Role of Phytochemicals in Chemoprevention of Cancer:
A Review

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ABSTRACT
Cancer is one of the most challenging health problems in the entire world today. It is a complex disease to treat. Even with advances in medical science disciplines such as surgery, radiotherapy and chemotherapy there is still no significant progress in its treatment. Conventional cancer therapies evoke severe side effects and in many cases, patients recover from cancer and die due to organ failure and immunosuppression. To redress these anomalies recourse to phytochemicals is advocated. The induction of apoptosis in a neoplastic cell line without affecting normal cells of the body is a key to the use of phytochemicals (chemopreventive agents) which perform a vital function in the battle against cancer. These active phytochemical chemopreventive agents such as sulforaphane, curcumin, gingerol and resveratrol found in fruits and vegetables modulate the molecular targets of cancer and induce cytoprotective enzymes that act in a co-ordinated fashion to detoxify and remove dangerous reactive substances formed by cancer causing agents. In addition, these chemopreventive agents inhibit, retard or reverse multi-stages of carcinogenesis via their anticarcinogenic and antimutagenic properties and also suppress cancer proliferation through induction and stimulation of cell death. Research has shown that they exert these abilities by counteracting certain cell signals that cause genotoxic damage and reduction-oxidation imbalance in cells. This discourse reviews the role of phytochemical chemopreventive agents, benefits and limitations associated with their use in cancer prevention as it portends great promise for normal cell protection.

1. INTRODUCTION
Cancer is one of leading cause of morbidity and mortality worldwide, despite enormous efforts of science researchers from various disciplines aimed at ameliorating the dismal outcome of cancer mortality. The rate of death from cancer has not declined significantly even with advances in surgery, radiotherapy and chemotherapy. Prevention of cancer remains evidently an essential part of the contest against cancer in the world (Zhao et al. 2010; Jermal et al. 2009).

Cancer cells occur as a result of unique multiple genetic disorders that may arise from exposure to environmental and occupational carcinogenic agents or dietary habits and infectious agents (Sugimura, 1992). The increased incidence of cancer in the world today justifies the application of phytochemical chemoprevention. This is the use of common natural dietary compounds from plants to inhibit, block or reverse tumour multiplication at various stages such as initiation, promotion or progression of carcinogenesis. These phytochemicals lower the risk of cancer development in humans via for example, radical scavenging, antioxidation mechanisms, anti-inflammatory and anti-proliferative mechanisms (Kwak and Kensler, 2010; Parys et al. 2010; Surh, 2003).

Phytochemicals are naturally occurring, non-nutritive biologically active chemical compounds in plants which act as a natural defence system for host plants and provide colour, aroma and flavour (Liu, 2003). Phytochemicals are a potential alternative source of safer chemicals with anticarcinogenic effects. Some sources of phytochemicals include broccoli, lettuce, cabbage, spinach, tomatoes, soybean, green tea, ginger, chilli pepper, turmeric, grapes, garlic, aloe and carrot (Aggarwal and Shishodia, 2006; Arts and Hollman, 2005).

The potential mechanisms of phytochemical chemopreventive agents are categorised into two basic groups namely; blocking agents and suppressing agents.
Blocking agents
These are substances like indole-3-carbinol, sulforaphane and flavonoids which avert cancer causing agents from accomplishing their effects on the normal cells, inhibit their metabolic stimulation, and also enhance their detoxification.

Suppressing agents
They function by interfering with the promotion and progression of carcinogenesis through their effect on cell proliferation, integration and programmed cell death which inhibits translation of initiated cells to form cancerous cells (Manson et al. 2000; Surh, 2003). These agents such as beta-carotene, curcumin, gingerol and resveratrol suppress carcinogenesis through blocking phase 1 enzymes, initiation of phase 2 enzymes, preventing reactive oxygen species from damaging DNA, suppressing type 2 cell multiplications generated by carcinogenesis and inhibiting normal cells from transforming to cancer cells (Tanaka et al. 2001).

The inherent potential of these phytochemicals in the chemoprevention of cancer cannot be overemphasized especially considering their robust safety records when compared with conventional anti-cancer therapies.

2. Chemoprevention and chemopreventive agents
Carcinogenesis or oncogenesis is a process by which healthy cells are transformed into cancerous cells. This process is as a result of genomic injury in gene elucidation which is the basic cause of all cancers. This damage occurs by abnormal changes in the genetic makeup of healthy cells through mutations (Mathers, 2004). These changes may occur as a result of hereditary or environmental factors such as chemical carcinogens and ionizing radiation (Shukla and Pal, 2004). Cancer development involves three different but closely related stages of carcinogenesis; initiation, promotion, and progression (Thangapazham et al. 2006).

Initiation results from direct contact of the DNA with cancer causing agents which occurs as a result of fast and incurable attack on the cell. Promotion leads to premalignancy which is irreversible and involves epigenetic mechanisms. Progression which is also irreversible owing to genetic mechanisms; is the span between transformations of initiated cells to cancer cells. Finally, additional changes allow the outgrowth of the clone with metastatic potential. Each of these events is likely to make the cell more unstable and causes an increase in the risk of subsequent changes (Tsao et al. 2004).

Chemoprevention simply means prevention of cancer by administering chemical compounds. It is a process by which specific natural or synthetic substances are used for preventing, interrupting or reversing carcinogenesis (Kucuk, 2002). Chemoprevention provides a novel promise which is realistic in lowering the occurrence of carcinogenesis. It is aimed at identifying the most efficient agents that can be able to delay the proliferation of cancer but not to cure already established cancer in the body (Surh, 1999). Chemopreventive agents are substances that have potent antigenic, anti-proliferative, anti-hormonal and anti-apoptotic effects and are classified by the way they exert protective actions on the specific stages of multistep carcinogenesis. These blocking, suppressing or other agents decrease tissue vulnerability to carcinogenesis.

Blocking agents are compounds that inhibit cancer initiation and prevent carcinogenic agents from reaching the targeted site. They are agents that decrease tissue vulnerability, preventing targeted tissues from receiving carcinogenic stimuli, while suppressing agents stop malignant proliferation of initiated cells in both promotion and progression stages of cancer transformation (Wattenberg, 1997). Some examples of chemical chemopreventive agents are tamoxifen and raloxifene used to suppress effects of breast cancer (Russo et al. 2005). Research has shown that finasteride can reduce the risk of prostate cancer while aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) can reduce cancer of the colon (Williams et al. 2009).

3. Phytochemicals in chemoprevention
The conventional radiotherapy and chemotherapy with synthetic drugs used in treating cancer evoke severe side effects such as immunosuppression, organ failure and infectious diseases which causes the death of patient after recovery from cancer (Barh, 2008). Thus from this point of view, induction of apoptosis in a neoplastic cell line without damaging the healthy cells of the body with phytochemical chemopreventive agents seems to be the best strategy in cancer management and treatment (Fan et al. 1998).

Phytochemicals are biologically active non-nutritive chemical compounds that occur naturally in plants. They are found as a substance responsible for the health-promoting properties of varieties of natural and functional foods due to their ability to alter cell communication, and DNA repair and influence cell processes that can cause development of cancer and other diseases (Liu, 2003).
Compounds are divided into two main groups as earlier stated: (Figure 1), the blocking agents such as ellagic acid, indole-3-carbinol, sulphoraphane and flavonoids which prevent cancer causing substances from getting to their target sites through many actions such as enhancement of carcinogen detoxification, modification of carcinogen uptake and metabolism, elimination of ROS and enhancement of DNA repair (Russo et al. 2005). Suppressing agents like beta-carotene, genistein, capsaicin, curcumin, gingerol and resveratrol suppress promotion and progression of cancer after stimulation of preneoplastic cells through their influence on cell differentiation, proliferation and apoptosis (Surh, 2003).

Figure 1 above shows chemopreventive agents that can inhibit the metabolic activation of pro-carcinogens, preventing them from transforming to carcinogens. On the other hand initiated cells are also suppressed by some of these agents inhibiting initiated cells from translating to neoplastic cells.

4. Classes of phytochemicals and their sources
Phytochemicals can be grouped into carotenoids, phenolics, alkaloids, and organosulphur compounds. Phenolics are secondary metabolites that are vital for plant growth and reproduction, and also serve as defence against pathogens, and predators that attack plants. They have been found useful in humans for lowering the effect of cancer and other chronic diseases. Phenolics possess an aromatic ring and hydroxyl groups and include phenolic acids, flavonoids stilbenes, coumarins and tannins. Their primary sources are vegetables, grapes, fruits, pineapple, banana, and green tea (Sun et al. 2002). Flavonoids are phenolic compounds that have antioxidant properties; examples include flavonal...
(querectin), flavones (apigenin), flavanols (epigallocatechin gallate) and isoflavonoids (genistein) (Hollman and Arts, 2000). Phenolic acids include resveratrol, curcumin, caffeic and ferulic acid (Table 1). Examples of carotenoids include β-carotene, lycopene, zeaxanthin and lutein. Their sources include carrots, tomatoes, sweet potatoes, broccoli and spinach (Britton, 1995). Another major class of phytochemicals are organosulphur compounds which include sulforaphane, diallyl sulphide, and indole-3-carbinol and s-allyl cysteine. Their dietary sources are onion, broccoli, garlic, and cruciferous vegetables (Russo et al. 2005).

Table 1: Dietary sources of agents with anti-cancer properties and their chemical structures (Surh, 2003)
Table 1 indicates our daily foods with anticancer properties. This can assist us in knowing some fruits and vegetables with health benefits in our daily food consumption and help us inform decisions on our choice of diets.

5. Mechanisms of phytochemicals in chemoprevention

In abnormal activation or silencing of mitogen-activated protein kinase (MAPK) pathways, protein kinase C (PKC) and phosphatidylinositol-3-kinase (P13k) result in uncontrollable cell growth which leads to translation of normal cells to cancer cells. Many phytochemical chemopreventive agents are capable of controlling these enzymes and preventing abnormal cell growth and proliferation (Bode and Dong, 2000).

Free radicals, inflammatory, cytokines, and cancer causing agents activate and release nuclear factor-kappa B (NF-kB). Then the released NF-kB is transferred to the nucleus. In the nucleus NF-kB binds and expresses genes that prevents normal cell death and causes abnormal cell multiplications, invasion, inflammation and metastasis in the cells (Aggarwal and Shishodia, 2006) (Figure 2). Activator protein 1 (AP 1) is a heterogeneous set of dimeric proteins consisting of c-JUN, c-FOS and ATF and are caused by TNF and interleukin 1 (IL-1), and environmental stress. Its stimulation is associated with control of cell development, inflammation and cell damage. Research has shown that it controls genes involved in apoptosis, cell adjustment, integration and multiplication, and causes cancer and tumour progression (Eferl and Wanger, 2003). The primary site of many phytochemical chemopreventive agents such as curcumin, gingerol, capsaicin, epigallocatechin gallate, genistein and resveratrol is NF-kB and AP1 (Figure 2).

![Fig. 2: Mechanism of action of phytochemical chemopreventive agents on NF-kB and AP1 (adapted from Surh, 2003)]
Figure 2 indicates specific phytochemical chemopreventive agents that can inhibit cancer proliferation by acting on NF-κB and AP1. In the figure curcumin, resveratrol and EGCG inhibit protein kinase C (PKC), c-JUN NH2-terminal kinase (JNK), while genistein and EGCG stop expression of AKT. EGCG also blocks activation of phosphatidylinositol-3-kinase (PI3K).

Curcumin: (diferuloylmethane or 1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione) is a derivative of turmeric which accounts for the characteristic yellow pigment in the rhizome of turmeric and can serve as a food additive (Anand et al. 2007). It has been observed that curcumin has a distinctive number of health-promoting properties such as anticarcinogenic, anti-inflammatory, antioxidative and antimutagenic activities in humans (Zhao et al. 2010). Curcumin inhibits inhibitory kappa B alpha (1KBa) degradation through controlling NF-kb inducing kinase (NIK) and IKB kinase (IKK) (figure 2). It also inhibits the expression of extracellular- signal-regulated kinase (ERK) 1/2 which indicates its capacity to stop NF-kb and cyclooxygenase-2(COX2) activities (Surh, 2003). It suppresses stimulation of IKK and blocks expression of TNF-dependent phosphorylation, and also stop translation and binding of NF-kb to nucleus (Aggarwal and Shishodia, 2006) (figure 2).

Gingerol: This is a phenolic compound that shows distinctive flavour of ginger. It inhibits cell developmental factor induced by AP1 stimulation and transcription to cancer formation (Surh, 2003).

Epigallocatechin gallate (EGCG): Is a polyphenol compound seen mostly in green tea which has great anti-proliferation and anti-cancerous effects (Tan and Spivack, 2009). It also inhibits Ras-activated AP1 activity and blocks vascular endothelial growth factor (VEGF) formation by suppressing both stimulation of signal transducer, or activator of transcription (STAT3) and NF-kb in breast , head and neck cancer cell lines (Surh, 2003). It has been reported that electron accepting forms of EGCG modulate cyteinyl thiolis in keap1 and stimulate production of Nrf2 for nuclear translocation (Zhao et al. 2010). Fig.2 shows that it blocks the action of AKT and PI3K thereby protecting the normal cell from damage.

Capsaicin: This is seen in pepper. It has distinctive pungent characteristics. It induces apoptosis and inhibits stimulation of NF-kb transformation expression and causes blockage of melanoma-cell expression (Surh and Na, 2008).

Genistein: Genistein, an isoflavone and is a dietary component of soybeans. It plays important roles in lowering occurrence of breast and prostate cancer by suppressing the expression of NF-kb and AKT signalling mechanisms, which control a metabolic equilibrium between normal cells and apoptotic cells. Inactivation of NF-kb with genistein is connected with down regulation of AKT in many cell lines (Russo et al. 2005). This suggests that blocking the interactions of AKT and NF-kb is the way by which genistein induces its mechanism of cell death (figure 2). Increased consumption of genistein in the diet controls cancer expression, tyrosine kinase regulated proteins, and insulin growth factor receptor (Russo et al. 2005).

Resveratrol: Resveratrol (3, 4’, 5-trihydroxy-transstibene) is a polyphenol abundantly seen in grapes (Russo et al. 2005). It inhibits PKC stimulation, and AP1 transformational changes. It also induces normal cell death and reduces stimulation of NF-kb in human pancreatic carcinoma cell lines (Surh, 2003). Banerjee et al. (2002) observed that the using resveratrol in controlling human breast cancer also helps suppress NF-kb stimulation and multiplication.

Ellagic acid: Ellagic acid (2,3,7,8-terahydroxychromeno[5,4,3-cde] chromene-5,10-dione) is a polyphenol compound seen abundantly in many fruits (Losso et al. 2004). It has antioxidant properties and causes inhibition of cancer proliferation by controlling the activities of the cell cycle and activates normal cell death (Saunders and Wallace, 2010).

Quercetin: Quercetin (3, 3’, 4’, 5, 7-pentahydroxyflavone) is a flavonol seen mostly in tea, apple and onion. It has anti-oxidant properties and also serves as an anti-inflammatory agent. Research has shown that it has potential for arresting the cell cycle in cancer and also induces caspase dependent apoptosis (Tanigawa et al. 2008). It also prevents normal cells from forming cancerous cells (Gosse et al. 2005).

Phytochemicals that activate NRF2
NF2 is a transcriptional factor that is very important in controlling enzymes that regi 9 detoxification and antioxidant genes (Surh and Na, 2008). It is present in the cytoplasm and is
controlled by kelch-like ECH-associated protein 1 (KEAP1) that prevents its release and translation to the nucleus. NRF2 can only be released from KEAP1 by modification of cysteine residues. Its dissociation is stimulated through phosphorylation of NRF2 by specific kinases such as MAPKs, PKC, PI3k and subsequent translocation to the nucleus (Figure 3). Once translocated to the nucleus, NRF2 combines with musculoaponeurotic-fibrosarcoma (MAF) to form a heterodimer and attaches itself to antioxidant-responsive element (ARE) causing abnormal cell proliferation (Surh and Na, 2008).

In figure 3 shows some phytochemical chemopreventive agents that interact with the NRF2 activation pathway. In the figure, curcumin and sulphoraphane act as analogues, and associate with KEAP1 to stop the dissociation of NRF2 from the KEAP1-NRF2 complex and also accelerate uptake of NRF2 by antioxidant responsive element (ARE).

One of the important approaches that phytochemicals use in prevention of cancer development is to block carcinogenic insult that can cause DNA damage. The toxic substances are detoxified by phase 2 enzymes and KEAP1 reduces the transcriptional factor activity of NRF2 through controlling the transcription factor in the cytoplasm and preventing NRF2 from being translocated to the nucleus (Surh, 2003). The KEAP1-NRF2 complex formed in the cells has a sensor that detects reduction-oxidation signalling through identification of the electrophilic substance. Treatment of human hepatoma (HepG2) cells with epigallocatechin-3-gallate induces expression of phase 2 detoxifying enzymes through antioxidant-response element (ARE) (Yu et al. 1997). Other phytochemicals such as phenethylisothiocyanate, sulforaphane and curcumin differentially regulate the stimulation of MAPKs and NRF as well as gene expression of phase 2 enzymes (Surh, 2003).

**Sulforaphane:** Sulforaphane is an isothiocyanate present in cruciferous vegetables like broccoli that has capacity to activate phase 2 detoxification enzymes. It can also induce NRF2 by modifying the sensor cysteine present in KEAP1 (fig.3) (Hong et al. 2005). Sulforaphane induces inactivation of NF-kB by directly combining to a vital group of p38, a functional reactive subunit of NF-kB (fig.3). It has been observed that sulforaphane may associate with reduced glutathione and reduction-oxidation controllers like thioredoxin (Heiss and Gerhauser, 2005).
Phytochemicals that target β-catenin

Catenin is a multifunctional protein that binds with the cytosolic tail of E-cadherin and links actin filaments through α-catenin which then forms the cytoskeleton. Curcumin is one of the phytochemical chemopreventive agents that inhibits tumourgenesis and decreases the cellular level of β-catenin (Jaiswal et al. 2002). Resveratrol is another phytochemical that down regulates β-catenin expression in a human colon cancer cell line. Surh, (2003) suggested that up regulation of cyclooxygenase-2 promotes tumourgenesis and β-catenin is seen to control cyclooxygenase-2 stimulation. This indicates that modification of β-catenin signalling pathways using chemoprevention phytochemicals could be another vital way of cancer management and treatment.

6. Benefits and limitations of phytochemicals in Chemoprevention

Most modern medicines currently used for treatment of cancer are not only very toxic, but are expensive in management of the disease. Recent research has indicated that consistent eating of whole fruits, vegetables and grain in our daily diets can minimise the risk of cancer diseases. These edible foods containing phytochemicals are essential to ensure a healthier population that has low incidence of cancer (Barh, 2008). These phytochemicals are inexpensive, effective, readily applicable and accessible bioactive compounds that neutralise free radicals that causes cell damage. They also inhibit cellular oxygenase, pro-inflammatory responses and nitric oxide production and induce apoptosis with increased neuroprotective effects (Juge et al. 2007). They have robust safety records compared to modern clinical methods of cancer treatment.

There are many challenges which limit the efficient use of phytochemicals as cancer chemopreventive agents. These include bioavailability and digestibility of these natural compounds in the body. Many researchers have observed that the use of phytochemicals in cancer chemoprevention is time consuming, and involves much expense during its clinical trials. All these problems put together correlate in making phytochemical chemoprevention a science its infancy (Russo, 2007).

CONCLUSION

Phytochemicals in cancer chemoprevention are considered as the cheapest option in cancer treatment. Despite little understanding of the mechanisms of some phytochemical chemopreventive agents, phytochemicals are believed to play significant roles in controlling, inhibiting, and blocking signals which can cause translation of normal cells to cancer cells (Issa et al. 2006). Thus from this point of view, there is a greater need for nutraceauticals (in phytochemicals) which will serve as functional supplement for cancer prevention. However, more studies should be focused on dose-dependent responses and toxicity of the phytochemical chemopreventive agents especially in relation to their effects on the normal human microflora to ascertain their safety before usage (Hodek et al. 2009). Although molecular mechanisms of action of phytochemicals have been characterised (of which most of them are in an early stage due to lack of extensive clinical studies), there is still much to do to enable us fill the gap in the knowledge of the molecular mechanisms of phytochemicals, to enhance a better understanding of their cellular effects which is vital for their proper utilization in cancer treatment.

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