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Nutrigenomics and Complementary Alternative Medicine

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ABSTRACT

Nutrigenomics applied high-throughput 'omics' techniques in nutrition research to enable investigation into interactions between nutrients with the genome at a molecular level. One of the emerging areas of research in nutri-genomics includes Complementary Alternative Medicine (CAM), which can be used to treat various diseases including type2 diabetes, cancer and obesity. Research in CAM includes identification of the active compounds present in various herbal and dietary products, and evaluating these compounds for their effects on human health. Only few studies have explored the effects of these compounds when used in synergistic, additive or antagonistic combinations. One of the striking features of CAM is the low toxicity of natural compounds used as supplements. However most of the active ingredients are not "hydrophyllic" but are "lypophyllic", resulting in limited absorption from GI tract, when ingested orally. This has led to limited bioavailability and it needs application of innovative techniques to overcome this problem. We have evaluated combination therapy and its effects as a solution to this problem. This report will discuss general concepts in nutrigenomics related to CAM, effects of combination therapies and possible mechanisms of action that come in to play with combination therapies, with particular focus on phytocompounds used as anti-cancer agents.

Key words: *Nutrigenomics, Phytochemicals, CAM, Cancer.*

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Nutrigenomics studies the effects of food and its constituents at molecular level so as to gain insight into the mechanisms of interaction between nutrients and other dietary bioactives with the genome. Nutrigenomics aims to understand the body's response to different types of diets and food through various 'omics' techniques including transcriptomics, proteomics and metabolomics, although the most common technique used is transcriptomic analysis (1). Tools used to measure the transcriptome are well developed including gene expression microarray profiling, single nucleotide polymorphisms (SNPs) and genotyping. In contrast, tools to measure the proteome and metabolome are less developed including techniques such as gel electrophoresis, mass spectophotometry, nuclear magnetic resonance imaging, and chromatography (2); This technique has provided a considerable amount of data on several factors such as novel function of food factors, the unknown mechanism of the effect of nutrients, and even safety issues of foods (3). Nutrigenomics is emerging as a new competent field in research that integrates genetics and dietary recommendations to study protein expression and metabolite production.

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Nutrigenomics can help improve our understanding of how nutrition influences metabolic pathways and homeostatic control, which can be used to discover naturally occurring chemical agents in food to help prevent the onset of diseases such as obesity, type-2 diabetes and cancer. Nutrigernomics, also involves determining certain genes and markers during the early phase of diet-related diseases. Once such a marker or a gene is identified and measured in an individual, the degree to which they can be susceptible to the onset of that particular disease can be quantified and a personalized dietary recommendation can be established for the individual.

Nutrigenomics aims to elucidate the effect of bioactive food compounds on health that can lead to the development of functional foods that keep people healthy according to their individual needs. One area of particular research interest in nutrigenomics can include Complementary Alternative Medicine (CAM). Recently, research in CAM includes identification of the active compounds present in various herbal and dietary products, and evaluating their anti-cancer properties. Polyphenols from green tea, grape seed/skin, anthocyanin and pigments from many flowers, algae, fruits and vegetables are some of the compounds that have been tested. A common property of many of these compounds is their anti-oxidant/free radical scavenging ability. However, some compounds preferentially induce high free radical formation selectively in cance cells, to cause growth inhibition and death of cancer cells without affecting normal cells.

Extensive studies on CAM have focused on effects of individual compounds derived from herbs/plants, using concentrations that are typically higher than their '*bioavailable*' concentration (the serum levels achieved by oral intake of extracts, as practiced in CAM). However, only few studies explored the effects of these compounds when used in synergistic, additive or antagonistic *combinations;* and each of the individual chemicals used in a combination could target multiple signaling pathways in the cancer cell. One of the striking features of oral administration of CAM was the low toxicity and showed effects on various types of cancers. The synergistic and / or additive mechanisms that come into play during combination therapies result in reducing the "effective dose" to 'bioavailable' levels. Thus while individual compounds are not effective by themselves, combination becomes effective.

In collaboration with Prof. Madhwa Raj's group (the Louisiana State University, New Orleans, Louisiana), and based on the idea of Synergism theory we performed extensive studies where we tested the effects of the combination of 2 compounds, Indole-3-carbinol (I3C) and Resveratrol, each used at '*bioavailable*' levels, on SK-OV-3 ovarian cancer cells (3). SK-OV-3 cells were treated with various doses of I3C, RE or I3C+RE and proliferation assay was used to examine cell growth. The study revealed that I3C+RE synergized to induce a higher number of cell death than each of these compounds used individually (3).

Analysis of apoptosis-associated genes revealed inhibition of Retinoblastoma protein (Rb) and Survivin (SVV) gene expression levels; this was accompanied by elevation of p21, a p53-downstream transcriptional target gene (3). Cell cycle was inhibited at both G1 and G2/M by individual treatments, and accentuated by a combination. ELISA revealed that while, CA125 was inhibited by either I3C or RE treatments, basal nitric oxide production was inhibited by I3C and I3C + RE but not RE alone (3), in addition microarray analysis was performed and we have identified several unique genes that are overexpressed as a result of combination therapy (manuscript in preparation).

Ongoing studies in our laboratories are testing the combination of dozens of other compounds in several cancers In addition; selected phytochemical combinations will be tested to validate their anti-cancer effects *in vivo* using xenograft model of breast cancer (4). Future work will include the establishment of a powerful combination of compounds (each

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individual compound is used at its bioavailable concentration in a synergistic/additive manner) that can potentially induce a maximal cell growth inhibition/cell death *in vitro and in vivo*. Furthermore, in addition to understanding the underlying molecular mechanisms of the combination, these studies will lead to the identification of potential biomarkers or candidate gene targets to guide the design of anti-cancer therapeutic strategies, follow progress of therapies as well as in early diagnosis.

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Table 1: Bioactive compounds and their mechanisms of action

Source	Active Ingredient	Literature
Broccoli	-Indole-3-Carbinol (I3C)	• I3C induces apoptosis, inhibits cell growth and has antiangiogenic activities • I3C induces G1 cell cycle arrest and inactivates Akt • I3C inhibits activation of transcription factors including nuclear factor-kappa B, SP1, estrogen receptor, androgen receptor and nuclear factor-E2-related factor 2 (Nrf2)
Grape skin and seeds	Resveratrol (RE)	• RE interferes with AKT, enhances p53, and induces apoptosis • RE exhibits Cox-1 inhibitory activity, and causes G1 arrest • RE induces apoptosis by TRAIL sensitization and down regulates survivin expression • RE possesses vasorelaxing, anti-inflammatory, anti-lipidemic, anti-estrogenic, antioxidant, anti-fungal and antibacterial properities
Tea	Epigallo-Catechin Gallate (ECG)	• ECG inhibits Hsp90 function, hypoxia and serum induced HIF-1 alpha protein accumulation, and VEGF expression • ECG enhanced responses induced by curcumin on breast cancer cells
Spirulina	Phycocyanin (PC)	• P inhibits cell proliferation and apoptosis in different cancer cell lines • P inhibits MDR1 through reactive oxygen species and cyclooxygenase-2 mediated pathways
Turmeric roots	Curcumin (CUR)	• CUR binds to a number of proteins and inhibits the activity of various kinases, induces apoptosis, and has anti-proliferative effect • CUR regulates expression of inflammatory enzymes, cytokines, adhesion molecules and cell survival proteins • CUR down regulates cyclin D1, cyclin E, MDM2 and up regulates tumor suppressors p21, p27 and p53 • CUR exhibits antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal and anticancer activities
Stamens of Saffron	Crocin (Cr)	• Saffron causes apoptosis inhibits DMBA-induced skin carcinogenesis • Saffron and its main constituents, such as crocusatin H, crocin-1 and crocin-3 have anticancer and anti-tumour activities
Plant food	Quercetin (Querc)	• Quercetin downregulates mutant p53 in BC cells leading to G1 phase arrest of cell cycle, inhibits tyrosine kinase, both *in- vitro* and *in- vivo* • A number of these actions have also been demonstrated in ovarian cancer cells *via* inhibition of heat shock protein 70 • It sensitized cisplatin in inhibiting proliferation of ovarian cancer cells • It increased TGF-β and inhibited OVCAR-433 ovarian cancer cell proliferation, as administration of a monoclonal antibody to TGF-β reversed these effects

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