MINI-REVIEW

# Luteolin, a Bioflavonoid Inhibits Colorectal Cancer through Modulation of Multiple Signaling Pathways: A Review

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## Abstract

**Luteolin, 3', 4', 5,7-tetrahydroxyflavone, belongs to a group of naturally occurring compounds called flavonoids that are found widely in the plant kingdom. It possesses many beneficial properties including antioxidant, anti-inflammatory, anti-bacterial, anti-diabetic and anti-proliferative actions. Colorectal cancer (CRC) is a leading cause of cancer related deaths worldwide. Many signaling pathways are deregulated during the progression of colon cancer. In this review we aimed to analyze the protection offered by luteolin on colon cancer. During colon cancer genesis, luteolin known to reduce oxidative stress thereby protects the cell to undergo damage *in vivo*. Wnt/β-catenin signaling, deregulated during neoplastic development, is modified by luteolin. Hence, luteolin can be considered as a potential drug to treat CRC.**

**Keywords:** Luteolin - colon cancer - Wnt/β-catenin - Nrf2

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## Introduction

Flavonoids are biologically active polyphenolic compounds widely distributed in plants. More than 5000 individual flavonoids have been identified, which are classified into at least 10 subgroups according to their chemical structure. Flavonoids of 6 principal subgroups- flavonols, flavones, anthocyanidins, catechins, flavanones, and isoflavones- are relatively common in human diets. Flavonoids are a large and diverse group of phytochemicals and research into their anti-carcinogenic potential with animal and cellular model systems supports a protective role (Kocic et al., 2013). Luteolin, 3', 4', 5, 7-tetrahydroxyflavone, belongs to a group of naturally occurring compounds called flavonoids that are found widely in the plant kingdom. Belonging to the flavone group of flavonoids, luteolin has a C6-C3-C6 structure and possesses two benzene rings (A, B), a third, oxygen-containing (C) ring, and a 2-3 carbon double bond. Luteolin also possesses hydroxyl groups at carbons 5, 7, 3', and 4' positions (Figure 1) (Ross and Kasum, 2002). The hydroxyl moieties and 2-3 double bonds are important structure features in luteolin that are associated with its biochemical and biological activities (Chan et al., 2003).

Vegetables and fruits such as celery, parsley, broccoli, onion leaves, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers are rich in luteolin (Neuhouser, 2004; Miean and Mohamed, 2001; Gates et al., 2007; Sun et al., 2007; Mencherini et al., 2007). As in other flavonoids, luteolin is often glycosylated in plants, and the glycoside is hydrolyzed to free luteolin during absorption (Hempel et al., 2009). Some portion of luteolin is converted to glucuronides when passing through the intestinal mucosa (Shimoi et al., 1998). Luteolin is heat stable and losses due to cooking are relatively low (Le Marchand, 2002). Luteolin, possess many beneficial properties including antioxidant (Ashokkumar and Sudhandiran, 2008), anti-inflammatory (Nishitani et al., 2013), cardio protective (Xu et al., 2012), anti-diabetic (Salib et al., 2013) and anti-proliferative (Ashokkumar and Sudhandiran, 2011).

Chemoprevention refers to the use of natural or synthetic compounds to prevent, reverse, or delay the development of cancer (Swan and Ford, 1997). Because food derived products exist universally and are expected to be safe, they are highly interesting for development as chemopreventive agents to treat cancer (Sengupta et al., 2002; Chihara et al., 2010). Luteolin act as a strong anticancer agent against many types of malignancies including liver, lung, breast, esophageal squamous carcinoma, colon, prostate and melanoma (Zhou et al., 2009; Hwang et al., 2011; Tang et al., 2011; Wang et al., 2012a; Wang et al., 2012b; Ruan et al., 2012; Pandurangan et al., 2014a). This review is aimed to emphasize the molecular action of luteolin on molecular targets of colorectal cancer.

## Luteolin Effects on Colon Cancer

Cancers of the large and small intestine are major contributors to worldwide cancer morbidity and mortality (Greenlee et al., 2000). Although CRC was well studied,

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the progress in the field of preventing or curing this disease has not been significant. CRC is a multi-step process involving three distinct stages, initiation that alters the molecular message of a normal cell, followed by promotion and progression that ultimately ends up with a phenotypically altered cancer cell (Pitot, 1986). Many signaling pathways are deregulated during the progression of colon cancer (Pandurangan, 2013; Pandurangan and Esa, 2013; Pandurangan and Esa, 2014; ). Epidemiological and experimental studies suggest that colon cancer is strongly influenced by nutritional factors, including the amount and composition of dietary fat (Willet et al., 1990; Pandurangan et al., 2013c; He et al., 2014).

Oxidative stress is defined as a disturbance between pro-oxidant and antioxidant balances in favor of the former, leading topotential damage. Oxidative stress can result in cell injury due to lipid peroxidation, DNA damage, mutagenesis and has been associated with various stage of tumor formation process (Halliwell and Gutteridge, 1989). Lipid peroxidation (LPO) is a free radical mediated process. It is involved in the formation of lipid radicals, a rearrangement of the unsaturated lipids that consequences in a variety of degraded products like alkanes, malondialdehyde (MDA), conjugated dienes and lipid hydroperoxides and eventually damage to cells (Upsani et al., 2001). Published reports showed that luteolin reduces tumor number, inhibits the lipid peroxidation and restores the antioxidant enzymes during 1, 2-Dimethyl hydroxide-induced colon cancer in rats (Manju et al., 2005; Manju and Nalini, 2005; Manju and Nalini, 2007). Administration of luteolin significantly reduced the levels of LPO and OH- in plasma and colonic mucosa as well as increases the antioxidant enzymes which might be due to the strong antioxidant property of luteolin (Ashokkumar and Sudhandiran, 2008).

Glycoproteins play crucial role in mediating cell surface function, such as cell-cell recognition, cellular adhesion, binding and clearance of serum glycoproteins and metabolic transport among others. Elevated levels of glycoprotein contents are valuable markers of carcinogenic process and these changes alter the rigidity of cell membrane (Selvam and Nagini, 1995).

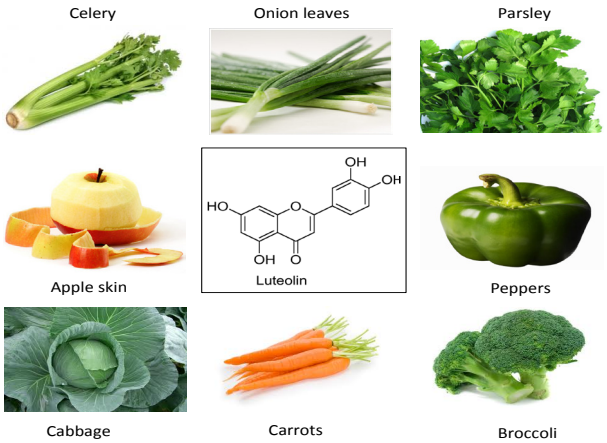


**Figure 1. Sources and Structure of Luteolin.** Vegetables and Fruits Such as Celery, Parsley, Broccoli, Onion Leaves, Carrots, Peppers, Cabbages, Apple Skins, and Chrysanthemum Flowers are Rich in Luteolin

Glycoconjugates are necessary for the assembly of the oligosaccharide moieties of the glycoprotein chains and their levels have been found to be elevated in neoplastic conditions and can therefore be designated as non-specific markers of malignancy (Sen et al., 1983). Its levels are high in tumor tissue due to increased lipid peroxidation resulting in lowered antioxidant status (Ashokkumar and Sudhandiran, 2008) and aberrant glycosylation (Hakomori, 1996). Pandurangan et al. (2012) reported that luteolin have the ability to control glycoproteins such as hexose, hexosamine, fucose and sialic acid in AOM-induced CRC. The multiple action of Luteolin on different models of colon cancer was represented in Table 1.

## Luteolin Effects on Preneoplastic Lesions

Aberrant crypt foci (ACF) is considered as putative pre-neoplastic lesion as an end point marker have been used to assess the influence of various modulatory factors (Bird, 1995; Bird and Good, 2000). ACF are characterized by one or more crypts that appear as a single focus but are larger than normal crypts. It is characterized by thickened epithelia, altered luminal openings, have an increased pericrytal area between them (McLellan et al., 1991). Finally, these can develop into polyps and eventually into CRC. Plant constituents and their derivatives may exert significant effects on decreasing the incidence of ACF in the colon (Waly et al., 2012; Tammasakchai et al., 2012; Ansil et al., 2013; Guizani et al., 2013; Madrigal-Bujaidar et al., 2013). Treating the animals with luteolin during the AOM-induced CRC animals showed reduced incidence of ACF (Ashokkumar and Sudhandiran, 2008).

## Luteolin Effects on iNOS

Nitric oxide (NO) is considered as one of the smallest signaling molecules that can diffuse into the cell. NO is present in all cells in the body, synthesized through several enzymatic and non-enzymatic pathways. As a free

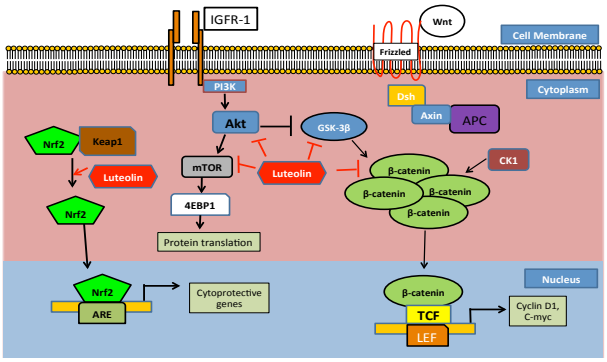


**Figure 2. Luteolin Alter Multiple Signaling Pathways.** Luteolin reported to that it dissociates the Nrf2/Keap1 Complex in the Cytoplasm. And the Nrf2 translocate into nucleus there it binds with ARE. ARE is highly conserved region where binding of Nrf2 leads to the transcription of cytoprotective genes occur. During cancer β-catenin accumulated in the cytosol, then translocated into nucleus. In nucleus it forms a complex with T-Cell factor and Leukocyte enhancer factor and activates C-Myc and cyclin D1. Reportedly Luteolin inhibits the translocation of β-catenin and also inhibits the Glycogen synthase kinase-3β

**Table 1. Chemopreventive and Chemotherapeutic Effects of Dietary Flavonoid Luteolin on Colorectal Cancer**

| S. No | Colon cancer model | Outcomes of the experiment | Reference |
|---|---|---|---|
| 1 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin decreases the MMP-9 and MMP-2 thereby acts as an anti-metastatic agent | Pandurangan et al., 2014c) |
| 2 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin decreased the expressions of iNOS and COX-2 | Pandurangan et al.,(2014b) |
| 3 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin decreased the phase 1 enzymes and increased the activities of Glutathione –S-transferase. Luteolin enhanced the expression of Nrf2 and activates GST-α and GST-$\mu$. | Pandurangan et al., (2014a) |
| 4 | HCT-15 colon adenocarcinoma cell line | Luteolin induces growth arrest by inhibiting wnt/β-catenin/GSK-3β signaling pathway. Luteolin also induces apoptosis by caspase-3 mediated manner. | Pandurangan et al., (2013) |
| 5 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin restores reduced glutathione and protein thiols | Pandurangan and Ganapasam , (2013) |
| 6 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin decreased the activities of lysosomal enzymes. Induces apoptosis by modulating Bcl2, Bax and Caspase-3. | Pandurangan and Ganapsam, (2013) |
| 7 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin decreased the incidence of mucin depleted foci (MDF). Luteolin decreased the levels of glycoconjugates | Pandurangan et al., (2012) |
| 8 | HT-29 colon adenocarcinoma cell line. | Luteolin downregulates the activation of the PI3K/Akt and ERK1/2 pathways via a reduction in IGF-1R signaling. | Lim et al., (2012) |
| 9 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin reduces the tumor number. Luteolin controls the levels of polyamines. Luteolin controls cell proliferation by inhibiting wnt/β-catenin/GSK-3β pathway. | Ashokkumar and Sudhandiran, (2011) |
| 10 | Caco-2 colon cancer cell line | Luteolin showed a protective effect against H2O2-induced DNA damage. | Ramos et al., (2010) |
| 11 | HT-29 colon adenocarcinoma cell line | Luteolin effectively increased the sub-G1 (apoptotic) fraction of cells through caspase-3 and -7 dependent pathways. | Attoub et al., (2011) |
| 12 | Azoxymethane induced colon cancer in Balb/C mouse | Luteolin reduces the incidence of aberrant crypt foci (ACF). Inhibits lipid peroxidation and Hydroxyl radical formation. Increased the activities of enzymic and non-enzymic antioxidants. | Ashokkumar and Sudhandiran, (2008) |
| 13 | 1,2-Dimethyl hydrazine induced colon cancer in wistar rats | Luteolin inhibits tumor formation. Decreased the activities of Bacterial enzymes. | Manju and Nalini, (2007) |
| 14 | HT-29 colon adenocarcinoma cell line | Luteolin induces cell cycle arrest by inhibiting CDK2 and cyclin D1. Luteolin induces apoptosis by activating Caspase 3,7 and 9. | Lim et al., (2007) |
| 15 | 1,2-Dimethyl hydrazine induced colon cancer in wistar rats | Luteolin reduces the tumor number and size. Increased the activities of enzymic and non-enzymic antioxidants. | Manju and Nalini, (2005); Manju et al., (2005) |
| 16 | SW480 and Caco-2 colon cancer cell lines | Luteolin induces cell cycle arrest at G2/M phase | Wang et al., (2012) |

radical with complex redox chemistry, NO can modify all biological molecules and is, therefore, implicated in all biological functions in living systems. NO is an important bioregulatory mediator involved in a variety of biological processes in both normal and pathophysiological conditions.

Nitric oxide synthase (NOS), particularly inducible NOS (iNOS or NOSII) and endothelial forms are overexpressed in various cancers in both humans and rodents (Rao et al., 1999; Rao et al., 2002). NO can exert its effects directly by forming reactive nitrogen–oxygen species and indirectly by post-translational modifications of proteins via S-nitrosylation or tyrosine nitration (Gow et al., 2002; Hess et al., 2005). Previous studies in both carcinogen-induced and genetic models support a role for iNOS in the promotion of colon carcinogenesis (Rao et al., 1999; Rao et al., 2002). Increased iNOS expression and activity were observed in carcinogen-induced rat dysplastic aberrant crypt foci (ACF), adenomas and adenocarcinomas, but not in hyperplastic ACF (Takahashi et al., 2000). The tumor-enhancing effects of iNOS in the colon may be associated with the ability of NO to increase the expression/activity of the enzyme COX-2 (Thun et al., 2002; Somchit et al., 2014). To support further the role iNOS in colon tumor promotion, mice from an $Apc^{Min/+}$-iNOS-knockout genetic background showed decreased intestinal tumor formation (Ahn and Ohshima, 2001). In humans, iNOS expression is up-regulated in carcinomas compared with patient's normal-appearing colonic mucosa (Yagihashi et al., 2000). Luteolin has an anti-inflammatory role was already reported by modulating the inflammatory mediators (Choi, 2007). But in chemically induced model luteolin decreased the expression of iNOS in mice (Pandurangan et al., 2014b), but the mechanism unknown.

## Luteolin Effects on COX-2

COX-2 is considered as an enhancer of carcinogenesis in many organs including the colon. Henceforth, assays of COX-2 expression may be used to monitor the process of carcinogenesis, and the suppression of COX-2 expression has become an important target for treatment and prevention of CRC (Tanaka et al., 2001; Turini and DuBois, 2002; Hamiza et al., 2012). COX-2 is induced by inflammatory cells, by various stimuli including cytokines, growth factors and tumor inducing factors. Overexpression of COX-2 results in dedifferentiation, adhesion to extracellular matrices and inhibition of programmed cell death in untransformed rat intestinal epithelial cells (Tsujii and DuBois, 2002). Inducibility of COX-2 in response to

mitogenic stimuli, oncogenes and tumor promoters link it to cell proliferation. Increased COX-2 expression leads to the elevated levels of PGE2 that is correlated with increased MDA, which forms adducts with DNA in human colon leads to carcinogenesis (Hanif et al., 1996) or inhibit apoptosis in epithelial tumor cells (Sheng et al., 1998). Treating with Non-steroidal anti-inflammatory drugs was the potential way to control the production of COX-2 during tumorigenesis. In this context, natural sources and flavonoids also a right approach to inhibit COX-2 (Shafie et al., 2013a). Especially plant polyphenols are the strong inhibitors of COX-2 (Banerjee et al., 2013; Wang et al., 2013) and Pandurangan et al., (2014b) reported that luteolin inhibits COX-2 during AOM-induced colorectal cancer in BALB/c mice.

## Luteolin Effects on the Nrf2/keap1 Pathway

NF-E2-related factor 2 (NRF2) transcription factor belongs to the Cap 'n' Collar subfamily of basic leucine zipper family of transcription factor. Under normal condition Kelch-like ECh-associated protein 1 (keap 1) play a central role and regulate NRF2 activity. NRF2 bound with KEAP1 due to an interaction between single NRF2 protein and a KEAP1 dimer through cysteines residue (Itoh et al., 1997). KEAP1 serves as a substrate linker protein for interaction of Cul3-based E2-ubiquitin ligase complex with NRF2 and its proteosomal degradation. NRF2 is activated by number of stressors such as ROS, reactive nitrogen species lipid aldehydes and certain variety of natural agents' results in the dissociation of one or both NRF2-interacting motifs from NRF2. The activated NRF2 translocate into the nucleus and transcribes GST, NQO1 which enables the cytoprotection (Holland et al., 2008; Yamamoto et al., 2008).

It is difficult to discuss the cancer chemoprevention without mentioning Nrf2 transcription factor, since the discovery of Nrf2 is attributed greatly to studies with anti-carcinogenic compounds (Zhang, 2006).There are many reports stating that Nrf2-deficient mice are more susceptible to toxicity, DNA adduct formation and cancer development in several models of chemical-induced carcinogenesis (Xu et al., 2006; Khor et al., 2008). Nrf2-null mice have decreased basal and inducible expression of antioxidant genes, increased oxidative stress, and decreased reducing activity and antioxidant capacity (Chan et al., 2000; Hirayama et al., 2003), suggesting that the Nrf2/ARE pathway is crucial in the regulation of intracellular redox status. During CRC the expression of Nrf2 was limited (Patel et al., 2008). However, treatment with flavonoid compounds such as EGCG and PBT has the potential to activate the Nrf2 by dissociating the Nrf2-keap1 complex (Chiou et al., 2012). Luteolin is reported to activate the Nrf2 in AOM-induced colon cancer (Pandurangan et al., 2014a). On the other hand luteolin sensitizes two oxaliplatin-resistant colorectal cancer cell lines to chemotherapeutic drugs via inhibition of the nrf2 pathway (Chian et al., 2014). This phenomenon was further confirmed by the elevated expression of GST-$\alpha$ and GST-$\mu$ (Summart et al., 2014). On other hand, supplementation of Luteolin elevates the intracellular reduced glutathione (GSH) (Pandurangan and Ganapasam, 2013a). Since GSH plays an intracellular radical scavenger and is the substrate of many xenobiotic elimination reactions (Gregus et al., 1996), an increased level of GSH also postulates that it activates GSH dependent enzyme GST (Pandurangan et al., 2014a).

## Luteolin Effects on IGF-1

Insulin-like growth factors (IGFs) are polypeptides that stimulate the growth of a variety of mammalian cells (Baserga et al., 1997). The IGF system (IGF-I, IGF-II, IGF-binding protein, and IGF-IR) performs an important role in the growth of various cancer cells, including colon cancer cells (Frasca et al., 2008; Jung et al., 2008). Luteolin, dose-dependently reduced the IGF-2 secretion of HT-29 cells. IGF-1 stimulated HT-29 cell growth but did not abrogate luteolin-induced growth inhibition. Luteolin reduced the levels of the IGF-IR precursor protein and IGF-1R transcripts. Luteolin reduced the IGF-1-induced tyrosine phosphorylation of IGF-1R and the association of p85 with IGF-IR. Additionally, luteolin inhibited the activity of PI3K activity as well as the phosphorylation of Akt, ERK1/2, and CDC25c in the presence and absence of IGF-1 stimulation (Kim et al., 2012).

## Luteolin Effects on the Wnt-β-catenin Pathway

The wnt/β-catenin pathway plays an essential role in embryonic development and contributes to tissue homeostasis and tumorigenesis. Frequent mutations in the Wnt pathway are considered an early, important step in human CRC and are responsible for colon tumor formation in patients with familial polyposis (FAP) (Moser et al., 1990; deLau et al., 2007). The oncogenic potential of the Wnt pathway derives from β-catenin protein stabilization and relocation from the cell membrane to the nucleus, where it is recruited into T-cell factor/lymphoid enhancer factor 1 (TCF/LEF) transcriptional regulatory complexes (Fuchs et al., 2005). TCF/LEF complexes bind to enhancer regionsof target genes involved in proliferation, invasion, and inhibition of apoptosis, including c-Myc and cyclin D1. These effects contribute directly to the development CRC (Kumar et al., 2012). In our laboratory we shown that luteolin inhibits the translocation of β-catenin from the cytosol to nucleus in CRC *in vitro* and *in vivo* (Pandurangan et al., 2013a; Ashokkumar and Sudhandiran, 2011). Inhibition of β-catenin is mediated by modulating the expression of p-GSK3β. Luteolin also shown that; it inhibits the expression of cyclin D1, a downstream target of wnt/β-catenin pathway (Pandurangan et al., 2013a). Baskar et al., (2011) reported that luteolin-7-O-glucoside isolated from ophiorrhizamungos Linn showed to decrease the expression of β-catenin in COLO 320 DM cells.

## Luteolin Effects on Apoptosis

Apoptosis is termed as a programmed cell death, which is characterized by cell shrinkage, chromatin condensation, DNA fragmentation, and the activation

of specific cysteine proteases known as caspases (Zou et al., 1997). In particular, caspase-3 is the most widely studied of effector caspases. It plays an important role in both death pathways and cleaves a wide range of cellular substrates, including structural proteins and DNA repair enzymes (Fernandes-Alnemri et al., 1995). Caspase-3 is a critical component of the cell death machinery, being regarded as the most downstream enzyme in the apoptotic process due to its location in the protease cascade pathway (Fernandes-Alnemri et al., 1995a). The ratio of Bax/Bcl-2 is a critical determinant of the overall predisposition of a cell to undergo apoptosis. An increase in Bax relative to Bcl-2 promotes release of cytochrome C from the mitochondria with subsequent activation of caspase-3, thereby inducing mitochondrial mediated apoptosis (Gupta and DuBois, 2001). Natural compounds has the ability to induce cytotoxicity thereby protects against cancer and many researcher's developing chemotherapeutic by based on its ability to induce apoptosis (Sriram et al., 2008; Acebedo et al., 2014; Shafie et al., 2013b; Zou et al., 2013). Lim et al. (2012) reported that luteolin induce cell cycle arrest and apoptosis in HT-29 human colon cancer cells. Many reports stating that Luteolin arrest cell cycle and induce apoptosis in colon cancer cells (Attoub et al., 2011; Pandurangan and Ganapsam, 2013). Another study from Attoub et al. (2011) showed that Luteolin induces apoptosis by activating caspase 3 in HT-29 colon cancer cells. A study from our laboratory showed that luteolin induces apoptosis in colon cancer by modulating the expressions of bax, Bcl-2 and caspase 3 *in vitro* and *in vivo* (Lim et al., 2007; Pandurangan et al., 2013; Pandurangan and Ganapasam, 2013b). On the other hand Luteolin acts against DNA damage and activates DNA repair mechanism in caco-2 colon cancer cells (Ramos et al., 2010).

## Conclusion

Epidemiological studies have indicated that colorectal cancer is strongly related with diet, and thus it may be possible to prevent the incidence of this cancer through dietary modification. Chemoprevention refers to the use of the naturally derived or synthetic compounds to prevent, reverse or delay the development of cancer. Because food-derived products exist universally and are expected to be safe, they are highly interesting for development as chemopreventive agents. To summarize the present scenario on luteolin against colon cancer, so far an ample of evidences available, that luteolin potentially controls colon cancer in multiple aspects.

## References

Acebedo AR, Amor EC, Jacinto SD (2014). Apoptosis-inducing activity of HPLC fraction from *Voacanga globosa (Blanco)* merr. on the human colon carcinoma cell. *Asian Pac J Cancer Prev*, **15**, 617-22.

Ahn B, Ohshima H (2001). Suppression of intestinal polyposis in Apc(Min/+) mice by inhibiting nitric oxide production. *Cancer Res*, **61**, 8357-60.

Ansil PN, Prabha SP, Nitha A, et al (2013). Chemopreventive effect of *Amorphophallus campanulatus* (Roxb.) blume tuber against aberrant crypt foci and cell proliferation in 1, 2-dimethylhydrazine induced colon carcinogenesis. *Asian Pac J Cancer Prev*, **14**, 5331-9.

Ashokkumar P, Sudhandiran G (2011). Luteolin inhibits cell proliferation during azoxymethane-induced experimental colon carcinogenesis via Wnt/β-catenin pathway. *Invest New Drugs*, **29**, 273-84.

Ashokkumar P, Sudhandiran P (2008). Protective role of luteolin on the status of lipid peroxidation and antioxidant defense against azoxymethane-induced experimental colon carcinogenesis. *Biomed Pharm*, **62**, 590-7.

Attoub S, Hassan AH, Vanhoecke B, et al (2011). Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. *Eur J Pharmacol*, **651**, 18-25.

Banerjee N, Kim H, Talcott S, et al (2013). Pomegranate polyphenolics suppressed azoxymethane-induced colorectal aberrant crypt foci (ACF) and inflammation: possible role of miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR. *Carcinogenesis*, **34**, 2814-22.

Baserga R, Hongo A, Rubini M, et al (1997). The IGF-I receptor in cell growth, transformation and apoptosis. *Biochim Biophys Acta*, **1332**, 105-26.

Baskar A, Ignacimuthu S, Micheal GP, et al (2011). Cancer chemopreventive potential of luteolin-7-O-glucoside isolated from ophiorrhizamungos linn. *Nutri Cancer*, **63**, 130-8.

Bird RP (1995). Role of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Cancer Lett*, **93**, 55-71.

Bird RP, Good CK (2000). The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Toxicol Lett*, **112-113**, 395-402.

Chan JY, Kwong M (2000). Impaired expression of glutathione synthetic enzyme genesin mice with targeted deletion of the Nrf2 basic-leucine zipper protein. *Biochim Biophys Acta*, **1517**, 19-26.

Chan TS, Galati G, Pannala AS, et al (2003). Simultaneous detection of the antioxidant and pro-oxidant activity of dietary polyphenolics in a peroxidase system. *Free Rad Res*, **37**, 787-94.

Chian S, Li YY, Wang XJ, Tang XW (2014). Luteolin sensitizes two oxaliplatin-resistant colorectal cancer cell lines to chemotherapeutic drugs via inhibition of the nrf2 pathway. *Asian Pac J Cancer Prev*, **15**, 2911-6.

Chihara T, Shimpo K, Kaneko T, Beppu H (2010). Inhibition of 1, 2-dimethylhydrazine-induced mucin-depleted foci and O6-methylguanine DNA adducts in the rat colorectum by boiled garlic powder. *Asian Pac J Cancer Prev*, **11**, 1301-4.

Chiou YS, Ma NJ, Sang S, et al (2012). Peracetylated (-)-epigallocatechin-3-gallate (AcEGCG) potently suppresses dextran sulfate sodium-induced colitis and colon tumorigenesis in mice. *J Agri Food Chem*, **60**, 3441-51.

Choi EM (2007). Modulatory effects of luteolin on osteoblastic function and inflammatory mediators in osteoblastic MC3T3-E1 cells. *Cell Biol Int*, **31**, 870-77.

deLau W, Barker N, Clevers H (2007). WNT signaling in the normal intestine and colorectal cancer. *Front Biosci*, **12**, 471-91.

Fernándes-Alnemri T, Litwack G, Alnmri ES (1995). Mch2, a new member of the apoptotic Ced-3/Ice cysteine protease gene family. *Cancer Res*, **55**, 2737-42.

Fernández-Alnemri T, Takahashi A, Armstrong R, et al (1995). Mch3, a novel human apoptotic cysteine protease highly related to CPP32. *Cancer Res*, **55**, 6045-55.

Frasca F, Pandini G, Sciacca L, et al (2008). The role of insulin receptors and IGF-I receptors in cancer and other diseases. *Arch Physiol Biochem*, **114**, 23-37.

Fuchs SY, Ougolkov AV, Spiegelman VS, et al (2005). Oncogenic beta-catenin signaling networks in colorectal cancer. *Cell Cycle*, **4**, 1522-39.

Gates MA, Tworoger SS, Hecht JL, et al (2007). A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. *Int J Cancer*, **121**, 2225-32.

Gow AJ, Chen Q, Hess DT, et al (2002). Basal and stimulated protein S-nitrosylation in multiple cell types and tissues. *J Biol Chem*, **277**, 9637-40.

Greenlee R, Murray R, Bolden S, et al (2000). Cancer statistics, 2000. *CA Cancer J Clin*, **50**, 7-33.

Gregus Z, Fekete T, Halaszi E, et al (1996). Lipoic acid impairs glycine conjucation of benzoic acid and renal excretion of benzoglycine. *Drug Metabol Dispos*, **24**, 682-8.

Guizani N, Waly MI, Singh V, et al (2013). Nabag (*Zizyphus spina-christi*) extract prevents aberrant crypt foci development in colons of azoxymethane-treated rats by abrogating oxidative stress and inducing apoptosis. *Asian Pac J Cancer Prev*, **14**, 5031-5.

Gupta RA, DuBois RN (2001). Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. *Nat Rev Cancer*, **1**, 11-21.

Hakomori S (1996). Tumor malignancy defined by aberrant glycosylation and sphingo (glyco) lipid metabolism. *Cancer Res*, **56**, 5309-18.

Halliwell B, Gutteridge JMC (1989). Protection against oxidants in biological systems: the superoxide theory of oxygen toxicity. In: Cheeseman Kh, Slater Tf, Editors. Free Radicals In Biology And Medicine. Oxford: Clarendon Press.144-7.

Hamiza OO, Rehman MU, Tahir M, et al (2012). Amelioration of 1,2 dimethylhydrazine (DMH) induced colon oxidative stress, inflammation and tumor promotion response by tannic acid in Wistar rats. *Asian Pac J Cancer Prev*, **13**, 4393-402.

Hanif R, Pittas A, Feng Y (1996). Effects of nonsteroidal anti-inflammatory drugs on proliferation and on induction of apoptosis in colon cancer cells by a prostaglandin-independent pathway. *Biochem Pharmacol*, **52**, 237-45.

He XQ, Cichello SA, Duan JL, et al (2014). Canola oil influence on azoxymethane-induced colon carcinogenesis, hypertriglyceridemia and hyperglycemia in Kunming mice. *Asian Pac J Cancer Prev*, **15**, 2477-83.

Hempel J, Pforte H, Raab B, et al (1999). Flavonols and flavones of parsley cell suspension culture change the antioxidative capacity of plasma in rats. *Mol Nutr Food Res*, **43**, 201-4.

Hess DT, Matsumoto A, Kim SO, et al (2005). Protein S-nitrosylation: preview and parameters. *Nat Rev Mol Cell Biol*, **6**, 150-66.

Hirayama A, Yoh K, Nagase S, et al (2003). EPR imaging of reducing activity in Nrf2 transcriptional factor-deficient mice. *Free Radic Biol Med*, **34**, 1236-42.

Holland R, Hawkins AE, Eggler AL, et al (2008). Prospective type 1 and type 2 disulfides of Keap 1 protein. *Chem Res Toxicol*, **21**, 2051-60.

Hwang JT, Park OJ, Lee YK, et al (2011). Anti-tumor effect of luteolin is accompanied by AMP-activated protein kinase and nuclear factor-κB modulation in HepG2 hepatocarcinoma cells. *Int J Mol Med*, **28**, 25-31.

Itoh K, Chiba T, Takahashi S, et al (1997). An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem Biophys Res Commun*, **236**, 313-22.

Jung JI, Cho HI, Kim J, et al (2008). trans-10, cis-12 conjugated linoleic acid inhibits insulin-like growth factor-I receptor signaling in TSU-Pr1 human bladder cancer cells. *J Med Food*, **13**, 13-9.

Khor TO, Huang MT, Prawan A, et al (2008). Increased susceptibility of Nrf2 knockout mice to colitis associated colorectal cancer. *Cancer Prev Res*, **1**, 187-91.

Kim DY, Cho HJ, Kim J, et al (2012). Luteolin decreases IGF-II production and downregulates insulin-like growth factor-I receptor signaling in HT-29 human colon cancer cells. *BMC Gastroenterol*, **12**, 9.

Kocic B, Kitic D, Brankovic S (2013). Dietary flavonoid intake and colorectal cancer risk: evidence from human population studies. *J BUON*, **18**, 34-43.

Kumar A, Pandurangan AK, Lu F, et al (2012). Chemopreventive sphingadienes downregulate wnt signaling via a PP2A/Akt/GSK3β pathway in colon cancer. *Carcinogenesis*, **33**, 1726-35.

LeMarchand L (2002). Cancer preventive effects of flavonoids-a review. *Biomed Pharmaco*, **56**, 296-301.

Lim DY, Cho HJ, Kim J, et al (2012). Luteolin decreases IGF-II production and downregulates insulin-like growth factor-I receptor signaling in HT-29 human colon cancer cells. *BMC Gastroenterol*, **12**, 9.

Lim DY, Jeong Y, Tyner AL, et al (2007). Induction of cell cycle arrest and apoptosis in HT-29 human colon cancer cells by the dietary compound luteolin. A*m J Physiol Gastroint Liver Physiol*, **292**, 66-75.

Madrigal-Bujaidar E, Martino Roaro L, Garcia-Aguirre K, Garcia-Medina S, Alvarez-Gonzalez I (2013). Grapefruit juice suppresses azoxymethane-induced colon aberrant crypt formation and induces antioxidant capacity in mice. *Asian Pac J Cancer Prev*, **14**, 6851-6.

Manju V, Balasubramaniyan V, Nalini N (2005). Rat colonic lipid peroxidation and antioxidant status: the effects of dietary luteolin on 1,2-dimethylhydrazine challenge. *Cell Mol Biol Lett*, **10**, 535-51.

Manju V, Nalini N (2005). Chemopreventive potential of luteolin during colon carcinogenesis induced by 1,2-dimethylhydrazine. *Ital J Biochem*, **54**, 268-75.

Manju V, Nalini N (2007). Protective role of luteolin in 1,2-dimethylhydrazine induced experimental colon carcinogenesis. *Cell Biochem Function*, **25**, 189-94.

McLellan EA, Medline A, Bird RP (1991). Dose responsive and proliferative characteristics of aberrant crypt foci: a putative preneolastic lesion in rat colon. *Carcinogenesis*, **12**, 2093-8.

Mencherini T, Picerno P, Scesa C, et al (2007). Triterpene, antioxidant, and antimicrobial compounds from melissa officinalis. *J Nat Products*, **70**, 1889-94.

Miean KH, Mohamed S (2001). Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) contentof edible tropical plants. *J Agri Food Chem*, **49**, 3106-12.

Moser A, Pitot HC, Dove WF (1990). A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse. *Science*, **247**, 322-4.

Neuhouser ML (2004). Dietary flavonoids and cancer risk: evidence from human population studies. *Nutr Cancer*, **50**, 1-7.

Nishitani Y, Yamamoto K, Yoshida M, et al (2013). Intestinal anti-inflammatory activity of luteolin: role of the aglycone in NF-κB inactivation in macrophages co-cultured with intestinal epithelial cells. *Biofactors*, **39**, 522-33.

Pandurangan AK (2013). Potential targets for the prevention of colorectal cancer: a focus on PI3K/Akt/mTOR and Wnt pathways. *Asian Pac J Cancer Prev*, **14**, 2201-5.

Pandurangan AK, Esa NM (2014). Signal transducer and activator of transcription 3: a promising target in colitis associated cancer. *Asian Pac J Cancer Prev*, **15**, 551-60.

Pandurangan AK, Dharmalingam P, Ananda Sadagopan SK, et al (2013). Luteolin induces growth arrest in colon cancer cells through involvement of Wnt/β-catenin/GSK-3β signaling. *J Environ Pathol Toxicol Oncol*, **32**, 131-9.

Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P, et

al (2013). Luteolin, a bioflavonoid attenuates azoxymethane-induced effects on mitochondrial enzymes in Balb/c mice. *Asian Pac J Cancer Prev*, **14**, 6669-72.

Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P, et al (2013). Inhibitory effect of luteolin on the status of membrane bound ATPases against azoxymethane-induced colorectal cancer. *J Chem Pharm Res*, **5**, 123-7.

Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P, et al (2014). Luteolin, a bioflavonoid inhibits azoxymethane-induced colorectal cancer through Nrf2 signaling. *Toxicol Mech Methods*, **24**, 13-20.

Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P, et al (2014). Inhibitory effect of luteolin on azoxymethane-induced colon carcinogenesis: involvement of iNOS and COX-2. *Pharmacog Mag*, **10**, 306-10.

Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P, et al (2014). Luteolin inhibits matrix metalloproteinase 9 and 2 in azoxymethane-induced colon carcinogenesis. *Human Exp Toxicol*, (Equb Ahead of Print).

Pandurangan AK, Dharmalingam P, Anandasadagopan SK, et al (2012). Effect of luteolin on the levels of glycoproteins during azoxymethane-induced colon carcinogenesis in mice. *Asian Pac J Cancer Prev*, **13**, 1569-73.

Pandurangan AK, Esa NM (2013). Dietary non-nutritive factors on regulatory molecules in colorectal cancer: an update. *Asian Pac J Cancer Prev*, **14**, 5543-52.

Pandurangan AK, Ganapasam S (2013a). Luteolin modulates cellular thiols on azoxymenthane-induced colon carcinogenesis. *Asian J Exp Biol Sci*, **4**, 245-50.

Pandurangan AK, Ganapasam S (2013). Cytotoxic effect of luteolin on human colorectal cancer cell line (HCT-15): crucial involvement of reactive oxygen species. *Middle East J Cancer*, **4**, 177-82.

Pandurangan AK, Ganapsam G (2013). Luteolin induces apoptosis in azoxymethane-induced colon carcinogenesis through involvement of Bcl-2, bax, and caspase-3. *J Chem Pharm Res*, **5**, 143-28.

Pitot HC (1986). Fundamentals of Oncology: Newyork: Marcer Dekker, Inc.

Ramos AA, Pereira-Wilson C, Collins AR (2010). Protective effects of ursolic acid and luteolin against oxidative DNA damage include enhancement of DNA repair in Caco-2 cells. *Mutat Res*, **692**, 6-11.

Rao CV, Cooma I, Simi B, et al (2002). Chemopreventive properties of a selective inducible nitric oxide synthase inhibitor in colon carcinogenesis, administered alone or in combination with celecoxib, a selective cyclooxygenase-2 inhibitor. *Cancer Res*, **62**, 165-70.

Rao CV, Kawamori T, Hamid R, et al (1999). Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. *Carcinogenesis*, **20**, 641-64.

Ross JA, Kasum CM (2002). Dietary flavonoids: bioavailability, metabolic effects, and safety. *Ann Rev Nutr*, **22**, 19-34.

Ruan JS, Liu YP, Zhang L, et al (2012). Luteolin reduces the invasive potential of malignant melanoma cells by targeting β3 integrin and the epithelial-mesenchymal transition. *Acta Pharmacol Sin*, **33**, 1325-31.

Salib JY, Micheal HN, Esande EF (2013). Anti-diabetic properties of flavonoid compounds isolated from hyphaenethebaicaepi carp. on alloxan induced diabetic rats. *Pharmacog Res*, **5**, 22-9.

Scholz D, Horpacsy G, Mebel M (1983). Late prognosis in acute post-transplant renal failure in 102 patients. *Eur Urol*, **5**, 14-7.

Selvam S, Nagini S (1995). Administration of the plasticizer di(engl hexyl)phthalate alters glycoconjugate profile. *Ind J Physiol Pharmacol*, **39**, 252-4.

Sen U, Guha S, Chowdhury JR (1983). Serum fucosyl transferase activity and serum fucose levels as diagnostic tools in malignancy. *Acta Med Okayama*, **37**, 457-62.

Sengupta A, Ghosh S, Das S (2002). Inhibition of cell proliferation and induction of apoptosis during azoxymethane induced colon carcinogenesis by black tea. *Asian Pac J Cancer Prev*, **3**, 41-6.

Shafie NH, Esa NM, Ithnin H, et al (2013a). Preventive Inositol hexaphosphate extracted from rice bran inhibits colorectal cancer through involvement of Wnt/β-catenin and COX-2 pathways. *Bio Med Res Int*, **2013**, 681027.

Shafie NH, Esa NM, Ithnin H, et al (2013b). Pro-apoptotic effect of rice bran inositol hexaphosphate (IP6) on HT-29 colorectal cancer cells. *Int J Mol Sci*, **14**, 23545-58.

Sharma RA, Gescher A, Plastaras JP (2001). Cyclooxygenase-2, malondialdehyde and pyrimidopurinone adducts of deoxyguanosine in human colon cells. *Carcinogenesis*, **22**, 1557-60.

Sheng H, Shao J, Morrow JD (1998). Modulation of apoptosis and Bcl-2 expression by prostaglandin E2 in human colon cancer cells. *Cancer Res*, **58**, 362-6.

Shimoi K, Okada H, Furugori M, et al (1998). Intestinal absorption of luteolin and luteolin 7-O-beta-glucoside in rats and humans. *FEBS Lett*, **438**, 220-4.

Somchit M, Changtam C, Kimseng R, et al (2014). Demethoxycurcumin from curcuma longa rhizome suppresses iNOS induction in an *in vitro* inflamed human intestinal mucosa model. *Asian Pac J Cancer Prev*, **15**, 1807-10.

Sriram N, Kalayrasan S, Ashokkumar P, et al (2008). Diallyl sulfide induces apoptosis in Colo 320 DM human colon cancer cells: involvement of caspase-3, NF-ϰB, and ERK. *Mol Cell Biochem*, **311**, 157-65.

Summart R, Chewonarin T, (2014). Purple rice extract supplemented diet reduces DMH-induced aberrant crypt foci in the rat colon by inhibition of bacterial β-glucuronidase. *Asian Pac J Cancer Prev*, **15**, 749-55.

Sun T, Xu Z, Wu CT, et al (2007). Antioxidant activities of different colored sweet bell peppers (Capsicum annuum L). *J Food Sci*, **72**, 98-102.

Swan DK, Ford B (1997). Chemoprevention of cancer: review of the literature. *Oncol Nursing Forum*, **24**, 719-27.

Takahashi M, Mutoh M, Kawamori T, et al (2000). Altered expression of β-catenin, inducible nitric oxide synthase and cyclooxygenase-2 in azoxymethane-induced rat colon carcinogenesis. *Carcinogenesis*, **21**, 1319-27.

Tammasakchai A, Reungpatthanaphong S, Chaiyasut C, et al (2012). Red strain oryza sativa-unpolished Thai rice prevents oxidative stress and colorectal aberrant crypt foci formation in rats. *Asian Pac J Cancer Prev*, **13**, 1929-33.

Tanaka T, Shimizu M, Kohno H, et al (2001). Chemoprevention of azoxymethane-induced rat aberrant crypt foci by dietary zerumbone isolated from zingiber zerumbet. *Life Sci*, **69**, 1935-45.

Tang X, Wang H, Fan L, et al (2011). Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung carcinoma A549 cells to therapeutic drugs. *Free Rad Biol Med*, **50**, 1599-609.

Thun MJ, Henley SJ, Patrono C (2002). Nonsteroidal anti-inflammatory drugs as anticancer agents:mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Ins*, **94**, 252-66.

Tsujii M, DuBois RN (1995). Alteration in cellular adhesion and apoptosis in epithelial cells over expressing prostaglandin endoperoxide synthase 2. *Cell*, **83**, 493-501.

Turini ME, DuBois RN (2002). Cyclooxygenase-2: a therapeutic target. *Ann Rev Med*, **53**, 35-57.

Upsani CD, Khera A, Balaraman R (2001). Effect of Lead and vitamin E, C orspiruline on malondialdehyde, conjugated dienes and hydroperoxides in rats. *Ind J Exp Biol*, **39**, 70-4.

Volate SR, Davenport DM, Muga SJ, et al (2005). Modulation of aberrantcrypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin). *Carcinogenesis*, **26**, 450-6.

Waly MI, Ali A, Guizani N, et al (2012). Pomegranate (Punicagranatum) peel extract efficacy as a dietary antioxidant against azoxymethane-induced colon cancer in rat. *Asian Pac J Cancer Prev*, **13**, 4051-5.

Wang LM, Xie KP, Huo HN, et al (2012). Luteolin inhibits proliferation induced by IGF-1 pathway dependent ERα in human breast cancer MCF-7 cells. *Asian Pac J Cancer Prev*, **13**, 1431-7.

Wang TT, Wang SK, Huang GL, et al (2012a). Luteolin induced-growth inhibition and apoptosis of human esophageal squamous carcinoma cell line Eca109 cells *in vitro*. *Asian Pac J Cancer Prev*, **13**, 5455-61.

Wang W, Van Alstyne PC, Irons KA, et al (2004). Individual and interactive effects of apigenin analogs on G2/M cell-cycle arrest in human colon carcinoma cell lines. *Nutr Cancer*, **48**, 106-14.

Willet WC, Stampfer MJ, Colditz GA, et al (1990). Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *New Eng J Med*, **323**, 1664-762.

Xu C, Huang MT, Shen G, et al (2006). Inhibition of 7,12-dimethylbenz(a)anthracene-induced skin tumorigenesis in C57BL/6mice by sulforaphane is mediated by nuclear factor E2-related factor 2. *Cancer Res*, **66**, 8293-6.

Xu T, Li D, Jiang D (2012). Targetting cell signaling and apoptotic pathways by luteolin: cardioprotective role in rat cardiomyocytes following ischemia/reperfusion. *Nutrients*, **4**, 2008-19.

Yagihashi N, Kasajima H, Sugai S, et al (2000). Increased in situ expression of nitric oxide synthase inhuman colorectal cancer. *Virchows Arch Int J Pathol*, **436**, 109-14.

Yamamoto T, Suzuki T, Kobayashi A, et al (2008). Physiological significance of reactive cysteine residues of Keap 1 in determining Nrf2 activity. *Mol Cell Biol*, **28**, 2758-70.

Zhang DD (2006). Mechanistic studies of the Nrf2-keap1 signaling pathway. *Drug Metab Rev*, **38**, 769-89.

Zhou Q, Yan B, Hu X (2009). Luteolin inhibits invasion of prostate cancer PC3 cells through E-cadherin. *Mol Cancer Ther*, **8**, 1684-91.

Zou H, Henzel WJ, Liu XS, et al (1997). Apaf-1, a human protein homologous to C. elegans CED-4, participates in cytochrome c-dependent activation of caspase-3. *Cell*, **90**, 405-13.

Zou X, Liu SL, Zhou JY, et al (2012). Beta-asarone induces LoVo colon cancer cell apoptosis by up-regulation of caspases through a mitochondrial pathway *in vitro* and *in vivo*. *Asian Pac J Cancer Prev*, **13**, 5291-8.