INTRODUCTION

Cancer may be defined as uncontrolled tissue growth that results from an imbalance between cell division and apoptosis. It is a dynamic process that involves many complex factors, which may explain why a “magic bullet” cure for cancer has not been found. In spite of the significant progress in the development of anticancer therapies the incidence of cancer is still on its rise worldwide. The existing treatment modules include chemotherapy, radiotherapy and surgery with a limited role in eradication of the disease. Multidisciplinary scientific investigations and approaches are making best efforts to fight this disease, but the adequate cure is yet to be brought into world medicine. So cancer patients who already got crippled with this disease followed by burden of drug induced toxic side effects have now turned to seek help from complimentary and alternative medicine hoping for the cure. Thus an alternative measure to the existing western medicine and some of its unavoidable side effects is the use of medicinal plant products to arrest this dangerous disease.

Natural products such as phytochemicals have been placed on the top of the pyramid in chemoprevention. Various studies indicate that phytochemicals can modulate the complex multistage process of carcinogenesis. Based on reports regarding anticancer activity of natural products National Cancer Institute has been cited to identify about 40 edible plants possessing potential chemopreventive compounds known as phytochemicals in global language. Although chemopreventive effect of these dietary phytochemicals is initially based on cell line culture, in vitro and animal model studies, yet many of them are at the verge of crossing phase III clinical trials. It is well known that human being is consuming vegetarian diet for the last thousands of years. In day to day life every body is ingesting a cocktail of thousands of phytochemicals in the form of vegetables, fruits, spices and other food additives however most of the population is unaware about its biochemical, physiological and pharmacological therapeutic inputs. Recently chemoprevention by the use of naturally occurring dietary substances is considered as a practical approach to reduce the ever-increasing incidence of cancer. This measure for cancer control is based on the presumption that as cancer develops through a multi-step process, each step may be an eventual target for reversing or suppressing the process. Thus, the design and development of chemopreventive agents that act on specific and/or multiple molecular and cellular targets is gaining support as a rational and potential approach to prevent and control cancer. So the interference of multistage carcinogenesis by modulating intracellular signaling pathways may provide molecular basis of chemoprevention with a wide variety of phytochemicals of dietary origin. It has been estimated that about 25000 different chemical compounds occur in fruits, vegetables and other plants eaten by man. As of 2002 more than 500 of these compounds have been shown to be identified as potential modifiers of cancer process. According to a survey out of 121 prescription drugs in use for cancer treatment, 90 have been derived from plant species and 74% of these drugs were discovered by pursuing studies on a folklore claim.
Table 1: Dietary phytochemicals from spices with site of their action in cell cycle or apoptosis

<table>
<thead>
<tr>
<th>Dietary source</th>
<th>Active component</th>
<th>Site of action in cell cycle or apoptotic pathway</th>
<th>Result</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mulethi (Glycerrhiza glabra)</td>
<td>Glycryrrhetic acid, Glycyrrhetinic acid, Glycyrrhizin</td>
<td>Inhibits the proliferation, cytotoxic, Release of cytochrome C from mitochondria, activation of caspases, Mitochondrial membrane potential, Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>30-31</td>
</tr>
<tr>
<td>2. Heeng, (Ferula asafoetida)</td>
<td>Luteolin, Fertinin, ferutidin</td>
<td>Sensitizes TRAIL induced apoptosis, Inhibit cell proliferation at level of DNA synthesis (S-phase).</td>
<td>Apoptosis/Cell cycle arrest</td>
<td>32-35</td>
</tr>
<tr>
<td>3. Ginger (Zingiber officinale)</td>
<td>Gingerol, 6-shogaol</td>
<td>Mitochondrial membrane potential, Release of cytochrome C from mitochondria, activation of caspases, increase in Bax.</td>
<td>Apoptosis</td>
<td>36-38</td>
</tr>
<tr>
<td>4. Fennel (Foeniculum vulgare)</td>
<td>Anethol</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>39</td>
</tr>
<tr>
<td>5. Turmeric (Curcuma longa)</td>
<td>Curcumin</td>
<td>Activation of caspases, TRAIL induction, Release of cytochrome C from mitochondria, arrest G2M phase, down regulates expression of cyclin D1, upregulation of Cdk inhibitors</td>
<td>Apoptosis</td>
<td>40-48</td>
</tr>
<tr>
<td>6. Clove (Syzygium aromaticum)</td>
<td>Eugenol</td>
<td>Activation of caspases-3, down regulation of Bcl-2</td>
<td>Apoptosis</td>
<td>49</td>
</tr>
<tr>
<td>7. Cardamom (Elettaria cardamomum)</td>
<td>Limonene</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
<tr>
<td>8. Coriander (Coriandrum sativum)</td>
<td>Linalool</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
<tr>
<td>9. Cinnamon</td>
<td>Polyphenols</td>
<td>G2M cell cycle arrest</td>
<td>Cell cycle arrest</td>
<td>50</td>
</tr>
<tr>
<td>10. Grape seed (Vitis vinifera)</td>
<td>Proanthocyanidins</td>
<td>Release of cytochrome C from mitochondria, Activation of caspases, Induction of Apaf-1, change in Bax/Bcl2 ratio</td>
<td>Apoptosis</td>
<td>51-54</td>
</tr>
<tr>
<td>11. Red pepper (Capsicum annum)</td>
<td>Capsaicin</td>
<td>Mitochondrial membrane potential, caspases-3</td>
<td>Apoptosis</td>
<td>55-57</td>
</tr>
<tr>
<td>12. Black pepper (Piper nigrum)</td>
<td>Piperine</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
</tbody>
</table>

According to an estimate, two-thirds of human cancers could be prevented by making modifications in the diet. In 1997, an international review panel of the World Cancer Research Fund’s American Institute for Cancer Research (AICR) concluded from an exhaustive collection of worldwide research on this topic that “diets high in vegetables and fruits (more than 400 g/day) could prevent at least 20% of all cancer incidence”. Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management. According to a very recent report an epidemiological survey describes the efficacy of relationship between fruit and vegetable consumption and cancer prevention. Available data suggests that it is not presently clear that cancer is among the diseases prevented by fruits and vegetable however consumption of a diet rich in vegetables and fruits has been shown to be one of the best approaches to improve health and reduce chronic disease.

Herbal medicines have a vital role in the prevention and treatment of cancer. Several studies have been conducted on herbs under a multitude of ethno botanical grounds. For example, Hartwell has collected data on about 3000 plants, those of which possess anticancer properties and have been used as potent anticancer drugs. Advances in pharmaceutical research in countries like USA, Germany, France, Japan, and China has been shown to considerably improve quality of herbal medicines used in the treatment of cancer. This review intends to focus on some of the components of daily diet which is inadvertently provided with a number of active constituents that have been shown to work on different target sites for anticancer activity.
The purpose of this communication is to put all the commonly used dietary components of potential and value in anticancer activity so that researchers may further put efforts in designing drugs which may partially explain the effectiveness of selected food factors as chemopreventive agents.

Table 2: Dietary phytochemicals from fruits with site of their action in cell cycle or apoptosis

<table>
<thead>
<tr>
<th>Dietary source</th>
<th>Active component</th>
<th>Site of action in cell cycle or apoptotic pathway</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grape, <em>(Vitis vinifera)</em> wine</td>
<td>Resveratrol</td>
<td>Release of cytochrome C from mitochondria, activation of caspases, decrease in survivin, increase in smac/DIABLO, sensitizes TRAIL induced apoptosis, down regulation of cyclin D1/Cdk4 complex, G2 arrest through Cdk7 and Cdc2 kinases, G1 arrest, S phase arrest</td>
<td>Apoptosis/ Cell cycle arrest</td>
<td>58-69</td>
</tr>
<tr>
<td>2. Citrus fruits <em>(Citrus limon, C. paradis, C retirulatai)</em></td>
<td>Limonene</td>
<td>Inhibits growth of cancer, Inhibit NF-kB activation pathway</td>
<td>Cell cycle arrest /Apoptosis</td>
<td>4</td>
</tr>
<tr>
<td>3. Himalayan may apple <em>(Podophyllum peltatum)</em></td>
<td>Podophyllin</td>
<td>Inhibit mitotic spindle in metaphase</td>
<td>Cell cycle arrest</td>
<td>4</td>
</tr>
<tr>
<td>4. Pineapple <em>(Ananas comosus)</em></td>
<td>Bromelain</td>
<td>Enhance cytotoxic activity of monocytes and macrophages</td>
<td>Cytotoxic</td>
<td>4</td>
</tr>
<tr>
<td>5. Mango <em>(Mangifera indica)</em></td>
<td>Lupeol</td>
<td>Activation of caspases, enhance the expression of Fas receptor and FADD protein</td>
<td>Apoptosis</td>
<td>70</td>
</tr>
<tr>
<td>6. Pomegranate <em>(Panica granatum), Strawberry.</em></td>
<td>Anthocyanin/ Delphinidin</td>
<td>Nuclear condensation, DNA fragmentation, Mitochondrial membrane potential changes, Activation of caspases, Release of cytochrome C from mitochondria</td>
<td>Apoptosis</td>
<td>71-77</td>
</tr>
<tr>
<td>7. Almond <em>(Prunus dulcis)</em></td>
<td>Morin</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>78</td>
</tr>
<tr>
<td>8. Guava <em>(Psidium guajava)</em></td>
<td>Gallic acid</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
<tr>
<td>9. Black Raspberries <em>(Rubus occidentalis)</em></td>
<td>Cynidin glycosides</td>
<td>Antiproliferative activity</td>
<td>Apoptosis</td>
<td>79-83</td>
</tr>
<tr>
<td>10. Mulberry <em>(Morus sps.)</em></td>
<td>Sanggenon- C</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
</tbody>
</table>

**MECHANISM OF ACTION**

Programmed cell death has received phenomenal attention in the past few years. Apoptosis was coined to describe programmed cell death, a process involved in cell death involved in cellular development and aging distinct from necrosis. Apoptotic cells die by design whereas necrotic cells die by accidental and lethal injury24. Apoptosis can be divided into three non-distinct phases: an induction phase, an effector phase, and a degradation phase. The induction phase depends on death inducing signals to stimulate pro-apoptotic signal transduction cascades. These death-inducing signals include reactive oxygen species, Ceramide signaling, over activation of Ca++ pathways, and Bcl-2 family proteins such as Bax and Bad. In phase two, the effector phase, the cell becomes committed to die by the action of a key regulator, which is the mitochondrion. The last phase, a degradation phase, involves both cytoplasmic and nuclear events. In the cytoplasm, a complex cascade of protein cleaving enzymes called caspases is activated. In the nucleus the chromatin condenses, the nuclear envelop breaks down, and the DNA fragments. Finally the cell is fragmented into apoptotic bodies, phosphatidyl serine on the membranes is recognized, and apoptotic bodies are phagocytosed by surrounding cells or macrophages 24-25. Apoptosis also involves characteristics changes within the nucleus. Endonucleases are activated and begin to degrade the nuclear DNA. In some cell types, DNA is degraded into fragments the size of oligonucleosomes, whereas in others larger DNA fragments are produced. So the search for therapeutic agents targeting cellular apoptotic components is regarded as a promising feature in the therapeutic treatment of a wide variety of diseases26. It is now known that mitochondria play a central regulatory role in apoptosis, particularly through cytochrome C pathway. Mitochondria and radical species are intimately involved in the apoptosis. Increased oxidative stress
from ROS and RNS changes the cellular redox potentials, depletes glutathione, and decreases reducing equivalents like NADP and NADPH. These intracellular changes are sufficient to induce the formation of mitochondrial permeability transition pores, leading to the subsequent release of cytochrome c and the activation of the caspases cascade.

Table 3: Dietary phytochemicals from vegetables with site of their action in cell cycle or apoptosis

<table>
<thead>
<tr>
<th>Dietary source</th>
<th>Active component</th>
<th>Site of action in cell cycle or apoptotic pathway</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Cruciferous vegetables</strong></td>
<td>Brassinin, Isothiocyanates, sulphoraphane</td>
<td>Activation of caspases, effect on p53, Apoptosis</td>
<td></td>
<td>84-88</td>
</tr>
<tr>
<td><strong>Brassica oleracea, Brassica campestris</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. <strong>Karela</strong> (Momordica charantia)</td>
<td>Momorcharaside B</td>
<td>Inhibited DNA and RNA synthesis</td>
<td>Cell cycle arrest</td>
<td>4</td>
</tr>
<tr>
<td>3. <strong>Pea seeds</strong> (Pisum sativum)</td>
<td>Metaxylo-hydroquinone</td>
<td>Antimitotic effect, depolymerise DNA</td>
<td>Cell cycle arrest/ Apoptosis</td>
<td>4</td>
</tr>
<tr>
<td>4. <strong>Garlic</strong> (Allium sativum), <strong>Onion</strong> (Allium cepa)</td>
<td>Ajoenin, Allicin, Alliumin, Allixin Organo-sulphur compounds</td>
<td>Activation of caspases, Release of cytochrome C from mitochondria, effect on p53, activation of Bax and down regulation of Bcl-2</td>
<td>Apoptosis</td>
<td>69-92</td>
</tr>
<tr>
<td>5. <strong>Artichoke</strong> (Silybum marianum)</td>
<td>Silymarin, Silibinin</td>
<td>Release of cytochrome C from mitochondria, Activation of caspases, Increase of p53, Mitochondrial membrane potential changes, G1 cell cycle arrest, G2/M arrest</td>
<td>Apoptosis /cell cycle arrest</td>
<td>93-98</td>
</tr>
<tr>
<td>6. <strong>Lettuce</strong></td>
<td>Apigenin</td>
<td>Activation of caspases, G2M arrest</td>
<td>Apoptosis /cell cycle arrest</td>
<td>99-101</td>
</tr>
<tr>
<td>7. <strong>Soyabeen</strong> (Pueraria labata)</td>
<td>Genistein, diadezine</td>
<td>Mitochondrial membrane potential changes, Release of cytochrome C from mitochondria, PARP cleavage, Activation of caspases, down regulation of Bcl-2, G2M cell cycle arrest,</td>
<td>Cell cycle arrest /Apoptosis</td>
<td>102-104</td>
</tr>
<tr>
<td>8. <strong>Tomato</strong> (Lycopersicum esculentum)</td>
<td>Lycopene, Lutein</td>
<td>Release of cytochrome C from mitochondria, activation of caspases, effect on p53, increase in Bax.</td>
<td>Apoptosis</td>
<td>103-108</td>
</tr>
<tr>
<td>9. <strong>Carrots</strong> (Daucus carota)</td>
<td>Beta carotenes, Transasarone</td>
<td>Mitochondrial membrane potential, Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>108-109</td>
</tr>
<tr>
<td>10. <strong>Aloe vera</strong></td>
<td>Acemannan, Emodin</td>
<td>Enhances activity of immune cells against cancer, induces growth inhibition , Inhibit NF-kB activation pathway</td>
<td>Cell cycle arrest</td>
<td>110</td>
</tr>
<tr>
<td>11. <strong>Chickpea</strong> (Cicer arrietinum)</td>
<td>Genistein,</td>
<td>Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>4</td>
</tr>
</tbody>
</table>

Most cells regenerate to replace dead or damaged cells or to grow. For this process the cell doubles its DNA content that forms two sets of chromosomes that line up on spindles within the cell before the cell divides into two equal halves through cell cycle. The cell cycle can be divided into three identifiable components known as G₀G₁, S and G₂M phase. G₀ is the phase where cells are quiescent and not taking part in the cell division. G₁ is the phase where cell is gearing up to move through cell division. S-phase is that part of cell cycle where synthesis of DNA occurs and where DNA staining increases. G₂ and M phases of cycle are where 4n DNA is present, just prior to and during mitosis,
respectively. Several proteins are known to monitor and regulate the timings of the events in the cell cycle. Cyclins and cyclin dependent kinases constitute the major switches in control panel. Out of a number of checkpoints in the cell cycle the G1/S phase transition constitutes an important regulatory point. In G1 phase various complex signals interact to decide a cell’s fate i.e. proliferation, quiescence, differentiation, or apoptosis. This phase is mainly characterized by gene expression and the synthesis of all proteins necessary for DNA replication in a cell thus making this part of cell cycle highly sensitive and responsive to various exogenous stimuli like therapies. So, tumorigenesis is associated with the overexpression of growth promoting cell cycle factors as well as the dysregulation of the cell cycle checkpoints.

From a wider perspective plant based compounds continue to play an essential role in the primary health care of 80% of world’s population. Currently over 60% of anticancer agents in use are derived from natural sources. Three major types of plant derived chemopreventive agents include inhibitors of carcinogen formation, blockers of carcinogen interaction with its target sites and suppressor of tumor production. So the dietary components can regulate apoptosis or cell division by working at various points of pathways mentioned in Table 1-4.

Table 4: Dietary phytochemicals from miscellaneous foods with site of their action in cell cycle or apoptosis

<table>
<thead>
<tr>
<th>Dietary source</th>
<th>Active component</th>
<th>Site of action in cell cycle or apoptotic pathway</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tulasi (Ocimum sanctum)</td>
<td>Orientin, Vicenin</td>
<td>DNA fragmentation, Shrunken cytoplasm</td>
<td>Apoptosis</td>
<td>111-112</td>
</tr>
<tr>
<td>2. Black tea (Camelia sinensis)</td>
<td>Theaflavins</td>
<td>Inhibit matrix metallo proteinases, Inhibit NF-kB activation pathway</td>
<td>Apoptosis</td>
<td>113-116</td>
</tr>
<tr>
<td>3. Green tea (Camelia sinensis)</td>
<td>Epigallocatechin gallate</td>
<td>Activates TRAIL induced apoptosis, activation of Fas, inhibition of Bcl2, Mitochondrial membrane potential</td>
<td>Apoptosis</td>
<td>117-129</td>
</tr>
<tr>
<td>4. Food colouring agent (Garcinia indica)</td>
<td>Garcinol</td>
<td>Release of cytochrome C from mitochondria, Activation of caspases,</td>
<td>Apoptosis</td>
<td>130-131</td>
</tr>
<tr>
<td>6. Olive oil</td>
<td>Secoiridoid Tyrosolder</td>
<td>Inhibit cell proliferation</td>
<td>Cell cycle arrest /Apoptosis</td>
<td>137-140</td>
</tr>
<tr>
<td>7. Honey (Apis mellifera)</td>
<td>Caffeic acid</td>
<td>Activation of caspases and Fas, Induction of p53,</td>
<td>Apoptosis</td>
<td>141</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Although only a few numbers of these phytochemicals have been selected for human phase III trials, yet other available friendly phytochemicals has not been discarded. A significant number of evidences suggest that an increased consumption of fruit and vegetables is a relatively easy and practical strategy to reduce incidence of cancer. Although a number of compounds that constitute food differ physically, chemically, biochemically, physiologically or pharmacologically yet they are subjected to additive, synergistic, cumulative or antagonistic effect that cannot be simply reproduced in a pill. At the same time because the length of chemopreventive treatments require the administration of low doses of chemopreventive agents to avoid toxic effects, daily diet seems to be the appropriate option. This will also provide a better patient compliance as compared to any new agent. So paradoxically or scientifically still most effective chemopreventive regimen is diet that also supports 2500 years old famous saying of Hippocrates “Let food be thy medicine and let medicine be thy food”.

© 2011, JDDT. All Rights Reserved  ISSN: 2250-1177
REFERENCES


29. Crag G, Newmann DJ. Plants as sources of anticaner agents, J Ethnopharmacol, 2005, 100, 72-79.


33. Shi RX, Ong CN, Shen HM. Protein kinase C inhibition and x-linked inhibition of apoptosis protein degradation contribute to the sensitization effect of luteolin on tumor necrosis factor related apoptosis inducing ligand induced apoptosis in cancer cells, Cancer Res, 2005, 65, 7815–7823.


41. Park MJ, Kim EH, Park IC, Lee HC, Woo SH, Lee YJ. Cucurmin inhibits cell cycle progression of immortalized human umbilical vein endothelial (ECV304) cells by up-
45. Shankar S, Srivastava RK, Bax and Bak genes are essential for maximum apoptotic response by curcumin a polyphenolic compound and cancer chemopreventive agent derived from turmeric, Carcinogenesis, 2007, 28(6), 1277-1286.
51. Mantena SK, Baliga MS, Katiyar SK, Grape seed proanthocyanidins induce apoptosis and inhibit metastasis of highly metastatic breast carcinoma cells, Carcinogenesis, 2006, 27(8), 1682-1691.
92. Xia L, Ng TB, Isolation of alliumin a novel protein with antimicrobial and antiproliferative activities from multiple cloved garlic bulbs, Peptides, 2005, 26(2), 177-183.


110. Kumar A, Dhawan S, Aggarwal BB. Emodin (3-methyl-1, 6, 8-trihydroxyanthraquinone) inhibits TNF- induced NF-kappaB activation, 1kappaB degradation, and expression of cell surface adhesion proteins in human vascular endothelial cells, Oncogene, 1998, 17(7), 913-918.


134. Lou YR, Lu YP, Xie JG, Huang MT, Conney AH. Effects of oral administration tea and decaffeinated tea and caffeine on the formation and growth of tumors in high-risk SKH-1 mice.
135. Lu YP, Lou YR, Li XH, Xie JG, Brash D, Huang MT, Conney AH, Stimulatory effects of oral administration tea and decaffeinated tea and caffeine on UVB light induced increase in epidermal wild type p53, p21 (WAF1/CIP1) and apoptotic sunburn cells in SKH-1 mice, Cancer Res, 2000, 60, 4785-4791.