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REVIEW ARTICLE

DIETARY PHYTOCHEMICALS IN CELL CYCLE ARREST AND APOPTOSIS - AN INSIGHT

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ABSTRACT

Recently chemoprevention by the use of naturally occurring dietary substances is considered as a practical approach to reduce the ever-increasing incidence of cancer. While a number of natural foods, fruit and vegetables are recommended for prevention of cancer and other diseases, their active ingredients and their mechanism of action are not well understood. A number of dietary phytochemicals are under phase III clinical trial due to their potent therapeutic effect against cancer. Moreover most of the drugs being used in chemotherapy have been derived from plant products. With an advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, world is in a much better position to identify various anticancer herbs and develop therapeutic agents for cancer. However lack of success with targeted mono-therapy and multi-drug resistance to existing chemotherapeutic agents has forced scientists to practice either combination therapy or use a number of agents working at different sites to get some synergistic effect. Since most of the cells do not show resistance to natural plant products; hence the use of natural plant products can be an alternative modality of treatment for multidrug resistant tumors. In this review article an attempt has been made to put some known phytochemicals of dietary origin that act at various stages of cell cycle and/or apoptotic pathway at a single platform, so that by understanding the synergistic, additive or antagonistic interactions of various constituents of anticancer herbs, the herbal regimens can be designed to fight cancer.

Keywords: Apoptosis, cell cycle arrest, vegetables, spices, fruits.

INTRODUCTION

Cancer may be defined as uncontrolled tissue growth that results from an imbalance between cell division and apoptosis[1]. 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[2]. Various studies indicate that phytochemicals can modulate the complex multistage process of carcinogenesis[3]. 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[4-5]. 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[6-7]. 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[8]. 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[9-10].

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Table 1: Dietary phytochemicals from spices with site of their action in cell cycle or apoptosis

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

According to an estimate, two-thirds of human cancers could be prevented by making modifications in the diet[11]. 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"[12]. 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[13].

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[14-22] has collected data on about 3000 plants, those of which possess anticancer properties and have been used as potent anticancer drugs[23]. 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.

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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

Dietary source	Active component	Site of action in cell cycle or apoptotic pathway	Result	Ref
1. **Grape,** (*Vitis vinifera*) wine	Resveratrol	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	Apoptosis/ Cell cycle arrest	58-69
2. **Citrus fruits** (*Citrus limon, C. paradis, C retirulatai*)	Limonene	Inhibits growth of cancer, Inhibit NF-kB activation pathway	Cell cycle arrest /Apoptosis	4
3. **Himalayan may apple** (*Podophylum peltatum)*	Podophyllin	Inhibit mitotic spindle in metaphase	Cell cycle arrest	4
4.**Pineapple** (*Ananas comosus*)	Bromelain	Enhance cytotoxic activity of monocytes and macrophages	Cytotoxic	4
5. **Mango** (*Mangifera indica*)	lupeol	Activation of caspases, enhance the expression of Fas receptor and FADD protein	Apoptosis	70
6. **Pomegranate** (*Punica granatum*), Strawberry.	Anthocyanin/ Delphinidin	Nuclear condensation, DNA fragmentation, Mitochondrial membrane potential changes, Activation of caspases, Release of cytochrome C from mitochondria	Apoptosis	71-77
7. **Almond** (*Prunus dulcis*)	Morin	Inhibit NF-kB activation pathway	Apoptosis	78
8.**Guava** (*Psidium guajava*)	Gallic acid	Inhibit NF-kB activation pathway	Apoptosis	4
9.**Black Raspberries** (*Rubus occidentalis*)	Cynidin glycosides	Antiproliferative activity	Apoptosis	79-83
10. **Mulberry** *Morus sps.*	Sanggenon- C	Inhibit NF-kB activation pathway	Apoptosis	4

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 injury[24]. 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^{+2} 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 diseases[26]. 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

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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

Dietary source	Active component	Site of action in cell cycle or apoptotic pathway	Result	Ref
1. **Cruciferous vegetables** *Brrasica oleracea*, *Brassica campestris*	Brassinin, Isothicyanates, sulphoraphane	Activation of caspases, effect on p53,	Apoptosis	84-88
2.**Karela** (*Momordica charantia*)	Momorcharaside B	Inhibited DNA and RNA synthesis	Cell cycle arrest	4
3.**Pea seeds** (*Pisum sativum*)	Metaxylo-hydroquinone	Antimitotic effect, depolymerise DNA	Cell cycle arrest/ Apoptosis	4
4.**Garlic** (*Allium sativum*), **Onion** (*Allium cepa*)	Ajoein, Allicin, Alliumin, Allixin Organo-sulphur compounds	Activation of caspases, Release of cytochrome C from mitochondria, effect on p53, activation of Bax and down regulation of Bcl-2	Apoptosis	89-92
5., **Artichoke** (*Silybum marianum*)	Silymarin, Silibinin	Release of cytochrome C from mitochondria, Activation of caspases, Increase of p53, Mitochondrial membrane potential changes, G1 cell cycle arrest, G2/M arrest	Apoptosis /cell cycle arrest	93-98
6. **Lettuce**	Apigenin	Activation of caspases, G2M arrest	Apoptosis /cell cycle arrest	99-101
7. **Soyabean** (*Pueraria labata*)	Genistein, diadezine	Mitochondrial membrane potential changes, Release of cytochrome C from mitochondria, PARP cleavage, Activation of caspases, down regulation of Bcl-2, G2M cell cycle arrest,	Cell cycle arrest /Apoptosis	102-104
8. **Tomato** (*Lycopersicum esculentum*)	Lycopene Lutein	Release of cytochrome C from mitochondria, activation of caspases, effect on p53, increase in Bax.	Apoptosis	103-108
9.**Carrots** (*Daucus carota*)	Beta carotenes, Transasarone	Mitochondrial membrane potential, Inhibit NF-kB activation pathway	Apoptosis	108-109
10.***Aloe vera***	Acemannan, Emodin	Enhances activity of immune cells against cancer, induces growth inhibition , Inhibit NF-kB activation pathway	Cell cycle arrest Apoptosis	110
11.**Chickpea** (*Cicer arietinum*)	Genistein,	Inhibit NF-kB activation pathway	Apoptosis	4

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 G_0G_1, S and G_2M phase. G_0 is the phase where cells are quiescent and not taking part in the cell division. G_1 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. G_2 and M phases of cycle are where 4n DNA is present, just prior to and during mitosis,

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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 G_1/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 check points[27].

From a wider perspective plant based compounds continue to play an essential role in the primary health care of 80% of world's population[28]. Currently over 60% of anticancer agents in use are derived from natural sources[29]. Three major types of plant derived chemopreventive agents include inhibitors of carcinogen formation, blockers of carcinogen interaction with it's 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

Dietary source	Active component	Site of action in cell cycle or apoptotic pathway	Result	Ref
1.**Tulasi** (*Ocimum sanctum*)	Orientin ,Vicenin	DNA fragmentation, Shrunken cytoplasm,	Apoptosis	111-112
2.**Black tea** (*Camelia sinensis*)	Theaflavins	Inhibit matrix metallo proteinases, Inhibit NF-kB activation pathway	Apoptosis	113-116
3.**Green tea** (*Camelia sinensis*)	Epigallocatechin gallate	Activates TRAIL induced apoptosis, activation of Fas, inhibition of Bcl2, Mitochondrial membrane potential	Apoptosis	117-129
4. **Food colouring agent** (*Garcinia indica*)	Garcinol	Release of cytochrome C from mitochondria, Activation of caspases,	Apoptosis	130-131
5. **Coffee** (*Theobroma cacao*)	Caffeine	Changes in p53, Inhibit NF-kB activation pathway	Apoptosis	132-136
6.**Olive oil**	Secoiridoid Tyrosol der.	Inhibit cell proliferation	Cell cycle arrest /Apoptosis	137-140
7. **Honey** (*Apis mellifera*)	Caffeic acid	Activation of caspases and Fas, Induction of p53,	Apoptosis	141

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*".

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