelland[7] and Dan Mercola[6]

[1]Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA; [2]Departments of Pathology and Urology, University of California at Irvine, Irvine, CA 92697, USA; [3]Department of Surgery, NorthShore University Health System, Evanston, IL 60201, USA; 4Cancer Biology and Epigenomics Program, Children's Memorial Research Center, Chicago IL 60614, USA; [5]Department of Urology, University of California at Irvine, Irvine, CA 92697, USA; [6]Department of Pathology, University of California at Irvine, Irvine, CA 92697, USA; [7]Department of Pathology and Laboratory Medicine, the University of California at Irvine, CA. 92697, USA

Abstract: Actions of many herbal medicine products for cancer treatment are linked to an altered production of TGF-β in the target cells. An altered TGF-β production in the target cells will have profound effects on the patients. Therefore, it is important that we review the pros and cons of these products on cancer development and progression in terms of TGF-β signaling. It has been well established that TGF-β is growth inhibitory to benign cells or early stages of cancer cells but it is tumor promoting and metastatic for advanced malignancies. Further, many dietary components can alter gene-specific DNA methylation levels in systemic and in target tissues. Since TGF-β signaling in cancer is closely linked to the DNA methylation profiles, we also review the effect of dietary components on DNA methylation. In light of this knowledge, it is important to note that many natural products that can induce TGF-β production in the target cells may be beneficial in preventing cancer development but may be harmful for cancer patients, especially when they harbor advanced stage cancer.

A discussion of the effect of herbal natural products on cancer can be divided into three categories. The first category of herbal medicine products will be those related to the induction of cancer as far as TGF-β is concerned. Since TGF-β is growth inhibitory and pro-apoptosis to benign cells, any herbal medication that can induce the production of TGF-β in the target cells will be beneficial to the patients. However, such herbal medicine may not necessarily be beneficial for patients with established and advanced cancer. The second category of herbal products will inhibit TGF-β signaling and will reduce TGF-β mediated growth promotion and metastasis in advanced cancers. For patients with established and advanced cancer, agents that can inhibit the production of TGF-β may also inhibit cancer growth and metastasis. Finally, the third category of herbal products has no impact on TGF-β signaling, such as lycopene.

Keywords: Dietary components, DNA methylation, non-Smad pathways, Smad pathways, TGF-β signaling, Tumor development and progression.

INTRODUCTION

It is known that TGF-β can inhibit growth in benign cells and early stage cancer cells, but it will promote progression and metastasis in advance stages of cancers. Since many herbal products used for cancer prevention and treatment have an effect on TGF-β signaling, it is therefore important that we understand the action of these herbal products in relationship to TGF-β signaling. In this review, we will briefly discuss three categories of herbal products used in prevention and treatment of cancer patients. The first class of herbal products will induce TGF-β production in the target cells. The second class of herbal products will inhibit TGF-β signaling. The third class of herbal products has no effect on TGF-β signaling.

Biology of TGF-β Signaling

TGF-β represents a family of pleiotropic growth factors with diverse functions, such as embryonic development, wound healing, organ development, immuno-modulation, and cancer progression [1, 2]. There are three known mammalian isoforms of TGF-β (TGF-β1, -β2, and -β3) with significant homology and similarities in function. The biological effect of TGF-β is mediated through type I (TβRI), type II (TβRII) receptors and downstream transcription factors, Smad [3, 4]. While this is the conventional pathway for TGF-β signaling, other signaling pathways, which lack the classical growth inhibitory functions of TGF-β, have also been identified, such as MAPK, PI3K, PP2A/p70s6K, and JNK [5]. The relative importance and interplay of the Smad and non-Smad pathways of TGF-β signaling are still under investigation.

TGF-β Paradox: Differential Response to TGF- β between Benign and Cancer Cells

The well known TGF-β paradox is that TGF-β is a potent inhibitor to benign cells but promotes proliferation and invasion in cancer cells. The molecular mechanism of this TGF-β paradox remains unexplained. The inhibition of cell proliferation by TGF-β is due to cell cycle arrest in the G1 phase. The signaling system responsible for this growth arrest mechanism includes activation of TGF-β receptors (type I and type II) and their downstream transcription factors, Smad signal transducers. However, in cancer cells, the inhibitory property of TGF-β is greatly diminished. In the majority of advanced cancer cases, TGF-β enhances proliferation, invasion, metastasis and evasion of host immune surveillance. In addition to the loss of responsiveness of the cancer cells to TGF-β mediated growth inhibition, these cells secrete increasing amounts of TGF-β, which itself serves as a pro-malignant factor by suppressing anti-tumor immune response of the host and by augmenting angiogenesis [6-8].

The effect of TGF-β on proliferation varies according to the type of target cells. In our recent study [8], we observed a differential regulation of proliferation and growth arrest between normal (benign) and cancer cells in response to TGF-β. We have investigated the mechanism of this dual effect on proliferation and growth arrest by TGF-β. Although TGF-β mediates Erk activation at low doses (0.1 ng/ml) in both benign and cancer cells, at high doses (10 ng/ml), TGF-β treatment resulted in an inactivation of Erk in benign cells but continue to activate Erk in cancer cells [8]. This differential activation of Erk in cancer cells by TGF-β but not in benign cells has not been appreciated before and provides the answer to the known TGF-β paradox.

DNA Methylation in Cancer and TGF-β Signaling in DNA Methylation

Epigenetic changes are characteristic of nearly all malignancies and include changes in DNA methylation, histone modification and microRNAs. DNA methylation plays a critical role in cancer development and progression [9]. Alteration of DNA methylation patterns leads to deregulation of gene expression, in the absence of mutation. All tumors that have been examined show changes in DNA methylation, suggesting that this may represent a basic element of cancer biology, which bears a significant impact on tumor pathology [10-12]. There is a close relationship between the status of DNA hypermethylation and TGF-β signaling in cancer cells. TGF-β is a key regulator for DNA methylation through an increase in DNMTs expression, especially in cancer [13, 14]. There exists a differential effect of TGF-β mediated DNMT activities between benign and malignant cells. In benign cells, TGF-β inhibits DNMT expression [15, 16]. In cancer cells, TGF-β stimulates DNMT expression [13, 14]. It should be noted that, in light of the importance of both TGF-β signaling and DNA methylation in tumor progression, the majority of the methylated gene in cancer are relevant to TGF-β signaling [13]. This is consistent with our observation that over-expression of TGF-β and/or DNMTs is associated with aggressiveness and poor prognosis in prostate cancer [14, 17, 18].

Three Classes of Natural Products in Relation to TGF-β Production in Target Cells

Table 1 lists three classes of natural products in relation to TGF-β production. Class I illustrates some examples of natural products that induce TGF-β production in target cells. Class II are natural products that inhibit TGF-β signaling; while Class III are examples of natural products that have no relation to TGF-β production.

Herbal Products that Induce TGF-β Production in Target Cells

Many herbal products have a protective effect against carcinogenesis. Aside from having the anti-oxidant property, they also induce TGF-β expression from the target cells. Since TGF-β is growth inhibitory and can induce apoptosis in normal non-cancer target cells, such property will be a suitable anti-cancer supplements for cancer prevention. Examples for these products include seaweed [19] and resveratrol [20]. Other products, such as Inchin-ko-to [21] and Long Dan Tan [22], also have the ability to induce TGF-β production in target cells. Additional studies revealed that *Scutellaria baicalensis Georgi* (Sb) and *Bupleurum scorzonerifolfium Willd* (Bs) can inhibit cell proliferation by an increase in TGF-β production in target cells [23]. Euonymus alatus (Thunb.) Sieb (EA), known as "gui-jun woo" in Korea, which is used for leiomyomal tumors, exhibited a much lower proliferation rate than untreated cells, suggesting that EA inhibited the cellular proliferation of uterine leiomyomal cells. TGF-β can achieve a similar effect in place of Thunb/EA in combination [24, 25]. It should be pointed out that, since these agents can induce TGF-β production in target cells, they are suitable for cancer prevention but should be careful in administrating these agents for the purpose of treatment of established cancers.

Herbal Products that Inhibit TGF-β Signaling in Target Cells

The best examples of this class of herbal products are flavenoids, such as genistein, with their ability to inhibit tumor progression and metastasis [26]. Aside from their ability to possess the anti-oxidant property, they can inhibit TGF-β signaling in the target cells, thus help to inhibit tumor growth and metastasis. The best example of this class of herbal products has been the recent paper by Lin et al. [27] who have delineated how Andrographolide down-regulates hypoxia-inducible factor-1β (HIF1β) by inhibiting TGF-β signaling in human non-small cell lung cancer A549 cells. Other natural products belonging to this class include green tea and black tea extracts [28, 29, 52], *angelica sinensis* [30], *machilus thunbergii* [31], Chunggan extract (CGX) [32], *esculentoside A* [33], rhubarb extract [34], compound *Astragalus* and *Salvia miltiorrhiza* extract [35], Momordica charantia leaf extract [36], and *Polypodium leucotomos* [37, 38].

Herbal Products that have no Impact on TGF-β Signaling in Target Cells

Herbal products such as water extracts of many Korean medicine for uterine leiomyoma and citrus unshiu (*Satsuma mandarian*) have no effect on TGF-β production in cancer cells under culture conditions [39, 40]. Further, lycopene is an effective preventive agent for prostate cancer but has not effect on TGF-β production in cancer cells [41-43].

Dietary Factors and DNA Methylation

Diet and environmental factors directly influence epigenetic mechanisms in humans [9]. Dietary polyphenols from green tea, turmeric, soybeans, broccoli and others have shown to possess multiple cell-regulatory activities within cancer cells [18]. Because epigenetic deregulation occurs early in carcinogenesis and is potentially reversible, intervention strategies targeting the epigenome have been proposed for cancer prevention. Dietary components with anticancer potential, including folate, polyphenols, selenium, retinoids, fatty acids, isothiocyanates and allyl compounds, influence DNA methylation and histone modification processes [9, 18, 54]. Such activities have been shown to affect the expression of genes involved in cell proliferation, death and differentiation that are frequently altered in cancer. Table 2 lists selected natural products that reversed DNA hypermethylation and restore the expression of many tumor suppressor genes in target cells. Many natural products are able to reverse DNA hypermethylation through an inhibition of DNA methylatransferases (DNMT) [9]. This is consistent with the action of TGF-β, especially in benign cells or in early stage cancers, it inhibits DNMT expression [15, 16]. However, in advanced cancers, TGF-β stimulates the expression of DNMT [13, 14]. It remains unclear, if in advanced cancer cells, these natural products are still able to inhibit DNMT expression in the presence of an aberrant signaling events of TGF-β mediated vicious cycle in tumor progression [8, 14].

Table 1. Three classes of natural products related to the effect on TGF-β signaling.

Name	Description	References
Class I: natural products that induce TGF-β production in target cells*		
Seaweed	A natural source of iodine	[19]
Resveratrol	A natural phytoestrogen in red wine	[20, 30, 44]
Inchin-ko-to (ICKT)	An ancient oriental herbal formulation for jaundice	[45]
Genipin	A metabolite component of inchin-ko-to	[46]
Scutellaria baicalensis Georgi	A herbal medicine for liver diseases	[23]
Gui-jun woo	A Korean herbal medicine used for treatment of tumors	[24, 25]
EGCG	A natural product of tea extracts	[47, 48]
Momordica charantia	Leaf extract from bitter melon	[35, 49]
Polypodium leucotomos	A tropical fern plant	[36, 37]
Curcumin	Active components of spice turmeric	[64]
Class II: natural products that inhibit TGF-β signaling**		
Genistein	An active flavonoid in soy	[50, 51]
EGCG	A natural product of tea extracts	[52]
Long Dan Tan	A herbal medicines for chronic liver disease	[22]
Andrograpgolide	A diterpenoid lactone from a traditional herbal medicine	[27]
Angelica Sinensis	The root of *Angelica sinensis*, known as *Danggui*	[53]
Machilus	Barks of *Machilus* DGA is glycosidic triterpene alkaloids	[30]
Chunggan extract	A hepatotherapeutic herbal formula	[31, 53]
Esculentoside A	A saponin isolated from herb *phytolacca esculenta*,	[32]
Rhubarb (*dahuang*)	Extractof the dried radix and rhizome of *Rheum palmatum* L	[33]
Compound Astragalus Salvia miltiorrhiza extract (CASE)		
Extract of Leguminosae and Lamiaceae	[34]	
Polypodium leucotomos	A tropical fern plant	[36, 37]
Rosmarinic acid	Naturally occurring polyphenol in Labitae plants	[65]
Class III: natural products that have no impact on TGF-β production***		
Lycopene	A natural product of tomato	[40, 45, 46]
Satsuma mandarian	The peel of citrus fruit	[39]

*Since these agents can induce TGF-β production in target cells, they are suitable for cancer prevention. But, we should exercise caution, when using these agents for the purpose of established cancers.

**These agents listed in Class II are known to inhibit TGF-β signaling. Aside from their anti-oxidant property, they can be used to help to inhibit tumor growth and metastasis.

***Although these products have established anti-cancer effects, they have nothing to do with TGF-β signaling. Therefore, no recommendation will be offered regarding their administration.

Table 2. Natural products that are able to reverse DNA hypermethylation in target cells.

Name	Description	References
EGCG	A natural product of tea extracts	[39, 54]
Genistein	An active flavonoid in soy	[56-58]
Lycopene	A natural product of tomato	[58, 59]
Curcumin	Active components of the spice turmeric	[60, 61]
Resveratrol	A natural phytoestrogen in red wine	[62, 63]
Rosmarinic acid	Naturally occurring polyphenol in Labitae plants	[66]

This list does not intend to be comprehensive. Rather, these products all have a common property of inhibiting DNMT expression.

CONCLUSION

A variety of herbal medicines have been used either as a major medication or as a supplement either for cancer prevention or for cancer treatment. These herbal products have been administered to the population without consideration if the product is used for prevention or for treatment. As we understand the role of TGF-β in cancer cells is different from that in benign cells, we should exercise caution when we are taking these herbal products. Aside from the many effects of these herbal products on the target cells, from the point of view of TGF-β signaling, it is important that we distinguish when we are using these products for prevention or for treatment of cancer.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This report was presented before the International Conference on Natural Products and Cancer Targets: Progress and Promises (August 24-25, 2011, Zhengzhou University, Zhengzhou (Henan Province), China. The work performed by the authors was supported in part by NIH/NCI grants (Prostate Cancer SPORE P50 CA90386, EDRN U01 CA152738, and SPECS grant UO1 CA114810, and CA122558), grants from the Department of Defense (W81XWH-08-1-0720, W81XWH-09-1-0311), a grant from Northshore University Healthsystem, and a gift from the Fred Turner Foundation,

ABBREVIATIONS

Bs	=	Bupleurum scorzonerifolfium Willd
CASE	=	Compound Astragalus Salvia miltiorrhiza extract
CGX	=	Chunggan extract
DNA	=	deoxyribonucleic acid
DNMT	=	DNA methyltransferases, which consist of DNMT1, DNMT 3a and DNMT 3b
EA	=	Euonymus alatus (Thunb.) Sieb
EGCG	=	epigallocatechin gallate
Erk	=	extracellular signal-regulated kinase is a member of MAPK
HIF1α	=	hypoxia-inducible factor-1α
ICKT	=	Inchin-ko-to
MAPK	=	Mitogen activated protein kinase
p70s6K	=	A members of the serine/threonine protein kinase and is a downstream effector of the PI3K
PI3K	=	phosphoinositide 3-kinase
PP2A	=	Protein phosphatase 2A is a serine/ threonine protein phosphatase
RNA	=	ribonucleic acid
Sb	=	Scutellaria baicalensis Georgi
TGF-β	=	Transforming growth factor-beta
TβR	=	Transforming growth factor receptor, which consists type I (TβRI) and type II (TβRII)

REFERENCES

[1] Massagué, J. How Cells read TGF-β signals. Nature Rev. Mol. Cell. Biol. 2000, 1, 169-178.

[2] Derynck, R.; Akhurst, R. J.; Balmain, A. TGF-beta signaling in tumor suppression and cancer progression. Nat. Genet. 2001, 29, 117-129.

[3] Massague, J.; Cheifetz, S.; Laiho, M.; Ralph, D. A.; Weis, F.; Zentella. A. TGF-β. Cancer Surv. 1992, 12, 81-103.

[4] Dernyck, R.; Feng, X. TGF-β receptor signaling. Biochem. et Biophs. Acta. 1997, 333, F105-F150.

[5] Mu, Y.; Gudey, S. K.; Landström, M. Non-Smad signaling pathways. Cell Tissue Res. 2012, 347 (1), 11-20.

[6] Kretzschmar, M. Transforming growth factor-beta and breast cancer: Transforming growth factor-beta/SMAD signaling defects and cancer. Breast Cancer Res. 2000, 2 (2), 107-15.

[7] Teicher, B. A. Malignant cells, directors of the malignant process: role of transforming growth factor-beta. Cancer Metastasis Rev. 2001, 20 (1-2), 133-43.

[8] Yu, N.; Kozlowski, J. M.; Park, I. I.; Chen, L.; Zhang, Q.; Xu, D.; Doll, J. A.; Crawford, S. E.; Brendler, C. B.; Lee, C. Over-expression of transforming growth factor β1 in malignant prostate cells is partly caused by a runaway of TGF-β1 auto-induction mediated through a defective recruitment of protein phosphatase 2A by TGF-β type I receptor. Urology 2010, 76 (6), 1519.e8-13.

[9] Link, A.; Balaguer, F.; Goel, A. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. Biochem. Pharmacol. 2010, 80 (12), 1771-92.

[10] Cedar, H.; Bergman, Y. Programming of DNA Methylation Patterns. Annu. Rev. Biochem. 2012, 81, 97-117.

[11] Chiam K, Ricciardelli C, Bianco-Miotto T. Epigenetic Biomarkers in Prostate Cancer: Current and Future Uses. Cancer Lett. 2012,[Epub ahead of print].

[12] Sandoval, J.; Esteller, M. Cancer epigenomics: beyond genomics. Curr. Opin. Genet. Dev. 2012, 22 (1), 50-5.

[13] Matsumura, N.; Huang, Z.; Mori, S.; Baba, T.; Fujii, S.; Konishi, I.; Iversen, E. S.; Berchuck, A.; Murphy, S. K.; Epigenetic suppression of the TGF-beta pathway revealed by transcriptome profiling in ovarian cancer. Genome Res. 2011, 21 (1), 74-82.

[14] Zhang, Q.; Chen, L.; Helfand, B. T.; Zhu, L. J.; Kozlowski, J.; Minn, A.; Jang, T.; Yang, X. J.; Javonovic, B.; Guo, Y.; Lonning, S.; Harper, J.; Teicher, B. A.; Yu, N.; Brendler, C.; Wang, J.; Catalona, W. J.; Lee, C. Transforming Growth Factor-beta-induced DNA methyltransferase contributes to aggressive prostate cancer phenotypes and predicts biochemical recurrence after radical prostatectomy PloS ONE 2011, 6, e25168.

[15] Luo, X.; Zhang, Q.; Liu, V.; Xia, Z.; Pothoven, K. L.; Lee, C. Cutting Edge: TGF-β Induced expression of Foxp3 in T cells is mediated through inactivation of ERK. J. Immunol. 2008, 180, 2757-2761.

[16] You, H.; Ding, W.; Rountree, C. B. Epigenetic regulation of cancer stem cell marker CD133 by transforming growth factor-beta. Hepatology 2010, 51 (5), 1635-44.

[17] Zhang, Q.; Helfand, B. T.; Jang, T. L.; Zhu, L. J.; Chen, L.; Yang, X. J.; Kozlowski, J.; Smith, N.; Kundu, S. D.; Yang, G.; Raji, A. A.; Javonovic, B.; Pins, M.; Lindholm, P.; Guo, Y.; Catalona, W. J.; Lee, C. NF-kB-Mediated Transforming Growth Factor- β -Induced Expression of Vimentin is an Independent Predictor of Biochemical Recurrence After Radical Prostatectomy. Clinical Cancer Res. 2009, 15, 3557-3567.

[18] Lim, U.; Song, M. A. Dietary and lifestyle factors of DNA methylation. Chapter 23. Methods Mol. Biol. 2012, 863, 359-376.

[19] Funahashi, H.; Imai, T.; Tanaka, Y.; Tsukamura, K.; Hayakawa, Y.; Kikumori, T.; Mase, T.; Itoh, T.; Nishikawa, M.; Hayashi, H.; Shibata, A.; Hibi, Y.; Takahashi, M.; Narita, T. Wakame seaweed suppresses the proliferation of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in rats. Jpn. J. Cancer Res. 1999, 90 (9), 922-927.

[20] Lu, R.; Serrero, G. Resveratrol, a natural product derived from grape, exhibits antiestrogenic activity and inhibits the growth of human breast cancer cells. J. Cell. Physiol. 1999, 179(3), 297-304.

[21] Yamamoto, M.; Ogawa, K.; Morita, M.; Fukuda, K.; Komatsu, Y. The herbal medicine Inchin-ko-to inhibits liver cell apoptosis induced by transforming growth factor beta 1. Hepatology 1996, 23 (3), 552-559.

[22] Chou, C. C.; Pan, S. L.; Teng, C. M.; Guh, J. H. Pharmacological evaluation of several major ingredients of Chinese herbal medicines in human hepatoma Hep3B cells. Eur. J. Pharm. Sci. 2003, 19(5), 403-12.

[23] Lee, C. Y.; Hsu, Y. C.; Wang, J. Y.; Chen, C. C.; Chiu, J. H. Chemopreventive effect of selenium and Chinese medicinal herbs on N-nitrosobis(2-oxopropyl)amine-induced hepatocellular carcinoma in Syrian hamsters. Liver Int. 2008, 28 (6), 841-855.

[24] Lee, T. K.; Kim, D. I.; Han, J. Y.; Kim, C. H. Inhibitory effects of Scutellaria barbata D. Don. and Euonymus alatus Sieb. on aromatase activity of human leiomyomal cells. Immunopharmacol. Immunotoxicol. 2004, 26 (3), 315-327.

[25] Lee, T. K.; Lee, J. Y.; Kim, D. I.; Lee, Y. C.; Kim, C. H. Differential regulation of protein kinase C activity by modulating factors and Euonymus alatus (Thunb.) Sieb in human myometrial and uterine leiomyomal smooth muscle cells. Int. J. Gynecol. Cancer 2005, 15 (2), 349-58.

[26] McCarty, M. F. Isoflavones made simple - genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits. Med. Hypotheses. 2006, 66 (6), 1093-114.

[27] Lin, H. H.; Tsai, C. W.; Chou, F. P.; Wang, C. J.; Hsuan, S. W.; Wang, C. K.; Chen, J. H. Andrographolide down-regulates hypoxia-inducible factor-1β in human non-small cell lung cancer A549 cells. Toxicol. Appl. Pharmacol. 2011, 250 (3), 336-345.

[28] Roomi, M. W.; Roomi, N.; Ivanov, V.; Kalinovsky, T.; Niedzwiecki, A.; Rath, M. Inhibitory effect of a mixture containing ascorbic acid, lysine, proline and green tea extract on critical parameters in angiogenesis. Oncol. Rep. 2005, 14 (4), 807-815.

[29] Mandal, D.; Bhattacharyya, S.; Lahiry, L.; Chattopadhyay, S.; Sa, G.; Das, T. Black tea-induced decrease in IL-10 and TGF-beta of tumor cells promotes Th1/Tc1 response in tumor bearer. Nutr. Cancer 2007, 58 (2), 213-221.

[30] Han, G.; Zhou, Y. F.; Zhang, M. S.; Cao, Z.; Xie, C. H.; Zhou, F. X.; Peng, M.; Zhang, W. J. Angelica sinensis down-regulates hydroxyproline and Tgfb1 and provides protection in mice with radiation-induced pulmonary fibrosis. Radiat. Res. 2006, 165 (5), 546-552.

[31] Park, E. Y.; Shin, S. M.; Ma, C. J.; Kim, Y. C.; Kim, S. G. meso-dihydroguaiaretic acid from Machilus thunbergii down-regulates TGF-beta1 gene expression in activated hepatic stellate cells via inhibition of AP-1 activity. Planta. Med. 2005, 71 (5), 393-398.

[32] Shin, J. W.; Son, J. Y.; Oh, S. M.; Han, S. H.; Wang, J. H.; Cho, J. H.; Cho, C. K.; Yoo, H. S.; Lee, Y. W.; Lee, M.M.; Hu, X.P.; Son,

C. G. An herbal formula, CGX, exerts hepatotherapeutic effects on dimethylnitrosamine-induced chronic liver injury model in rats. World J. Gastroenterol. 2006, 12 (38), 6142-6148.

[33] Xiao, Z.; Su, Y.; Yang, S.; Yin, L.; Wang, W.; Yi, Y.; Fenton, B. M.; Zhang, L.; Okunieff, P.. Protective effect of esculentoside A on radiation-induced dermatitis and fibrosis. Int. J. Radiat. Oncol. Biol. Phys. 2006, 65 (3), 882-889.

[34] Yu, H. M.; Liu, Y. F.; Cheng, Y. F.; Hu, L. K.; Hou, M. Effects of rhubarb extract on radiation induced lung toxicity via decreasing transforming growth factor-beta-1 and interleukin-6 in lung cancer patients treated with radiotherapy. Lung Cancer 2008, 59 (2), 219-226.

[35] Liu, X.; Yang, Y.; Zhang, X.; Xu, S.; He. S.; Huang, W, Roberts MS. Compound Astragalus and Salvia miltiorrhiza extract inhibits cell invasion by modulating transforming growth factor-beta/Smad in HepG2 cell. J. Gastroenterol. Hepatol. 2010, 25 (2), 420-426.

[36] Pitchakarn, P.; Ogawa, K.; Suzuki, S.; Takahashi, S.; Asamoto, M.; Chewonarin. T.; Limtrakul, P.; Shirai, T. Momordica charantia leaf extract suppresses rat prostate cancer progression in vitro and in vivo. Cancer Sci. 2010, 101 (10), 2234-2240.

[37] Philips, N.; Dulaj, L.; Upadhya, T. Cancer cell growth and extracellular matrix remodeling mechanism of ascorbate; beneficial modulation by P. leucotomos. Anticancer Res. 2009, 29 (8), 3233-3238.

[38] Philips, N.; Conte, J.; Chen, Y. J.; Natrajan, P.; Taw, M.; Keller, T.; Givant, J.; Tuason, M.; Dulaj, L.; Leonardi, D.; Gonzalez, S. Beneficial regulation of matrixmetalloproteinases and their inhibitors, fibrillar collagens and transforming growth factor-beta by Polypodium

leucotomos, directly or in dermal fibroblasts, ultraviolet radiated fibroblasts, and melanoma cells. Arch. Dermatol. Res. 2009, 301 (7), 487-495.

[39] Bajracharya, P.; Lee, E. J.; Lee, D. M.; Shim, S. H.; Kim, K. J.; Lee, S. H.; Bae, J. J.; Chun, S. S.; Lee, T. K.; Kwon, S. H.; Choi, I. Effect of different ingredients in traditional Korean medicine for human uterine leiomyoma on normal myometrial and leiomyomal smooth muscle cell proliferation. Arch. Pharm. Res. 2009, 32 (11), 1555-1563.

[40] Lee, S.; Ra, J.; Song, J. Y.; Gwak, C.; Kwon, H. J.; Yim, S. V.; Hong, S. P.; Kim, J.; Lee, K. H.; Cho, J. J.; Park, Y. S.; Park, C. S.; Ahn, H. J. Extracts from Citrus unshiu promote immune-mediated inhibition of tumor growth in a murine renal cell carcinoma model. J. Ethnopharmacol. 2011, 133 (3), 973-979.

[41] Gunasekera, R. S.; Sewgobind, K.; Desai, S.; Dunn, L.; Black, H. S.; McKeehan, W. L.; Patil, B. Lycopene and lutein inhibit proliferation in rat prostate carcinoma cells. Nutr. Cancer 2007, 58 (2), 171-177.

[42] Wertz, K.; Siler, U.; Goralczyk, R. Lycopene: modes of action to promote prostate health. Arch. Biochem. Biophys. 2004, 430 (1), 127-134.

[43] Nantz, M. P.; Rowe, C. A.; Nieves, C. Jr.; Percival, S. S. Immunity and antioxidant capacity in humans is enhanced by consumption of a dried, encapsulated fruit and vegetable juice concentrate. J. Nutr. 2006, 136 (10), 2606-2610.

[44] Jang. M.; Pezzuto, J. M. Cancer chemopreventive activity of resveratrol. Drugs Exp. Clin. Res. 1999, 25 (2-3), 65-77.

[45] Tamura, T.; Kobayashi, H.; Yamataka, A.; Lane, G. J.; Koga, H.; Miyano, T. Inchin-ko-to prevents medium-term liver fibrosis in postoperative biliary atresia patients. Pediatr. Surg. Int. 2007, 23 (4), 343-347.

[46] Kitano, A.; Saika, S.; Yamanaka, O.; Reinach, P. S.; Ikeda, K.; Okada, Y.; Shirai, K.; Ohnishi, Y. Genipin suppression of fibrogenic behaviors of the alpha-TN4 lens epithelial cell line. J. Cataract Refract. Surg. 2006, 32 (10), 1727-1735.

[47] Vittal, R.; Selvanayagam, Z. E.; Sun, Y.; Hong, J.; Liu, F.; Chin, K. V.; Yang, C. S. Gene expression changes induced by green tea polyphenol (-)-epigallocatechin-3-gallate in human bronchial epithelial 21BES cells analyzed by DNA microarray. Mol. Cancer Ther. 2004, 3 (9), 1091-1099.

[48] Zhang, D.; Al-Hendy, M.; Richard-Davis, G.; Montgomery-Rice, V.; Rajaratnam, V.; Al-Hendy, A. Antiproliferative and proapoptotic effects of epigallocatechin gallate on human leiomyoma cells. Fertil. Steril. 2010, 94 (5), 1887-1893.

[49] Manabe, M.; Takenaka, R.; Nakasa, T.; Okinaka, O. Induction of anti-inflammatory responses by dietary Momordica charantia L.(bitter gourd). Biosci. Biotechnol. Biochem. 2003, 67 (12), 2512-2517.

[50] Pavese, J. M.; Farmer, R. L.; Bergan, R. C. Inhibition of cancer cell invasion and metastasis by genistein. Cancer Metastasis Rev. 2010, 29 (3), 465-482.

[51] Ji, G.; Yang, Q.; Hao, J.; Guo, L.; Chen, X.; Hu, J.; Leng, L.; Jiang, Z. Anti-inflammatory effect of genistein on non-alcoholic steatohepatitis rats induced by high fat diet and its potential mechanisms. Int. Immunopharmacol. 2011, 11 (6), 762-768.

[52] Whyte, L.; Huang, Y. Y.; Torres, K.; Mehta, R. G. Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. Cancer Res. 2007, 67 (24), 12007-12017.

[53] Kwak, K. G.; Wang, J. H.; Shin, J. W.; Lee, D. S.; Son, C. G. A traditional formula, Chunggan extract, attenuates thioacetamide-induced hepatofibrosis via GSH system in rats. Hum. Exp. Toxicol. 2011, 30 (9), 1322-1332.

[54] Fang, M.; Chen, D.; Yang, C. S. Dietary polyphenols may affect DNA methylation. J. Nutr. 2007, 137(1 Suppl), 223S-228S.

[55] Li, Y.; Tollefsbol, T. O. Impact on DNA methylation in cancer prevention and therapy by bioactive dietary components. Curr. Med. Chem. 2010, 17 (20), 2141-2151.

[56] Adjakly, M.; Bosviel, R.; Rabiau, N.; Boiteux, J. P.; Bignon, Y. J.; Guy, L.; Bernard-Gallon, D. DNA methylation and soy phytoestrogens, quantitative study in DU-145 and PC-3 human prostate cancer cell lines. Epigenomics 2011, 3 (6), 795-803.

[57] Majid, S.; Dar, A.A.; Shahryari, V.; Hirata, H.; Ahmad, A.; Saini, S.; Tanaka, Y.; Dahiya, A. V.; Dahiya, R. Genistein reverses hypermethylation and induces active histone modifications in tumor suppressor gene B-Cell translocation gene 3 in prostate cancer. Cancer 2010, 116 (1), 66-76.

[58] King-Batoon, A.; Leszczynska, J. M.; Klein, C. B. Modulation of gene methylation by genistein or lycopene in breast cancer cells. Environ. Mol. Mutagen 2008, 49 (1), 36-45.

[59] Liu, A. G.; Erdman, J. W. Jr. Lycopene and apo-10'-lycopenal do not alter DNA methylation of GSTP1 in LNCaP cells. Biochem. Biophys. Res. Commun. 2011, 412 (3), 479-482.

[60] Khor, T. O.; Huang, Y.; Wu, T. Y.; Shu, L.; Lee, J.; Kong, A. N. Pharmacodynamics of curcumin as DNA hypomethylation agent in restoring the expression of Nrf2 via promoter CpGs demethylation. Biochem. Pharmacol. 2011, 82(9), 1073-1078.

[61] Liu, Y. L.; Yang, H. P.; Gong, L.; Tang, C. L.; Wang, HJ. Hypomethylation effects of curcumin, demethoxycurcumin and bisdemethoxycurcumin on WIF-1 promoter in non-small cell lung cancer cell lines. Mol. Med. Report 2011, 4 (4), 675-679.

[62] Papoutsis, A. J.; Borg, J. L.; Selmin, O. I.; Romagnolo, D. F. BRCA-1 promoter hypermethylation and silencing induced by the aromatic hydrocarbon receptor-ligand TCDD are prevented by resveratrol in MCF-7 Cells. J. Nutr Biochem. 2011, 23 (10), 1324-32.

[63] Zhu, W.; Qin, W.; Zhang, K.; Rottinghaus, G. E.; Chen, Y. C.; Kliethermes, B.; Sauter, E. R. Trans-resveratrol alters mammary promoter hypermethylation in women at Increased risk for breast cancer. Nutr. Cancer 2012, 64 (3), 393-400.

[64] Ruiz-Torres, M. P.; Perez-Rivero, G.; Diez-Marques, M. L.; Griera, M.; Ortega, R.; Rodriguez-Puyol, M.; Rodríguez-Puyol, D. Role of activator protein-1 on the effect of arginine-glycine-aspartic acid containing peptides on transforming growth factor-beta1 promoter activity. Int. J. Biochem. Cell. Biol. 2007, 39 (1), 133-145.

[65] Li, G.; S, Jiang, W. L.; Tian, J. W.; Qu, G. W.; Zhu, H. B.; Fu, F.H. In vitro and in vivo antifibrotic effects of rosmarinic acid on experimental liver fibrosis. Phytomedicine 2010, 17 (3-4), 282-288.

[66] Paluszczak, J. ; K rajka-Ku□niak, V.; Baer-Dubowska, W. The effect of dietary polyphenols on the epigenetic regulation of gene expression in MCF7 breast cancer cells. Toxicol. Lett. 2010, 192 (2), 119-125.

*Address correspondence to this author at the Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA; Tel: 312-908-2004; Fax: 312-908-7275;

E-mail: c-lee7@northwestern.edu