



Anticancer Phytochemicals of Citrus Fruits –A Review

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ABSTRACT

Citrus is one of the important fruits with many commercial varieties such as sweet orange, grapefruit, lime and lemon. Accumulated evidence from experimental and epidemiological studies indicates that dietary consumption of citrus fruit or juice appears to be inversely associated with lower risk of many infectious diseases including cancers. These beneficial effects of the citrus fruits can in particular be attributed to their chemical constituents. Citrus fruits contain a range of key nutrients such as vitamin C, vitamin A, carotenes of various kinds as well as many non-nutrient phytochemicals including classes of flavonoids, glucarates, coumarins, monoterpenes, triterpenes and phenolic acids. While there are several compounds unique to citrus, which are relatively rare in other plants, their individual components such as hesperidin, naringin, tangeritin limonene, quercetin, tangeretin and nobiliten have also demonstrated anticancer activity against different cell lines. The present review summarizes the existing bibliography on biological and pharmacological studies on citrus fruits on the aspect of and cancer therapy.

Keywords: Citrus fruits, traditional medicine, phytochemicals, anticancer

Natural products have historically been a rich source of lead molecules in drug discovery. They are among the major players in pharmacology in general and in cancer therapy in particular. Although the potential of natural products is increasingly recognized in oncology, it has been estimated that only 15% of all plant species have been investigated exhaustively for potential medical applications. The literature indicates that many natural products are available as chemoprotective agents against commonly occurring cancers occurring worldwide. However, the full potential of natural products will be developed in the years to come. A major group of these products are the powerful antioxidants, such as phenolic group, and remainder includes carotenoids, terpenoids, alkaloids that confer protective properties. These natural products are found in vegetables, fruits, plant extracts, and herbs. Natural products research is based on screening of extracts bioassay-



guided isolation, structure elucidation and subsequent scale up production. Until now, most of the evidence concerning the protective effect of citrus against risk of cancer has come from case-control studies, and studies showed that citrus intake is associated with a reduced risk of multiple cancer types, including cancer of the digestive tract, respiratory tract, pancreatic cancer, prostate cancer, breast cancer, nasopharyngeal cancer and cutaneous melanoma (Jian *et al.*, 2005; Foschi *et al.*, 2010). Recent findings suggest that citrus consumption is associated with reduced all-cancer incidence, especially for subjects having simultaneously high green tea consumption. Accumulated evidence from experimental and epidemiological studies also indicates that dietary consumption of citrus fruit or juice appears to be inversely associated with lower risk of many infectious diseases including cancers (Huang *et al.*, 2009).

Citrus belongs to family Rutaceae and several commercial citrus varieties such as sweet orange, grapefruit, lime and lemon and were considered to possess natural compounds with several health benefits. Citrus is one of the important fruits of high medicinal value and have long been the basis of commonly used traditional medicines in several Asian countries (Kubo *et al.*, 2005). In addition to use as medicine, citrus fruits are also widely used in cuisine materials as salad dressing, sauces, jams and vinegar as well as whole fresh fruits. The medicinal and commercial importance of these products leads to extensive scientific study resulting in a broad base knowledge of their chemical composition and bioactivities. These beneficial effects of the citrus fruits can in particular be attributed to their chemical constituents including vitamins, dietary fiber, carotenoids, flavonoids, lipids and essential oils (Patil *et al.*, 2009 Hardin *et al.*, 2010). The anti cancer benefits of citrus fruits are mainly found in the significant quantities of monoterpenes and flavanones, two classes of compounds that are believed to cut the risks of cancers of the digestive track in half. These compounds reduce cancer risks in two significant ways. First, they interfere with some of the processes necessary for cancer cell growth, making it difficult for tumours to develop, and second, they inhibit inflammation, an important stimulus for cancer cell growth. While there are several compounds unique to citrus, which are relatively rare in other plants, their individual components have also demonstrated anticancer activity against different cell lines (Park *et al.*, 2011; Yoshimizu *et al.*, 2004). A plethora of data from previous studies indicated that significant contributions were made on the evaluation of anticancer properties of citrus species (Gyawali *et al.*, 2012). Studies have reported that citrus fruits have anticancer effects, including neuroblastoma, cervical carcinoma and human gastric cancer cells (Poulose *et al.*, 2006). Since, a huge amount of by-product components of citrus juice industry e.g. peel, pulp, rag and seeds) containing a variety of biologically active compounds are fritter away, their anticancer activity and chemical profile is currently of considerable interest that would facilitate the utilization of individual pulp and peel into high

value-added products (Saidani *et al.*, 2004). The decoction and oils obtained from *C. hassaku* fruits have been employed for medicinal purposes, to alleviate coughs, ulcers, swellings, epilepsy and obesity (Hariya, 2003). The phytochemical profile and biological activities of citrus species may significantly vary among cultivars within the same species or even within the same cultivar grown in diverse climatic conditions or under different cultural practices (Itoh *et al.*, 2009; Kubo *et al.*, 2005). Besides, there are several groups of phytochemicals found in fruit of the citrus genus which possesses anticancer potentiality. Therefore this review was undertaken in order to prepare an accumulative profile of phytochemical constituents of citrus fruits and their anticancer property.

CITRUS LIMONOIDS

Limonoids are heavily oxygenated, modified triterpenes dominant in the plant family Meliaceae, and to a lesser extent in Rutaceae. Citrus species are known for unique limonoids. Most citrus species accumulate large amounts of flavonoids and limonoids during development and much is known about the cancer-preventing potential of the dietary bioactive compounds in citrus fruits (Castillo *et al.*, 1992). In the last few years, many studies from a number of laboratories have concentrated on the anticancer activities of citrus limonoids. Inhibition of proliferation of colon cancer cells and neuroblastoma by four limonoids of citrus has been reported (Poulose *et al.*, 2006). Studies have also shown that apoptosis is the major cause for inhibition of proliferation of colon cancer cells by citrus limonoids. The antiproliferative effects of limonoids have been shown in various cancers including breast cancer (Tian *et al.*, 2001), colon cancer and stomach cancer (Lam *et al.*, 1989) and neuroblastoma cancer (Poulose *et al.*, 2005). Researchers were able to demonstrate that certain limonoids have antiproliferative and caspase mediated apoptosis inducing effects on human cancer cells in vitro (Poulose *et al.*, 2005).

ESSENTIAL OILS

Citrus essential oil comes from the fruits and leaves of different citrus species. It can be either steam processed or cold pressed to produce the essential oil. Fruits and vegetables contain an abundance of terpenoids, phenolic substances and other natural anti-oxidants that have been associated with protection from and treatment of chronic diseases such as cancer and heart disease. Terpenoids class of compound from citrus has been shown to be beneficial to maintain and improve health, and include several subclasses such as monoterpenes limonene, carvone, myrcene, and carveol), sesquiterpenes β -cubebene, β -elemene, β -caryophyllene, δ -cadinene), diterpenes retinoids), triterpenes oleanic acid and ursolic acid). These subclasses have been shown to possess an array of mechanisms of action that affect among others) oxidative stress, carcinogenesis and cardiovascular diseases



(Wagner and Elmadfa, 2003). Many monoterpenes are non-nutritive dietary components found in the essential oils of citrus fruits and herbs. Limonene is a well-established chemopreventive and therapeutic agent against many tumor cells and has chemopreventive activity against rodent mammary cancer during the initiation phase as well as the promotion/progression phase. In most of the studies of volatile composition of citrus fruits obtained by different conventional methods of extractions, limonene was found in a proportion of >94.8 % (Kamal *et al.*, 2011). Lime volatile oil showed 78% inhibition of human colon cancer cells SW-480) with 100 lg/ml concentration at 48 h. Lime volatile oil showed DNA fragmentation and induction of caspase-3 which was due to the involvement of apoptosis and thus suggested that lime volatile oil has potential benefits in colon cancer prevention (Gyawali *et al.*, 2012; Patil *et al.*, 2009). Some of the reported chemical compositions of citrus volatile oil consists of D-limonene α -terpineol, 4-terpineol, 1,4-cineole, 1,8-cineole, p-cymene, bpinene, b-bisabolene, citral, geranial and neral. Recently, some more additional flavour compounds such as neryl acetate, bergamotene, valencene and germacrene-D have been reported. Tests in animals have proven the effectiveness of limonene against some types of cancer including gastric, mammary, pulmonary adenoma and liver. Accumulative evidence suggests citrus oils are rich in several possible anticancer agents such as; caryophyllene oxide, limonene, β -caryophyllene. Other constituents of fruits also contribute its cytotoxic activity as shown by 2,4-di-tert-butylphenol and β -elemene (Park *et al.*, 2011).

CITRUS CAROTENOIDS AND VITAMINS

Vitamin C is a major contributor to the antioxidant capacity of fruits. This water-soluble antioxidant vitamin is present in many fruits and vegetables, especially citrus and peppers. Enhancement of the immune system by carotenoids and vitamin E has also been demonstrated, which may inhibit the growth of cancers. Citrus is a complex source of carotenoids, with the largest number of carotenoids found in fruit. In citrus fruit, peel and juice colors are mainly due to the presence of these pigment namely phytoene, zeta-carotene, beta-carotene, lutein, gamma-carotene, cryptoxanthin, zeaxanthin, and violaxanthin etc. In addition, some carotenoids serve as precursors for vitamin A, which is essential to human and animal diets, and as antioxidants, which play a role in reducing the risk of chronic diseases and reduction in the incidence of cancer (Michaud *et al.*, 2000; Gallicchio *et al.*, 2008). A carotenoids such as β -carotene, α -carotene and cryptoxanthin contribute to the supply of vitamin A, which may be associated with slowing the growth of cancer cells. The largest number of carotenoids found in any fruit are those of citrus fruits, more than 115 different compounds (Dugo *et al.*, 2006). The carotenoid content in mandarin *C. reticulata* Blanco) is the highest among all the varieties of citrus fruits in China.. The peels of citrus fruit occupy 30–40

% of the total fruit weight while the carotenoid content in the peels is higher than the pulp. Of the many anticarcinogens already detected in plant foods, the antioxidants vitamins C and E and the provitamin b-carotene have received the most attention (Handelman, 2001). Although there has been considered enthusiasm for the potential anticarcinogenic properties of beta-carotene, research findings suggest that several different carotenoids are likely to be associated with reduced cancer risks. Lycopene does not have pro-vitamin activity, but as a strong dietary antioxidant, it plays a role in the prevention of cancer and chronic disease, and exhibits significant tumor suppression activity which has attracted interest in its pharmaceutical potential. The typical lycopene-pigmented citrus is deep coloured grapefruit (Bowman, 1990). The level of total carotenoids in citrus peel vary between varieties, being abundant in citrus members (Xu, 2006). In addition, there is increasing evidence that α -tocopherol, a well-known potent natural lipophilic antioxidant, can inhibit proliferation of cancer cells and influence apoptosis (Reddy and Fernandes, 2000). In the intestine, it has been suggested that vitamin C and other phenolics eg α -tocopherol and other polyphenolics) may inhibit nitrosation, a reductive process leading to the production of carcinogenic nitrosamines, and protect against gastric cancer.

CITRUS COUMARINS

Naturally occurring coumarins possess anti-carcinogenic activities in part by inducing carcinogen detoxifying Enzymes. Citrus peels contain a number of coumarins that possess mevalonatederived side chains with various oxidation levels. Researchers have demonstrated that orally administered citrus coumarin, limettin, imperatorin and isopimpinellin blocked 7,12-dimethylbenz[a]anthracene (DMBA) DNA adduct formation in mouse mammary glands (Prince *et al.*, 2006). Interestingly, citrus oils, in particular, contain abundant amounts of both simple as well as furanocoumarins. Three known citrus coumarins namely bergamottin, oxypeucedanin and 5-[6', 7'-dihydroxy-3',7'-dimethyl-2-octenyl]oxy]psoralen, have been isolated from *Citrus hystrix* DC as inhibitors of both lipopolysaccharide (LPS) and interferon- γ (IFN- γ)-induced nitric oxide (NO) generation in RAW 264.7 cells. Consequently, suppression of the iNOS-induced NO generation in excess amounts is now accepted widely as a new paradigm for the chemoprevention of cancer (Murakami *et al.*, 1999). *Citrus* auraptene inhibited the development of azoxymethane (AOM)-induced aberrant crypt foci, which are precursor lesions for colorectal carcinoma (Tanaka *et al.*, 1998). Auraptene is a major coumarin of citrus plants, has been found in citrus plants such as the orange *C. aurantium*, Natsudaidai *C. atsudaidai*, grapefruit *C. paradisi*, and trifoliate orange *Poncirus trifoliata* as well as in some species belonging to Rutales (Gray and Waterman, 1978). The juice oil of *C. hassaku* is a rich source of coumarins, and auraptene. The presence of auraptene exhibiting its cancer-preventing property is regarded as a character



incidental to citrus fruits. Recent study on citrus coumarin osthole showed that the compound it induces apoptosis in lung cancer by modulating PI3K/Akt pathway (Xu *et al.*, 2011). Cytotoxicity of xanthotoxin were determined in vitro against L1210, HL-60, K562, and B16F10 tumor cell lines by MTT method and shown prominent results (Thanh *et al.*, 2004). Two coumarins, bergapten and citropten, were also found in *C. bergamia* and *C. medica* cv. Diamante, respectively and tested for biological activity against the A375 cell line and strong antiproliferative activity demonstrated with bergapten (Menichini *et al.*, 2010). Seselin has it has antiproliferative effects on several cancer cell lines such as leukemia and lymphoma cells (Lin *et al.*, 1999).

CITRUS FATTY ACIDS

Citrus fruits are known to be an abundant resource of compounds that might help prevent lifestyle-related diseases such as diabetes, high blood pressure and cancer. Several fatty acids were reported from the seed and peel of citrus species (Saidani *et al.*, 2004). Antioxidant activity of citrus extract is also assessed by measuring free fatty acid content, since unsaturated fatty acids plays vital role to control the different types of cancers. The constituents of total lipids and neutral lipid classes, i.e., hydrocarbons, wax esters, sterol esters, triacylglycerols, free fatty acids, 1,3-diacylglycerols, 1,2-diacylglycerols, free sterols, alcohols, and monoacylglycerols of three species of Citrus namely *C. sinensis*, *C. paradisi*, *C. aurantium* were investigated by thin layer and gas chromatography. Palmitic, oleic and linoleic acids were the major components in all the lipids and lipid classes studied (Waheed *et al.*, 2009). It is known fact that, exogenous supplementation of cultured breast cancer cells with oleic acid significantly downregulates the expression of Her-2/neu, a well-characterized oncogene (Menendez *et al.*, 2005) and pancreatic cancer cells also exhibit morphological features of apoptosis after exposure to oleic acid, linoleic acid (Cury-Boaventura *et al.*, 2004). Other possible anticancer compounds of fatty acids present in citrus fruits are, hexadecanoic acid, dodecanoic acid (Lee *et al.*, 2001; Ji *et al.*, 2005).

CITRUS FLAVONOIDS

Flavonoids comprise a large group of naturally occurring organic compounds found in a wide variety of plants including fruits, vegetables, nuts, seeds, grains, tea, and wine. Citrus fruits stand out among the most common phenolic rich dietary sources. Citrus flavonoids exert their anticancer effects through a number of these diverse mechanisms (Manthey *et al.*, 2000). Indeed, naringin plays an important role in regulating antioxidative capacity by increasing superoxide dismutase and catalase activities and by up-regulating the gene expressions of superoxide dismutase, catalase, and glutathione peroxidase in cholesterol-rich diet-fed rabbits (Jeon *et al.*, 2001). Since naringin blocks H_2O_2 -induced cytotoxicity and apoptosis,

naringin might affect H₂O₂-induced expression of an apoptosis-associated gene or protein as one of its pharmacological actions (Kanno *et al.*, 2003). Citrus flavonoids inhibit ornithine decarboxylase induction of skin tumor promotion, increasing the inorganic phosphate ³²P incorporation rate in the phospholipid membrane and activation of protein kinase C (Manach *et al.*, 2003). Hesperetin and naringenin were inhibited the development of breast cancer (So *et al.*, 1996). Quercetin markedly increases the effect of adriamycin in a multidrugresistant MCF-7 human breast-cancer cell line (Scambia *et al.*, 1994). Naringenin stimulates DNA repair following oxidative damage in human prostate cancer cells (Gao *et al.*, 2006). Citrus flavonoids can inhibit invasion, by rat malignant cells, in cardiac and hepatic tissue of syngenetic rats. The growth-inhibitory action of nobiletin in mouse fibroblast clone A-31 and various human gastric cancer cells (Yoshimizu *et al.*, 2004). The main flavonoid glycoside in orange *C. sinensis* L.), hesperidin, and its flavone analogue, diosmin, have exhibited anticarcinogenic activities in various in vivo studies. Citrus flavonoids, their structural activity relationship and anticancer activities were also summarized in previous review. Tangeretin is also well known phytochemical for its chemopreventive properties (Tripoli *et al.*, 2007).

CONCLUSION

The studies performed both *in vitro* and *in vivo* have shown that citrus compounds play an important role in the prevention of different type of cancer diseases. The beneficial effects of the dietary citrus fruits can in particular be attributed due to presence of limonoids, flavanoids, essential oils, fatty acids, coumarins and vitamins. Therefore a diet rich in citrus fruits has beneficial effects on human health.

REFERENCES

- Bowman, K.D. and Gmitter, J.F.G. 1990. Caribbean forbidden fruit: grapefruit's missing link with the past and bridge to the future. *Fruit Var. J.*, **44**: 41-44.
- Castillo, J., Benavente, O. and Del Rio, J.A. 1992. Naringin and neohesperidin levels during development of leaves, flower buds, and fruits of *Citrus aurantium*. *Plant Physiol.*, **99**: 66-67.
- Cury-Boaventura, M.F., Pompeia, C. and Curi, R. 2004. Comparative toxicity of oleic acid and linoleic acid on Jurkat cells. *Clin. Nutr.*, **23**: 721-732.
- Dugo, P., Skerikov'a, V., Kumm, T., Trozzi, A., Jandera, P. and Mondello, L. 2006. Elucidation of carotenoid patterns in citrus products by means of comprehensive normalphase x reversed-phase liquid chromatography. *Anal. Chem.*, **78**: 7743-7750.
- Foschi, R., Pelucchi C., Dal Maso L., Rossi M., Levi F., Talamini R., Bosetti C., Negri E., Serraino D., Giacosa A., Franceschi S. and La Vecchia C. 2010. Citrus fruit and



- cancer risk in a network of case-control studies. *Cancer Causes Control*, **21**:237-242.
- Gallicchio, L., Boyd, K., Matanoski, G., Tao, X.G., Chen, L.W., Lam, T.K., Shiels, M., Hammond, E., Robinson, K.A., Caulfield, L.E., Herman, J.G., Guallar, E. and Alberg, A.J., 2008. Carotenoids and the risk of developing lung cancer: a systematic review. *Am. J. Clin. Nutr.*, **88**: 372-383.
- Gao, K., Henning, S.M., Niu, Y., Youssefian, A.A., Seeram, N. P., Xu, A. and Heber, D. 2006. The citrus flavonoid naringenin stimulates DNA repair in prostate cancer cells. *J. Nutr. Biochem.*, **17**:89-95.
- Gray, A.I. and Waterman, P.G. 1978. Coumarins in the Rutaceae. *Phytochem.*, **17**:845-864.
- Gyawali, R., Jeon, D.H., Moon, J.Y., Kim, H.J., Song, Y.W., Hyun, H.B., Moon S.Y., Kang T.H., Moon K.S. and Cho S.K. 2012. Chemical composition and antiproliferative activity of supercritical CO₂ extracts of citrus fruits. *Food Sci. Technol. Res.*, **18**(6): 813-823.
- Gyawali, R., Jeon, D.H., Moon, J.Y., Kim, H.J., Song, Y.W., Hyun, H.B., Moon, S.Y. and Cho, S.K. 2012. Chemical composition and antiproliferative activity of supercritical extract of pummelo *Citrus grandis* (L.) Osbeck fruits from Korea. *J. Essent. Oil-Bear. Plants*, **15** (6): 915- 925.
- Handelman, G.J. 2001. The evolving role of carotenoids in human biochemistry. *Nutr.*, **17**: 818-822.
- Hardin, A., Crandall, G.P. and Stankus, T. 2010. Essential oils and antioxidants derived from citrus by-products in food protection and medicine: an introduction and review of recent literature. *J. Agr. Food Inform.*, **11**: 99-122.
- Hariya, T. 2003. The possibility of regulating the function of adipose cells by odorants. *Aroma Res.*, **13**: 72-78.
- Huang, W. Y., Cai Y. Z. and Zhang Y. 2009. Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. *Nutr. Cancer*, **62**: 1-20.
- Itoh, K., Hirata, N., Masuda, M., Naruto, S., Murata, K., Wakabayashi, K. and Matsuda, H. 2009. Inhibitory effects of *Citrus hassaku* extract and its flavanone glycosides on melanogenesis. *Biol. Pharm. Bull.*, **32**: 410-415.
- Jeon, S.M., Bok, S.H., Jang, M.K., Lee, M.K., Nam, K.T., Park, Y.B., Rhee, S.J. and Choi, M.S. 2001. Antioxidative activity of naringin and lovastatin in high cholesterol-fed rabbits. *Life Sci.*, **69**:2855-2866.
- Ji, j., Zhang, L., Wang, P., Mu, Y.M., Zhu, X.Y., Wu, Y.Y., Yu, H., Zhang, B., Chen, S.M. and Sun, X.Z. 2005. Saturated free fatty acid, palmitic acid, induces apoptosis in fetal hepatocytes in culture. *Exp. Toxicol. Pathol.*, **56**: 369-376.
- Jian, L., Du C.J., Lee A.H. and Binns C.W. 2005. Do dietary lycopene and other carotenoids protect against prostate cancer ? *Int. J. Cancer*, **113**:1010-1014.

- Kamal, G.M., Anwar, F., Hussain, A.I., Sarri, N. and Ashraf, M.Y., 2011. Yield and chemical composition of Citrus essential oils as affected by drying pretreatment of peels. *Int. Food Res. J.*, **184**: 1275-1282.
- Kanno, S.I., Shouji, A., Asou, K. and Ishikaw, M. 2003. Effects of naringin on hydrogen peroxide-induced cytotoxicity and apoptosis in P388 cells. *J. Pharm.Sci.* , **92**: 166-170.
- Kubo, M., Matsuda, H., Tomohiro, N. and Harima, S. 2005. Historical and pharmalogical study of *Citrus hassaku*. *Yakushigaku Zasshi* (Japanese), **40**: 47-51.
- Lam, L.K.T. and Li, Y. 1989. Hasegawa S, Effects of citrus limonoids on glutathione S-transferase activity in mice. *J. Agric. Food Chem.* 37: 878-880.
- Lee, J.Y., Sohn, K.H., Rhee, S.H. and Hwang, D. 2001. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through toll-like receptor 4. *J. Biol. Chem.*, **276**: 16683-16689.
- Lin, C.Y., Ku, F.M., Kuo, Y.C., Chen, C.F., Chen, W.P., Chen, A. and Shiao, M.S. 1999. Inhibition of activated human mesangial cell proliferation by the natural product of *Cordyceps sinensis* H1-A): an implication for the treatment of IgA mesangial nephropathy. *J. Lab. Clin. Med.*, **133**:55-63.
- Manach, C., Morand, C., Gil-Izquierdo, A., Bouteloup-Demange, C. and Remesy, C. 2003. Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. *Eur. J. Clin. Nutr.*, **57**:235-242.
- Manthey, J.A., Guthrie, N. and Grohmann, K. 2000. Biological properties of citrus flavonoids pertaining to cancer and inflammation. *Curr. Med. Chem.*, 8:135-153.
- Menendez, J.A., Vellon, L., Colomer, R. and Lupu, R. 2005. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab Herceptin) in breast cancer cells with Her-2/neu gene amplification. *Ann. Oncol.*, **163**:359-371.
- Menichini, F., Tundis, R., Loizzo, M.R., Bonesi, M., Provenzano, E., de Cindio, B. and Menichini, F. 2010. In vitro photo-induced cytotoxic activity of *Citrus bergamia* and *C. medica* L. cv. Diamante peel essential oils and identified active coumarins. *Pharm. Biol.*, **48**: 1059-1065.
- Michaud, D.S., Fesknic, D., Rimm, E.B., Colditz, G. A., Speizer, F.E., Willett, W.C. and Giovannucci, E. 2000. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. *Am. J. Clin. Nutr.*, **72**: 990-997.
- Murakami, A., Gao, G., Kim, O.K., Omura, M., Yano, M., Ito, C., Furukawa, H., Jiwajinda, S., Koshimizu, K. and Ohigashi, H. 1999. Identification of Coumarins from the Fruit of *Citrus hystrix* DC as Inhibitors of Nitric Oxide Generation in Mouse Macrophage RAW 264.7 Cells. *J. Agric.Food Chem.* **47**: 333-339.
- Park, K.R., Nam, D.W., Yun, H.M., Lee, S.G., Jang, H.J., Sethi, G., Cho, S.K. and Ahn, K.S. 2011. β -Caryophyllene oxide inhibits growth and induces apoptosis through



- the suppression of PI3K/AKT/mTOR/S6K1 pathways and ROS-mediated MAPKs activation. *Cancer Lett.*, **312**: 178-188.
- Patil Jaiprakash, R., Jayaprakasha G.K., Chidambara Murthy, K.N., Tichy, S. E., Chetti, M. B. and Patil, B.S. 2009. Apoptosis-mediated proliferation inhibition of human colon cancer cells by volatile principles of *Citrus aurantifolia*. *Food Chem.*, **114**: 1351-1358.
- Poulose, S.M., Harris, E.D. and Patil, B.S. 2005. Citrus Limonoids Induce Apoptosis in Human Neuroblastoma Cells and Have Radical Scavenging Activity. *J. Nutr.* **135**: 870-877.
- Poulose, S.M., Harrie, E.D. and Patil, B.S. 2006. Antiproliferative effects of citrus limonoids against human neuroblastoma and colonic adenocarcinoma cells. *Nutr. Cancer*, **56**:103-112.
- Prince, M., Campbell, C.T., Robertson, T.A., Wells, A.J. and Kleiner, H.E. 2006. Naturally occurring coumarins inhibit 7,12-dimethylbenz[a]anthracene DNA adduct formation in mouse mammary gland. *Carcinogenesis*, **27**:1204-1213.
- Reddy Avula, C.P. and Femandes, G. 2000. Effect of dietary vitamin E on apoptosis and proliferation of murine splenocytes. *Nutr. Res.*, **20**: 225-236.
- Saidani, M., Dhifi, W. and Marzouk, B. 2004. Lipid evaluation of some Tunisian Citrus seeds. *J. Food lipids*, **11**:242-250.
- Scambia, G., Ranelletti, F.O., Benedetti-Panici, P., De Vincenzo, R., Bonanno, G., Ferrandina, G., Piantelli, M., Bussa, S., Rumi, C., Cianfriglia, M. and Mancuso, S. 1994. Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF-7 human breastcancer cell line: P-glycoprotein as a possible target. *Cancer Chemoth. Pharm.*, **34**:459-464.
- So, F.V., Guthrie, N., Chambers, A.F., Moussa, M. and Carroll, K.K. 1996. Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices. *Nut. Cancer*, **26**:167-181.
- Tanaka, T., Kawabata, K., Kakumoto, M., Hara, A., Murakami, A., Kuki, W., Takahashi, Y., Yonei, H., Maeda, M., Ota, T., Odashima, S., Yamane, T., Koshimizu, K. and Ohigashi, H. 1998. Citrus auraptene exerts dose-dependent chemopreventive activity in rat large bowel tumorigenesis: the inhibition correlates with suppression of cell proliferation and lipid peroxidation and with induction of phase II drug-metabolizing enzymes. *Cancer Res.*, **58**: 2550-2506.
- Thanh, P. N., Jin, W. Y., Song, G. Y., Bae, K. H. and Kang, S. S. 2004. Cytotoxic Coumarins from the Root of *Angelica dahurica*, *Arch. Pharm. Res.*, **27**: 1211-1215.
- Tian, Q., Miller, E.G., Ahmad, H., Tang, L. and Patil, B.S. 2001. Differential inhibition of human cancer cell proliferation by Citrus limonoids. *Nutr. Cancer* **40**: 180-184.
- Tripoli, E., Guardia, M.L., Giammanco, S. and Majo, D.D. 2007. Giammanco M, Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. *Food Chem.*, **104**:466-479.

- Wagner, K.H. and Elmadfa, I. 2003. Biological relevance of terpenoids. *Ann. Nutr. Metab.*, **47**: 95-106.
- Waheed, A., Mahmud, S., Saleem, M. and Ahmad, T. 2009. Fatty acid composition of neutral lipid: Classes of citrus seed oil. *J. Saudi Chem. Soc.*, **13**:269-272.
- Xu, C.J., Fraser, P.D., Wang, W.J. and Bramley, P. M. 2006. Differences in the carotenoid content of ordinary citrus and lycopene-accumulating mutants. *J. Agr. Food Chem.*, **54**:5474-5481.
- Xu, X., Zhang, Y., Qu, D., Jiang, T. and Li, S. 2011. Osthole induces G2/M arrest and apoptosis in lung cancer A549 cells by modulating PI3K/Akt pathway. *J Exp. Clin. Cancer Res.*, **30**:33.
- Yoshimizu, N., Otani, Y., Saikawa, Y., Kubota, T., Yoshida, M., Furukawa, T., Kumai, K., Kameyama, K., Fujii, M., Yano, M., Sato, T., Ito, A. and Kitajima, M. 2004. Anti-tumour effects of nobiletin, a citrus flavonoid, on gastric cancer include: antiproliferative effects, induction of apoptosis and cell cycle deregulation. *Aliment. Pharmacol. Ther.*, **20**:95-101.