LifeOne Formula is a United States patented “Patent Number US 6,544,564 B1, and Patent Number 6,767,563 B2” mixture of several naturally occurring plant compounds carried in a liposomal base. It was developed to be a healthy dietary supplement for use in general support of the immune system.

LifeOne contains the following natural plant and mushroom phytochemicals:

Description of LifeOne ingredients

Chrysin
Chrysin is a flavonoid compound from the Passionflower plant. The anticancer effects are:
Acts as an antioxidant
Inhibits 6 of 7 procancer events
Enhances Tumor Necrosis Factor (TNF) cytotoxicity to cancer cells
Inhibits abnormal hormone action, binds estrogen receptors, alters steroid hormone metabolism, normalizes testosterone and other androgen levels
Inhibits HIV expression and invasion in cell cultures, inhibits HIV-1 transactivation, exhibits anti-HIV activity

Coriolus versicolor
Coriolus versicolor is a Chinese herbal mushroom with anticancer action with the following anti-cancer effects:
Potently stimulates the immune system
Increases the cytotoxicity of natural killer cells against cancer cells
Inhibits the invasion of cancer cells (metastasis and local proliferation)
Inhibits 4 of the 7 procancer events
Increases survival rate in post chemotherapy cancer patients
Provides an anti-viral agent for HIV therapy

3,3’Diindolymethane (DIM)
DIM is a phytochemical from cruciferous vegetables (broccoli, Brussels sprouts, and cabbage) with the following anticancer effects:
Provides a strong anti-estrogen effect on cancer cells
Inhibits adhesion, motility, and invasiveness of cancer cells
Inhibits 5 of the 7 procancer events

Resveratrol
Resveratrol is found in wines and grapes. It is a stilbene which is a nonflavonoid phenolic compound. Resveratrol is thought to be one of the compounds responsible for the reduced risk of cardiovascular disease in red wine. The anticancer effects are:
Acts as an antioxidant
Inhibits platelet aggregation and reduces inflammation
Inhibits 6 of the 7 procancer events
Inhibits insulin resistance
Inhibits abnormal estrogen action

Produces anti-HIV activity: inhibits viral replication and proliferation

Tumeric Extract (Curcumin)
The most effective anticancer compound in tumeric is the yellow pigmented curcumin with the following anti-cancer effects:
Acts as a potent antioxidant
Has a strong anti-inflammatory effect
Inhibits insulin resistance
Inhibits cancer cell proliferation in vitro
Inhibits metastasis in vivo
Inhibits 5 of the 7 procancer events
Curcumin inhibits Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat". Tat is a protein secreted by the HIV1- infected cells that may have additional action in the pathogenesis of AIDS.

Green Tea Extract (GTE)
GTE is another flavonoid. The major compound in GTE is epigallocatechin gallate (EGCG). The primary anticancer agent in GTE is EGCG which provides the following anticancer effects:
Acts as an antioxidant
Provides in-vitro and in-vivo anticancer activity
Inhibits 6 of the 7 procancer events
Inhibits activities of HIV-1 reverse transcriptase

L-Selenium Methionine
The best utilized form of Selenium is the organic form, L-Selenium Methionine:
Acts as an antioxidant
Inhibits 6 of the 7 procancer events
In-vitro and in-vivo studies shows anticancer effects
Provides strong immune stimulation effect
Helps restore the depleted plasma levels of Selenium that are very low in cancer and HIV patients, a critical property of this formula

Liposomal Delivery System

The liposomal delivery system provides a unique mechanism of delivery of these phytochemicals to the body and allows for longer action of the plant products.

Listed below are a few abstracts on the properties of each of the individual plant products found in LifeOne Formula.

We encourage interested readers to search the web for independent third party studies on LifeOne Formula’s effects on the immune system.

Chrysin
Colorius Versicolor
3,3'Diindolymethane (DIM)
Resveratrol
Tumeric Extract
Green Tea Extract
Quercitin Dihydrate
L-Selinium Methionine
Liposome Delivery system
Patent Number US 6,544,564 B1

Chrysin

1: Steroids 1997 Apr;62(4):365-72
The estrogenic and antiestrogenic activities of phytochemicals with the human estrogen receptor expressed in yeast.
Collins BM, McLachlan JA, Arnold SF.
Tulane-Xavier Center for Bioenvironmental Research, Tulane University Medical Center, New Orleans, LA 70112, USA.

We have used the expression of the human estrogen receptor (hER) and two estrogen response elements linked to the lacZ gene in yeast (YES) to study the estrogenic and antiestrogenic activities of various phytochemicals. Coumestrol, alpha-zearalenol, or genistein could produce beta-galactosidase activity comparable to estradiol, but these required concentrations 100 to 1000-fold greater than estradiol. These compounds did not possess antiestrogenic activity. Narigenin, kaempferide, phloretin, biochanin A, flavone, or chrysin only partially induced beta-galactosidase activity in the YES at any concentration tested. When narigenin, kaempferide, or phloretin was given concurrently with estradiol, the estradiol-dependent beta-galactosidase activity was not inhibited by more than 50%. However, biochanin A, flavone, or chrysin could inhibit the activity of estradiol in a dose-response manner with IC50 values of 500 nM, 2 microM, and 10 microM, respectively. Combinations of biochanin A, chrysin, and flavone decreased estradiol-dependent beta-galactosidase activity in an additive fashion. Similar to the antiestrogens tamoxifen or ICI 182, 780, the antiestrogenic activity of these compounds with the exception of chrystin involved the disruption of hER dimerization, as demonstrated in the yeast two-hybrid system. Biochanin A, chrysin, or flavone were less effective in inhibiting the activity of an estrogenic polychlorinated biphenyl than they were inhibiting the activity of estradiol. Interestingly, this latter group of antiestrogenic phytocompounds did not inhibit the estrogenic activity of such phytochemicals as coumestrol or genistein. These results suggest that the antiestrogenic activity of biochanin A and flavone occurs by a mechanism similar to tamoxifen or ICI 182,780. Moreover, it seems that phytochemicals functioning as antiestrogens do not inhibit the activity of all estrogenic chemicals to the same extent. This suggests that conformational changes induced by different estrogens bound to the hER may regulate the antiestrogenic activity of a compound.

PMID: 9090797 [PubMed - indexed for MEDLINE]

1: Arch Pharm Res 1999 Jun;22(3):309-12
Inhibition of aromatase activity by flavonoids.
Jeong HJ, Shin YG, Kim IH, Pezzuto JM.
Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 60612, USA. hyehjean@nmdhst.cc.nih.gov

In searching for potent cancer chemopreventive agents from synthetic or natural products, 28 randomly selected flavonoids were screened for inhibitory effects against partially purified aromatase prepared from human placenta. Over 50% of the flavonoids significantly inhibited aromatase activity, with greatest activity being demonstrated with apigenin (IC50: 0.9 microg/mL), chrysin (IC50: 1.1 microg/mL), and hesperetin (IC50: 1.0 microg/mL).
PMID: 10403137 [PubMed - indexed for MEDLINE]

1: J Nat Prod 1997 Aug;60(8):775-8
Flavonoids as inhibitors or enhancers of the cytotoxicity of tumor necrosis factor-alpha in L-929 tumor cells.
Habtemariam S.
Department of Physiology and Pharmacology, University of Strathclyde, Glasgow, U.K. s.habtemariam@strath.ac.uk

The effects of some selected flavonoids on tumor necrosis factor-alpha (TNF)-induced cytotoxicity in murine fibroblast L-929 cells were studied. All of the flavanones tested as well as a flavan, epicatechin, protected L-929 cells from TNF-induced cell death of the flavanones tested, hesperetin, isosakuranetin, and pinocembrin failed to modify TNF cytotoxicity, but the 3',4'-dihydroxyflavanones, eriodictyol and taxifolin, showed a protective effect. Eriodictyol was the most potent protective agent of all the flavonoids tested, while a 4'-hydroxyflavanone, naringenin, rather showed enhancement of TNF cytotoxicity. Of the flavones tested, chrysin and apigenin markedly augmented the cytotoxicity of TNF, while luteolin showed a weak protective effect. The magnitude of protection and potentiation by these flavonoids were concentration-dependent and these effects were not altered when the flavonoids were added as much as 2 h after TNF treatment.
PMID: 9287415 [PubMed - indexed for MEDLINE]

1: J Steroid Biochem Mol Biol 1993 Sep;46(3):381-8
Flavonoid inhibition of aromatase enzyme activity in human preadipocytes.
Campbell DR, Kurzer MS.
Department of Food Science and Nutrition, University of Minnesota, St. Paul 55108, USA.

Eleven flavonoid compounds were compared with aminoglutethimide (AG), a pharmaceutical aromatase inhibitor, for their abilities to inhibit aromatase enzyme activity in a human preadipocyte cell culture system. Flavonoids exerting no effect on aromatase activity were catechin, daidzein, equol, genistein, beta-naphthoflavone (BNF), quercetin and rutin. The synthetic flavonoid, alpha-naphthoflavone (ANF), was the most potent aromatase inhibitor, with an I50 value of 0.5 microM. Three naturally-occurring flavonoids, chrysin, flavone, and genistein 4'-methyl ether (Biochanin A) showed I50 values of 4.6, 68, and 113 microM, respectively, while AG showed an I50 value of 7.4 microM. Kinetic analyses showed that both AG and the flavonoids acted as competitive inhibitors of aromatase. The Ki values, indicating the effectiveness of inhibition, were 0.2, 2.4, 2.4, 22, and 49 microM, for ANF, AG, chrysin, flavone, and Biochanin A, respectively. Chrysin, the most potent of the naturally-occurring flavonoids, was similar in potency and effectiveness to AG, a pharmaceutical aromatase inhibitor used clinically in cases of estrogen-dependent carcinoma. These data suggest that flavonoid inhibition of peripheral aromatase activity may contribute to the observed cancer-preventive hormonal effects of plant-based diets.
PMID: 9831487 [PubMed - indexed for MEDLINE]

Colorius Versicolor

1: Curr Med Chem 2000 Jul;7(7):715-29
Immunomodulation and anti-cancer activity of polysaccharide-protein complexes.
Ooi VE, Liu F.
Department of Biology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong.

In the last three decades, numerous polysaccharides and polysaccharide-protein complexes have been isolated from mushrooms and used as a source of therapeutic agents. The most promising biopharmacological activities of these biopolymers are their immunomodulation and anti-cancer effects. They are mainly present as glucans with different types of glycosidic linkages such as (1-->3), (1-->6)-beta-glucans and (1-->3)-alpha-glucans, and as true herteroglycans, while others mostly bind to protein residues as polysaccharide-protein complexes. Three antitumor mushroom polysaccharides, i.e. lentinan, schizophyllan and protein-bound polysaccharide (PSK, Krestin), isolated respectively, from Lentinus edodes, Schizophyllum commune and Coriolus versicolor, have become large market items in Japan. Lentinan and schizophyllan are pure beta-glucans, whereas PSK is a protein-bound beta-glucan. A polysaccharide peptide (PSP), isolated from a strain of Coriolus versicolor in China, has also been widely used as an anti-cancer and immunomodulatory agent. Although the mechansim of their antitumor action is still not completely clear, these polysaccharides and polysaccharide-protein complexes are suggested to enhance cell-mediated immune responses in vivo and in vitro and act as biological response modifiers. Potentiation of the host defense system may result in the activation of many kinds of immune cells that are vitally important for the maintenance of homeostasis. Polysaccharides or polysaccharide-protein complexes are considered as multi-cytokine inducers that are able to induce gene expression of vaious

immunomodulatory cytokines and cytokine receptors. Some interesting studies focus on investigation of the relationship between their structure and antitumor activity, elucidation of their antitumor mechanism at the molecular level, and improvement of their various biological activities by chemical modifications.
PMID: 10702635 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother 2001 Jun;50(4):191-8
Protein-bound polysaccharide K and interleukin-2 regulate different nuclear transcription factors in the NKL human natural killer cell line.
Garcia-Lora A, Pedrinaci S, Garrido F.
Servicio de Analisis Clinicos e Inmunologia, Hospital Universitario Virgen de las Nieves, Universidad de Granada, Spain.

The activation of natural killer cells and induction of cytotoxicity are complex processes whose molecular mechanisms have not been clearly elucidated. Stimulation of the NKL human NK cell line with interleukin-2 (IL-2) or protein-bound polysaccharide K (PSK) leads to sustained growth and cytolytic activity in comparison to unstimulated NKL cells. However, it is not known whether both agents give rise to the same or different intracellular signals. To determine the molecular basis for the action of IL-2 and PSK, the binding activity of AP-1, CRE, NF-kappaB, PU.1, SP-1, NFAT, STAT1, STAT5/6, GAS/ISRE and IRF-1 transcription factors was compared in IL-2- and PSK-stimulated NKL cells. Here we report that PSK enhanced AP-1 and CRE binding activities, whereas IL-2 increased AP-1 and SP-1 and modified GAS/ISRE, IRF-1 and STAT5. Our results indicate that IL-2 and PSK regulate different nuclear transcription factors in NKL cells, and that the signal transduction pathway used by these inducers is different.
PMID: 11459171 [PubMed - indexed for MEDLINE]
1: Altern Med Rev 2000 Feb;5(1):4-27
The use of mushroom glucans and proteoglycans in cancer treatment.
Kidd PM.

Immunoceuticals can be considered as substances having immunotherapeutic efficacy when taken orally. More than 50 mushroom species have yielded potential immunoceuticals that exhibit anticancer activity in vitro or in animal models and of these, six have been investigated in human cancers. All are non-toxic and very well tolerated. Lentinan and schizophyllan have little oral activity. Active Hexose Correlated Compound (AHCC) is poorly defined but has shown early clinical promise. Maitake D-Fraction has limited proof of clinical efficacy to date, but controlled research is underway. Two proteoglycans from Coriolus versicolor - PSK (Polysaccharide-K) and PSP (Polysaccharide-Peptide - have demonstrated the most promise. In Japanese trials since 1970, PSK significantly extended survival at five years or beyond in cancers of the stomach, colon-rectum, esophagus, nasopharynx, and lung (non-small cell types), and in a HLA B40-positive breast cancer subset. PSP was subjected to Phase II and Phase III trials in China. In double-blind trials, PSP significantly extended five-year survival in esophageal cancer. PSP significantly improved quality of life, provided substantial pain relief, and enhanced immune status in 70-97 percent of patients with cancers of the stomach, esophagus, lung, ovary, and cervix. PSK and PSP boosted immune cell

production, ameliorated chemotherapy symptoms, and enhanced tumor infiltration by dendritic and cytotoxic T-cells. Their extremely high tolerability, proven benefits to survival and quality of life, and compatibility with chemotherapy and radiation therapy makes them well suited for cancer management regimens.
PMID: 10696116 [PubMed - indexed for MEDLINE]

1: Psychoneuroendocrinology 1999 Oct;24(7):713-26
Time-dependent effects of stressor application on metastasis of tumor cells in the lung and its regulation by an immunomodulator in mice.
Ishihara Y, Matsunaga K, Iijima H, Fujii T, Oguchi Y, Kagawa J.
Department of Hygiene and Public Health (I), School of Medicine, Tokyo Women's Medical University, Japan.

The effects of the timing of stressor application on transplanted tumor cells and its possible regulation by an immunomodulator was investigated. Male C57 BL/6N mice were subjected to rotational stressor for 7 days relative to tumor cell inoculation: stressor after inoculation of Lewis lung cancer cells, stressor during inoculation and stressor before inoculation. Stressor application and tumor cell inoculation induced transient decreases in body weight, particularly in mice stressed after inoculation. The mice exposed to the stressor during inoculation or before inoculation showed significant increases in the number of metastatic foci relative to control mice. Early administration of an immunomodulator, PSK, significantly attenuated the increase of metastatic foci in stressed mice. The weights of thymus gland and spleen at 14 days after inoculation were similar in the three stressor groups and the control group. Application of the stressor reduced NK cell activity of the normal mice as well as tumor bearing mice. The lowest pre-inoculation NK cell activity was observed in mice stressed for 7 days beginning on the day of inoculation. The NK cell activity decreased in the tumor bearing mice which were stressed at the time of tumor inoculation. Decreased NK cell activity was reversed at day 14 after tumor inoculation. The mice exposed to the stressor after inoculation showed lowest level of NK cell activity relative to mice exposed to the stressor before or during inoculation. The treatment of mice with PSK reduced these changes significantly. The present results suggest that the rotational stress reduces splenic NK cell activity, which may influence the magnitude of tumor metastasis, depending on the time of tumor cell injection. Further, administration of an immunomodulator may counteract the reduction of the NK cell activity.
PMID: 10451907 [PubMed - indexed for MEDLINE]

3,3'Diindolymethane (DIM)

1: Carcinogenesis 1998 Sep;19(9):1631-9
Aryl hydrocarbon receptor-mediated antiestrogenic and antitumorigenic activity of diindolylmethane.
Chen I, McDougal A, Wang F, Safe S.
Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station 77843-4466, USA.

Phytochemicals such as indole-3-carbinol (I3C) and sulforaphane are components of cruciferous vegetables which exhibit antitumorigenic activity associated with altered carcinogen metabolism and detoxification. Diindolylmethane (DIM) is a major acid-catalyzed metabolite of I3C formed in the gut that binds to the aryl hydrocarbon receptor (AhR) and treatment of MCF-7 human breast cancer cells with 10-50 microM DIM resulted in rapid formation of the nuclear AhR complex and induction of CYP1A1 gene expression was observed at concentrations >50 microM. Previous studies have demonstrated that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a high affinity AhR ligand, inhibits 17beta-estradiol (E2)-induced responses in MCF-7 cells and growth of E2-dependent 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats. Results of this study show that like TCDD, DIM inhibits E2-induced proliferation of MCF-7 cells, reporter gene activity in cells transiently transfected with an E2-responsive plasmid (containing a frog vitellogenin A2 gene promoter insert) and down-regulates the nuclear estrogen receptor. Moreover, DIM (5 mg/kg every other day) also inhibits DMBA-induced mammary tumor growth in Sprague-Dawley rats and this was not accompanied by induction of hepatic CYP1A1-dependent activity. Thus, DIM represents a new class of relatively non-toxic AhR-based antiestrogens that inhibit E2-dependent tumor growth in rodents and current studies are focused on development of analogs for clinical treatment of breast cancer.
PMID: 9771935 [PubMed - indexed for MEDLINE]

1: Anticancer Drugs 1998 Feb;9(2):141-8
Selective cytostatic and cytotoxic effects of glucosinolates hydrolysis products on human colon cancer cells in vitro.
Gamet-Payrastre L, Lumeau S, Gasc N, Cassar G, Rollin P, Tulliez J.
INRA, Laboratoire des Xenobiotiques, Toulouse, France.

Glucosinolates hydrolysis products are attracting increasing attention since many studies have suggested that they may be involved in the anticarcinogenic property of cruciferous vegetables. In this study, we show that diindolylmethane (DIM) and sulforaphane, produced during the hydrolysis of glucobrassicin and glucoraphanin, respectively, exert a dose-dependent cytotoxicity on human colon adenocarcinoma HT29 cells. Moreover, these products are able to inhibit quiescent cells to re-enter the cell cycle. Interestingly, our results clearly show that low doses of DIM and sulforaphane, although very effective on undifferentiated intestinal HT29 cells, do not affect the viability of the differentiated CaCo2 cells. The reversibility of their effects has also been tested and is discussed.
PMID: 9510500 [PubMed - indexed for MEDLINE]

1: Biochem Biophys Res Commun 1996 Nov 1;228(1):153-8
3,3'-Diindolylmethane induces apoptosis in human cancer cells.
Ge X, Yannai S, Rennert G, Gruener N, Fares FA.

Department of Food Engineering and Biotechnology, Technion-Israel Institute of Technology, Haifa, Israel.

3,3'-Diindolylmethane is a dimer of indole-3-carbinol formed both in vivo and in vitro. In this study, human cancer cells MCF-7 (with wild-type p53), T47-D (mutant p53), and Saos-2 (deficient in p53 gene), were used to examine the anticancer activities of 3,3'-diindolylmethane. The dose-dependent growth inhibitory effect was found in all these cell lines. Exposure of the cells to 50 microM solution of 3,3'-diindolylmethane for 48 h, apoptosis (programmed cell death) was evidenced by the characteristic morphology of cell nuclei under fluorescence microscope and the DNA "ladder" in agarose gel electrophoresis. The percentage of apoptotic cells in each cell line was found to be 12% for MCF-7, 14% for T47D and 13% for Saos2 cells. Exposure of MCF-7 cells to 100 microM 3,3'-diindolylmethane for 24 h, 19% of apoptotic cells were detected by flow cytometry analysis. The lowest dose required for induction of apoptosis in MCF-7 cells was found to be 10 microM after 72 h incubation. Western blot showed that wild-type p53 protein was unchanged after MCF-7 cells had been exposed to 50 microM 3,3'-diindolylmethane for 8 h. This study provides evidences that 3,3'-diindolylmethane induces apoptosis in human cancer cells and that the induction of apoptosis is independent of p53 pathway.
PMID: 8912651 [PubMed - indexed for MEDLINE]

1: J Biochem Toxicol 1995 Aug;10(4):191-201
The anticarcinogen 3,3'-diindolylmethane is an inhibitor of cytochrome P-450.
Stresser DM, Bjeldanes LF, Bailey GS, Williams DE.
Department of Food Science and Technology, Oregon State University, Corvallis 97331-6602, USA.

Dietary indole-3-carbinol inhibits carcinogenesis in rodents and trout. Several mechanisms of inhibition may exist. We reported previously that 3,3'-diindolylmethane, an in vivo derivative of indole-3-carbinol, is a potent noncompetitive inhibitor of trout cytochrome P450 (CYP) 1A-dependent ethoxyresorufin O-deethylase with Ki values in the low micromolar range. We now report a similar potent inhibition by 3,3'-diindolylmethane of rat and human CYP1A1, human CYP1A2, and rat CYP2B1 using various CYP-specific or preferential activity assays. 3,3'-Diindolylmethane also inhibited in vitro CYP-mediated metabolism of the ubiquitous food contaminant and potent hepatocarcinogen, aflatoxin B1. There was no inhibition of cytochrome c reductase. In addition, we found 3,3'-diindolylmethane to be a substrate for rat hepatic microsomal monooxygenase(s) and tentatively identified a monohydroxylated metabolite. These observations indicate that 3,3'-diindolylmethane can inhibit the catalytic activities of a range of CYP isoforms from lower and higher vertebrates in vitro. This broadly based inhibition of CYP-mediated activation of procarcinogens may be an indole-3-carbinol anticarcinogenic mechanism applicable to all species, including humans.
PMID: 8568833 [PubMed - indexed for MEDLINE]

Resveratrol

1: Int J Tissue React 1999;21(4):93-104
Resveratrol, a natural stilbene in grapes and wine, enhances intraphagocytosis in human promonocytes: a co-factor in antiinflammatory and anticancer chemopreventive activity.
Bertelli AA, Ferrara F, Diana G, Fulgenzi A, Corsi M, Ponti W, Ferrero ME, Bertelli A.
Institute of Human Anatomy, Faculty of Medicine, University of Milan, Italy.
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Trans-resveratrol, a natural stilbene present in wine and grapes, has been studied mainly for its antiinflammatory and anticancer activities. In this study the activity of resveratrol on proliferative immunological parameters (differentiation, apoptosis, phagocytosis and intracellular killing) was studied using a U937 human promonocytic cell line in comparison with another polyphenol, quercetin. After incubation of the pathogen, Candida albicans, intracellular killing by macrophage-like cells was decreased by quercetin and resveratrol 10 microM but was enhanced by resveratrol 1 microM after 20 h of treatment. Phagocytosis rate, expressed as phagocytosis frequency, (i.e., percentage number of phagocytosing cells/total cells) at 20 h was highest with resveratrol 10 microM and was higher with quercetin 10 microM than with resveratrol 1 microM. The phagocytosis index exhibited the same trend. While both polyphenols demonstrated cytostatic activity on U937 growth, a prointraphagocytic effect for resveratrol 10 microM-treated cells at 10 min, resveratrol 1 microM-treated cells at 20 h and resveratrol 10 microM-treated cells at 48 h was observed. Morphological examination with optic microscopy demonstrated both apoptotic and differentiating cells, even after 10 min treatment. Resveratrol-induced apoptosis (following 4 h treatment) was confirmed by flow cytometry at concentrations as low as 1 microM and 100 nM in the assay for detection of membrane phosphatidylserine. Resveratrol- or quercetin-treated, but unstimulated cells, did not produce tumor necrosis factor-alpha protein. As phosphatidylserine externalization triggers specific recognition by monocytes and macrophages, removal of intact apoptotic cells is important a) in cell population selection and differentiation for antiblastic therapy, and b) in preventing the release of toxic inflammatory substances such as reactive oxygen substances and proteolytic enzymes by dying cells. This observation suggests that wine polyphenols, at the same concentrations as those found in plasma after moderate wine consumption, are important cofactors in antiinfective, antiinflammatory and anticancer nonspecific immune reactions.
PMID: 10761539 [PubMed - indexed for MEDLINE]

1: Biochem Biophys Res Commun 2000 Sep 7;275(3):804-9
Resveratrol reverses tumor-promoter-induced inhibition of gap-junctional intercellular communication.
Nielsen M, Ruch RJ, Vang O.
Department of Chemistry and Life Sciences, Roskilde University, Roskilde, DK-4000, Denmark.

The naturally occurring stilbene/alexin trans-resveratrol (trans-3,5, 4'-trihydroxystilbene) is a promising agent for the prevention of cancer. We investigated the effect of resveratrol on gap-junctional intercellular communication (GJIC) in WB-F344 rat liver epithelial cells because inhibition of GJIC is an important mechanism of tumor promotion. Seventeen to 50 microM resveratrol increased GJIC significantly by a factor of 1.3 compared with solvent vehicle controls, when the WB-F344 cells were exposed to resveratrol for 6 h. Most tumor promoters, including the phorbol ester TPA and the insecticide DDT, block GJIC. Resveratrol at 17-50 microM also significantly prevented down-regulation of GJIC by TPA and DDT, by a factor of 2.7 and 1.8, respectively. This recovery of GJIC from TPA inhibition was partly correlated with hindered hyperphosphorylation of Cx43. In conclusion, resveratrol was found to enhance GJIC and counteract the effects of tumor promoters on GJIC, and this is likely a mechanism that contributes to the antipromotional and anticarcinogenic properties of resveratrol.

PMID: 10973802 [PubMed - indexed for MEDLINE]

1: Br J Haematol 2000 May;109(2):405-12
Resveratrol induces Fas signalling-independent apoptosis in THP-1 human monocytic leukaemia cells.
Tsan MF, White JE, Maheshwari JG, Bremner TA, Sacco J.
Research and Medical Services, Stratton VA Medical Center, Albany, NY 12208, USA.

Resveratrol, a natural product present in wine, has recently been shown to inhibit the growth of a number of cancer cell lines in vitro. In the current study, we have demonstrated that resveratrol inhibits the growth of THP-1 human monocytic leukaemia cells in a dose-dependent manner with a median effective dose of 12 microM. It did not induce differentiation of THP-1 cells and had no toxic effect on THP-1 cells that had been induced to differentiate into monocytes/macrophages by phorbol myristate acetate. A significant fraction of resveratrol-treated cells underwent apoptosis as judged by flow cytometric analysis of DNA content, DNA fragmentation and caspase-specific cleavage of poly(ADP-ribosyl) polymerase. Resveratrol treatment had no effect on the expression of Fas receptor or Fas ligand (FasL) in THP-1 cells, nor did it induce clustering of Fas receptors. In addition, THP-1 cells were resistant to activating anti-Fas antibody, and neutralizing anti-Fas and/or anti-FasL antibodies had no protective effect against resveratrol-induced inhibition of THP-1 cell growth. The effect of resveratrol on THP-1 cells was reversible after its removal from the culture medium. These results suggest that (1) resveratrol inhibits the growth of THP-1 cells, at least in part, by inducing apoptosis, (2) resveratrol-induced apoptosis of THP-1 cells is independent of the Fas/FasL signalling pathway and (3) resveratrol does not induce differentation of THP-1 cells and has no toxic effect on differentiated THP-1 cells. Thus, resveratrol may be a potential chemotherapeutic agent for the control of acute monocytic leukaemia.
PMID: 10848832 [PubMed - indexed for MEDLINE]

1: J Cell Biochem 2000 Jun 6;78(3):429-41

Potent inhibitory action of red wine polyphenols on human breast cancer cells.
Damianaki A, Bakogeorgou E, Kampa M, Notas G, Hatzoglou A, Panagiotou S, Gemetzi C, Kouroumalis E, Martin PM, Castanas E.
Laboratory of Experimental Endocrinology, University of Crete, School of Medicine and University Hospital, Heraklion, Greece.

Breast cancer (one of the most common malignancy in Western societies), as well as esophagus, stomach, lung, bladder, and prostate cancer, depend on environmental factors and diet for growth and evolution. Dietary micronutriments have been proposed as effective inhibitory agents for cancer initiation, progression, and incidence. Among them, polyphenols, present in different foods and beverages, have retained attention in recent years. Red wine is a rich source of polyphenols, and their antioxidant and tumor arresting effects have been demonstrated in different in vitro and in vivo systems. In the present study, we have measured the antiproliferative effect of red wine concentrate, its total polyphenolic pool, and purified catechin, epicatechin, quercetin, and resveratrol, which account for more than 70% of the total polyphenols in red wine, on the proliferation of hormone sensitive (MCF7, T47D) and resistant (MDA-MB-231) breast cancer cell lines. Our results indicate that polyphenols, at the picomolar or the nanomolar range, decrease cell proliferation in a dose- and a time-dependant manner. In hormone sensitive cell lines, a specific interaction of each polyphenol with steroid receptors was observed, with IC(50)s lower than previously described. Interaction of polyphenols with steroid receptors cannot fully explain their inhibitory effect on cell proliferation. In addition, discrete antioxidant action on each cell line was detected under the same concentrations, both by modifying the toxic effect of H(2)O(2), and the production of reactive oxygen species (ROS), after phorbol ester stimulation. Our results suggest that low concentrations of polyphenols, and consecutively, consumption of wine, or other polyphenol-rich foods and beverages, could have a beneficial antiproliferative effect on breast cancer cell growth.
PMID: 10861841 [PubMed - indexed for MEDLINE]

Tumeric Extract

1: Mol Urol 2000 Spring;4(1):1-6
Therapeutic potential of curcumin in human prostate cancer. II. Curcumin inhibits tyrosine kinase activity of epidermal growth factor receptor and depletes the protein.
Dorai T, Gehani N, Katz A.
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PURPOSE: In a search for alternative and preventive therapies for prostate cancer, attention was focused on the ways in which curcumin (Turmeric), used in food and medicine in India for centuries, could interfere with the growth factor signaling pathways in both androgen-dependent and androgen-independent prostate cancer cells, as exemplified by the epidermal growth factor receptor (EGF-R) signaling. MATERIALS

AND METHODS: The androgen-sensitive LNCaP and androgen-insensitive PC-3 cell lines were grown in 5 to 50 microM curcumin and analyzed for EGF-R protein by Western blotting and for EGF-R tyrosine kinase activity. RESULTS: Curcumin was a potent inhibitor of EGF-R signaling, and it accomplished this effect by three different means (1) down regulating the EGF-R protein; (2) inhibiting the intrinsic EGF-R tyrosine kinase activity; and (3) inhibiting the ligand-induced activation of the EGF-R. CONCLUSIONS: These results, taken together with our previous results that curcumin can induce apoptosis in both androgen-dependent and androgen-independent prostate cancer cells, support our view that curcumin may be a novel modality by which one can interfere with the signal transduction pathways of the prostate cancer cell and prevent it from progressing to its hormone-refractory state.
PMID: 10851300 [PubMed - indexed for MEDLINE]

1: Carcinogenesis 2000 May;21(5):921-7
Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis.
Mahmoud NN, Carothers AM, Grunberger D, Bilinski RT, Churchill MR, Martucci C, Newmark HL, Bertagnolli MM.
The New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, NY 10021, USA.

Epidemiological studies consistently indicate that consumption of fruits and vegetables lowers cancer risk in humans and suggest that certain dietary constituents may be effective in preventing colon cancer. Plant-derived phenolic compounds manifest many beneficial effects and can potentially inhibit several stages of carcinogenesis in vivo. In this study, we investigated the efficacy of several plant-derived phenolics, including caffeic acid phenethyl ester (CAPE), curcumin, quercetin and rutin, for the prevention of tumors in C57BL/6J-Min/+ (Min/+) mice. These animals bear a germline mutation in the Apc gene and spontaneously develop numerous intestinal adenomas by 15 weeks of age. At a dietary level of 0.15%, CAPE decreased tumor formation in Min/+ mice by 63%. Curcumin induced a similar tumor inhibition. Quercetin and rutin, however, both failed to alter tumor formation at dietary levels of 2%. Examination of intestinal tissue from the treated animals showed that tumor prevention by CAPE and curcumin was associated with increased enterocyte apoptosis and proliferation. CAPE and curcumin also decreased expression of the oncoprotein beta-catenin in the enterocytes of the Min/+ mouse, an observation previously associated with an antitumor effect. These data place the plant phenolics CAPE and curcumin among a growing list of anti-inflammatory agents that suppress Apc-associated intestinal carcinogenesis.
PMID: 10783313 [PubMed - indexed for MEDLINE]

1: J Surg Res 2000 Apr;89(2):169-75
Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile.
Churchill M, Chadburn A, Bilinski RT, Bertagnolli MM.

Department of Surgery, The New York Presbyterian Hospital, New York, New York, USA.

BACKGROUND: The C57BL/6J-Min/+ (Min/+) mouse bears a germline mutation in Apc and is therefore a model for familial adenomatous polyposis and sporadic colorectal cancer. Min/+ intestinal mucosa exhibits a marked tendency for spontaneous adenoma formation. Curcumin is a phenolic antioxidant known for its antitumor and immune modulatory functions in vitro. Curcumin prevents adenoma formation in Min/+ mice, through a mechanism that may be related to its immunomodulatory properties. MATERIALS AND METHODS: To study the relationship between intestinal immunity and curcumin-induced antitumor response, we used immunohistochemistry to characterize the effect of curcumin treatment on resident intestinal immune effector cells in Min/+ mice. RESULTS/CONCLUSION: These results show that mucosal CD4(+) T cells and B cells increase in animals treated with curcumin, suggesting that curcumin modulates lymphocyte-mediated immune functions.
PMID: 10729246 [PubMed - indexed for MEDLINE]

1: Mol Med 1998 Jun;4(6):376-83
Curcumin is an in vivo inhibitor of angiogenesis.
Arbiser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, Fisher C, Flynn E, Byers HR.
Department of Dermatology, Harvard Medical School, Boston, Massachusetts, USA. jlarbiser@bics.bwh.harvard.edu

BACKGROUND: Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In animal models, curcumin and its derivatives have been shown to inhibit the progression of chemically induced colon and skin cancers. The genetic changes in carcinogenesis in these organs involve different genes, but curcumin is effective in preventing carcinogenesis in both organs. A possible explanation for this finding is that curcumin may inhibit angiogenesis. MATERIALS AND METHODS: Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin and its derivatives were subsequently tested for their ability to inhibit bFGF-induced corneal neovascularization in the mouse cornea. Finally, curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production. RESULTS: Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin and its derivatives demonstrated significant inhibition of bFGF-mediated corneal neovascularization in the mouse. Curcumin had no effect on phorbol ester-stimulated VEGF production. CONCLUSIONS: These results indicate that curcumin has direct antiangiogenic activity in vitro and in vivo. The activity of curcumin in inhibiting carcinogenesis in diverse organs such as the skin and colon may be mediated in part through angiogenesis inhibition.
PMID: 10780880 [PubMed - indexed for MEDLINE]

Green Tea Extract

1: Br J Cancer 2001 Mar 23;84(6):844-50
EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells.
Jung YD, Kim MS, Shin BA, Chay KO, Ahn BW, Liu W, Bucana CD, Gallick GE, Ellis LM.
Chonnam University Research Institute of Medical Sciences, Chonnam University Medical School, Kwangju, Korea 501-190.

Catechins are key components of teas that have antiproliferative properties. We investigated the effects of green tea catechins on intracellular signalling and VEGF induction in vitro in serum-deprived HT29 human colon cancer cells and in vivo on the growth of HT29 cells in nude mice. In the in vitro studies, (-)-epigallocatechin gallate (EGCG), the most abundant catechin in green tea extract, inhibited Erk-1 and Erk-2 activation in a dose-dependent manner. However, other tea catechins such as (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) did not affect Erk-1 or 2 activation at a concentration of 30 microM. EGCG also inhibited the increase of VEGF expression and promoter activity induced by serum starvation. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day(-1)mouse(-1)starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth (58%), microvessel density (30%), and tumour cell proliferation (27%) and increased tumour cell apoptosis (1.9-fold) and endothelial cell apoptosis (3-fold) relative to the control condition ($P < 0.05$ for all comparisons). EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF.
PMID: 11259102 [PubMed - indexed for MEDLINE]

1: Biofactors 2000;13(1-4):67-72
Mechanisms of cancer prevention by tea polyphenols based on inhibition of TNF-alpha expression.
Suganuma M, Sueoka E, Sueoka N, Okabe S, Fujiki H.
Saitama Cancer Center Research Institute, Japan.

Among various biochemical and biological activities of tea polyphenols, we believe inhibition of the expression and release of tumor necrosis factor-alpha (TNF-alpha) is crucial, since our study with TNF-alpha-deficient mice has revealed that TNF-alpha is an essential factor in tumor promotion. We found that EGCG dose-dependently inhibited AP-1 and NF-kappaB activation in BALB/3T3 cells treated with okadaic acid, resulting in inhibition of TNF-alpha gene expression. Furthermore, treatment with 0.1% green tea extract in drinking water reduced TNF-alpha gene expression as well as TNF-alpha protein level in the lung of TNF-alpha transgenic mice; and IL-1beta and IL-10 gene expression in the lung was also inhibited by treatment with green tea extract, indicating

that green tea inhibits both TNF-alpha and the cytokines induced by TNF-alpha in organs. We recently found synergistic effects of EGCG and cancer preventive agents such as tamoxifen and sulindac, on cancer preventive activity. Taken together, the results show that green tea is efficacious as a non-toxic cancer preventive for humans.
PMID: 11237202 [PubMed - indexed for MEDLINE]

1: Life Sci 2001 Jan 26;68(10):1207-14
Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells.
Chung LY, Cheung TC, Kong SK, Fung KP, Choy YM, Chan ZY, Kwok TT.
Department of Biochemistry, The Chinese University of Hong Kong, Shatin.

Green tea catechins (GTCs) including (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC) were shown to suppress cell growth and induce apoptosis in various cell systems in addition to their chemo-preventive effect. In this study, except EC which was inactive, green tea extract (TE) and other 3 GTCs were found to suppress the growth and induce apoptosis in human prostate cancer DU145 cells largely through an increase in reactive oxygen species formation and mitochondrial depolarization. The conclusion was supported by the fact that the profiles for different GTCs in growth suppression, apoptosis induction, ROS formation and mitochondrial depolarization are in a similar order, i.e. ECG > EGCG > EGC > EC. Although the molecular mechanisms are still not clear, apoptosis induced by GTCs is not related to the members of BCL-2 family as EGCG did not alter the expression of BCL-2, BCL-X(L) and BAD in DU145 cells.
PMID: 11228105 [PubMed - indexed for MEDLINE]

1: Cancer Lett 1998 Jul 17;129(2):173-9
Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts.
Chen ZP, Schell JB, Ho CT, Chen KY.
Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway 08855-0939, USA.

(-)-Epigallocatechin gallate (EGCG), a catechin polyphenol compound, represents the main ingredient of green tea extract. Although EGCG has been shown to be growth inhibitory in a number of tumor cell lines, it is not clear whether the effect is cancer-specific. In this study we compared the effect of EGCG on the growth of SV40 virally transformed WI38 human fibroblasts (WI38VA) with that of normal WI38 cells. The IC50 value of EGCG was estimated to be 120 and 10 microM for WI38 and WI38VA cells, respectively. Thus, EGCG at 40 microM completely inhibited the growth of WI38VA cells, but had little or no inhibitory effect on the growth of WI38 cells. Similar differential growth inhibition was also observed between a human colorectal cancer cell line (Caco-2), a breast cancer cell line (Hs578T) and their respective normal counterparts. EGCG at a concentration range of 40-200 microM induced a significant amount of

apoptosis in WI38VA cultures, but not in WI38 cultures, as determined by terminal deoxynucleotidyl transferase assay. After exposure to EGCG at 200 microM for 8 h, more than 50% of WI38VA cells in a confluent culture became apoptotic. In contrast, less than 1% of WI38 cells displayed apoptotic labeling under the same condition. EGCG did not affect the serum-induced expression of c-fos and c-myc genes in normal WI38 cells. However, it significantly enhanced their expression in transformed W138VA cells. It is possible that differential modulation of certain genes, such as c-fos and c-myc, may cause differential effects of EGCG on the growth and death of cancer cells.
PMID: 9719459 [PubMed - indexed for MEDLINE]

1: Int J Oncol 1998 Mar;12(3):617-20
Exaggerated precocious centromere separation in cells of a human breast cancer line treated with a green tea extract.
Hsu TC, Zhao Y, Wang RY, Dickerson R, Liang JC, Wang X, Wu Y.
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In a breast cancer cell line, MDA-MB-468, established in our laboratory, an average of 3% of the mitotic cells exhibited a phenomenon known as centromere splaying, which is a characteristic feature of cells of patients with Roberts syndrome. However, centromere splaying in cells of Roberts syndrome patients is limited to i) the centromere region and ii) chromosomes with large amounts of heterochromatin. When the breast cancer cells were treated with an extract of green tea GTE-TP91, up to 45% of the metaphases were observed to exhibit this behavior; and the precocious centromere separation was highly exaggerated, affecting all chromosomes in such metaphases. Apparently, as the sister centromeres continued to pull apart, they carried the chromatids with them, except for the telomere regions, giving a ring-like configuration. Eventually, the sister chromatids became completely separated. Whether this bizarre phenomenon was induced by the polyphenols contained in this green tea extract GTE-TP91 is not known, but this phenomenon, upon further investigation, may throw some light on chromosomal proteins, centromere behavior, telomere behavior and related questions.
PMID: 9472101 [PubMed - indexed for MEDLINE]

Quercitin Dihydrate

1: Nutr Cancer 1999;34(1):88-99
Quercetin-induced apoptosis in colorectal tumor cells: possible role of EGF receptor signaling.
Richter M, Ebermann R, Marian B.
Institute for Tumor Biology-Cancer Research, University of Vienna, Austria.

Flavonoids are among the best candidates for mediating the protective effect of diets rich in fruits and vegetables with respect to colorectal cancer. To gain additional information

about their growth effects on colorectal tumors and their cellular mechanisms of action, a series of related flavonoids was added to cultures of colonic tumor cells. Most compounds induced growth inhibition and cell loss at concentrations of 1-100 microM, relative effectivity being quercetin > apigenin > fisetin > robinetin and kaempferol. Myricetin was only slightly effective. Quercetin was the strongest inducer of apoptosis in a process that was reversible until 10 hours by flavonoid removal and until 24 hours by fetal calf serum. Cells were preferentially retained in the S phase. On the cellular level, quercetin sensitivity was correlated with epidermal growth factor (EGF) receptor levels, rapid growth, and poor differentiation, indicating the possibility of targeting those cells most harmful for the organism. The flavonoid transiently inhibited EGF receptor phosphorylation but had only little effect on other signaling molecules. Even after recovery of receptor phosphorylation, cells remained resistant to EGF stimulation. In summary, the data indicate that inhibition of EGF receptor kinase is an integral part of quercetin-induced growth inhibition, but additional mechanisms also contribute to the overall effect.
PMID: 10453447 [PubMed - indexed for MEDLINE]

1: Carcinogenesis 2000 May;21(5):959-63
Suppression of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells by chemopreventive agents with a resorcin-type structure.
Mutoh M, Takahashi M, Fukuda K, Matsushima-Hibiya Y, Mutoh H, Sugimura T, Wakabayashi K.
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Cyclooxygenase-2 (COX-2) is abundantly expressed in colon cancer cells. It has been reported that inhibition of COX-2 enzyme activity is shown to prevent colon carcinogenesis. Thus, suppression of COX-2 expression may also be an effective chemopreventive strategy. In the present study, we constructed a beta-galactosidase reporter gene system in human colon cancer DLD-1 cells, and measured COX-2 promoter-dependent transcriptional activity in the cells. Interferon gamma suppressed this COX-2 promoter activity, while 12-O-tetradecanoylphorbol-13-acetate and transforming growth factor alpha (TGFalpha) exerted enhancing effects. We then tested the influence of 14 candidate cancer chemopreventive compounds on COX-2 promoter activity. Chemopreventive agents such as quercetin, kaempferol, genistein, resveratrol and resorcinol, all having a common resorcin moiety, were found to effectively suppress the COX-2 promoter activity with and without TGFalpha-stimulation in DLD-1 cells. Since all these compounds have a resorcin moiety as a common structure, a resorcin-type structure may play an active role in the inhibition of COX-2 expression in colon cancer cells.
PMID: 10783318 [PubMed - indexed for MEDLINE]

1: Carcinogenesis 2001 Mar;22(3):409-14

Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells.
Xing N, Chen Y, Mitchell SH, Young CY.

Department of Urology and Biochemistry and Molecular Biology, Mayo Graduate School, Mayo Foundation, Rochester, MN 55905, USA.
The androgen receptor (AR) is involved in the development and progression of prostate cancer. In order to find new compounds that may present novel mechanisms to attenuate the function of AR, we investigated the effect of a natural flavonoid chemical, quercetin, on androgen action in an androgen-responsive LNCaP prostate cancer cell line. Western blot analysis showed that AR protein expression was inhibited by quercetin in a dose-dependent manner. To demonstrate that the repression effects on AR expression can actually reduce its function, we found that quercetin inhibited the secretion of the prostate-specific, androgen-regulated tumor markers, PSA and hK2. The mRNA levels of androgen-regulated genes such as PSA, NKX3.1 as well as ornithine decarboxylase (ODC) were down-regulated by quercetin. Transient transfections further showed that quercetin inhibited AR-mediated PSA expression at the transcription level. Finally, it was demonstrated that quercetin could repress the expression of the AR gene at the transcription level. Our result suggests that quercetin can attenuate the function of AR by repressing its expression and has the potential to become a chemopreventive and/or chemotherapeutic agent for prostate cancer.
PMID: 11238180 [PubMed - indexed for MEDLINE]

1: Phytother Res 2000 Aug;14(5):347-51
Chemopreventive activity of quercetin during carcinogenesis in cervix uteri in mice.
De S, Chakraborty J, Chakraborty RN, Das S.
Department of Cancer Chemoprevention, Chittaranjan National Cancer Institute, Calcutta, India.

The chemopreventive action of quercetin was examined during 20-methyl cholanthrene induced cervical neoplasia in virgin Swiss albino mice. The effects were evaluated on the basis of histopathological observation of the cervical epithelium, micronucleus frequency in vaginal exfoliated cells and some biochemical parameters in the host liver. Quercetin was found to arrest or reverse the progression of cervical neoplasia. The micronucleus frequency was reduced following its administration. The potential anti-carcinogenic effect of quercetin noted in this study is attributed to its antioxidant property which was reflected in the lipid peroxides and their role in the host detoxification system, as expressed in liver glutathione level, glutathione-S-transferase, glutathione peroxidase, catalase and superoxide dismutase activity. As an integral part of the diet quercetin may offer protection to the epithelium from the damaging effects of carcinogenic chemicals.

PMID: 10925400 [PubMed - indexed for MEDLINE]

L-Selenium Methionine

1: Cancer Lett 1998 Mar 13;125(1-2):103-10
Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines.
Redman C, Scott JA, Baines AT, Basye JL, Clark LC, Calley C, Roe D, Payne CM, Nelson MA.
Pharmacology/Toxicology Department, The University of Arizona, Tucson 85724, USA.

Selenium supplementation has been shown for many years to work as an anticarcinogenic agent both in epidemiology and in in vitro studies. Selenium supplementation has recently been shown to decrease total cancer incidence. However, the mechanism of action of selenium as an anticarcinogenic agent has yet to be elucidated. Selenomethionine was the predominant form of selenium in the dietary supplement in the study by Clark et al. (Clark, L.C., Combs, G.F., Turnbull, W.B., Slate, E.H., Chalker, D.K., Chow, J., Davis, L.S., Glover, R.A., Graham, G.F., Gross, E.G., Krongrad, A., Lesher, J.L., Park, H.K., Sanders, B.B., Smith, C.L., Taylor, J.R. and The Nutritional Prevention of Cancer Study Group (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. J. Am. Med. Assoc., 276 (24), 1957-1963) and therefore we evaluated the growth inhibitory effects of selenomethionine against human tumor cells. Selenomethionine was tested against each of three human tumor cell lines (MCF-7/S breast carcinoma, DU-145 prostate cancer cells and UACC-375 melanoma) and against normal human diploid fibroblasts. All cell lines demonstrated a dose-dependent manner of growth inhibition by selenomethionine. Selenomethionine inhibited the growth of all of the human tumor cell lines in the micromolar (microM) range (ranging from 45 to 130 microM) while growth inhibition of normal diploid fibroblasts required 1 mM selenomethionine, approximately 1000-fold higher than for the cancer cell lines. In short, normal diploid fibroblasts were less sensitive than the cancer cell lines to the growth inhibitory effects of selenomethionine. Furthermore, we show that selenomethionine administration to these cancer cell lines results in apoptotic cell death and aberrant mitoses. These results demonstrate the differential sensitivity of tumor cells and normal cells to selenomethionine.
PMID: 9566703 [PubMed - indexed for MEDLINE]

1: Cancer Lett 2000 Nov 28;160(2):193-8
The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts.
Baines AT, Holubec H, Basye JL, Thorne P, Bhattacharyya AK, Spallholz J, Shriver B, Cui H, Roe D, Clark LC, Earnest DL, Nelson MA.
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We evaluated the effects of dietary selenomethionine supplementation on colonic polyamine levels and the ability of L-selenomethionine supplementation to modulate the carcinogenic activity of azoxymethane (AOM) in the rat colon. Four-week-old male F344 rats were treated with 15 mg/kg body weight of AOM once a week for 2 weeks. Dietary selenomethionine at a concentration of either 1 or 2 ppm was administered in AIN-76A

rodent diet to AOM-treated animals for 16 weeks. Aberrant crypt foci (ACF), precursor lesions of colon cancer, were investigated after the 16 week treatment course. Selenomethionine given in the diet at 2 ppm markedly reduced the number of aberrant crypt foci. The multiplicity of ACFs (i.e. the number of aberrant crypts/focus) and the percentage of microadenomas were also affected by selenomethionine in a dose dependent manner. However, evaluation of the colonic tissue polyamine levels between control and treated groups showed no significant difference. These results demonstrate that selenomethionine can modulate the development of AOM-induced premalignant lesions through a polyamine-independent mechanism.
PMID: 11053649 [PubMed - indexed for MEDLINE]

1: J Urol 2001 Dec;166(6):2034-2038
PLASMA SELENIUM LEVEL BEFORE DIAGNOSIS AND THE RISK OF PROSTATE CANCER DEVELOPMENT.
Brooks JD, Metter EJ, Chan DW, Sokoll LJ, Landis P, Nelson WG, Muller D, Andres R, Carter HB.
Department of Urology, Stanford University Medical Center, Stanford, California, and Laboratory of Clinical Investigation, National Institute on Aging, Gerontology Research Center and Departments of Urology, Oncology and Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

PURPOSE: Epidemiological studies and a randomized intervention trial suggest that the risk of prostate cancer may be reduced by selenium intake. We investigated whether plasma selenium level before diagnosis correlated with the risk of later developing prostate cancer. MATERIALS AND METHODS: A case control study was performed on men from the Baltimore Longitudinal Study of Aging registry, including 52 with known prostate cancer and 96 age matched controls with no detectable prostatic disease. Plasma selenium was measured at an average time plus or minus standard deviation of 3.83 +/- 1.85 years before the diagnosis of prostate cancer by graphite furnace atomic absorption spectrophotometry. Adjusted odds ratio and 95% confidence interval were computed with logistic regression. RESULTS: After correcting for years before diagnosis, body mass index, and smoking and alcohol use history, higher selenium was associated with a lower risk of prostate cancer. Compared with the lowest quartile of selenium (range 8.2 to 10.7 &mgr;g./dl.), the odds ratios of the second (10.8 to 11.8), third (11.9 to 13.2) and fourth (13.3 to 18.2) quartiles were 0.15 (95% confidence interval 0.05 to 0.50), 0.21 (0.07 to 0.68) and 0.24 (0.08 to 0.77, respectively, p =0.01). Furthermore, plasma selenium decreased significantly with patient age (p <0.001). CONCLUSIONS: Low plasma selenium is associated with a 4 to 5-fold increased risk of prostate cancer. These results support the hypothesis that supplemental selenium may reduce the risk of prostate cancer. Because plasma selenium decreases with patient age, supplementation may be particularly beneficial to older men.
PMID: 11696701 [PubMed - as supplied by publisher]

1: Cancer Res 2001 Oct 1;61(19):7071-8

Redox-mediated effects of selenium on apoptosis and cell cycle in the LNCaP human prostate cancer cell line.
Zhong W, Oberley TD.
Department of Pathology and Laboratory Medicine, University of Wisconsin Medical School, Madison, Wisconsin 53706, USA.

The effects of selenium exposure were studied in LNCaP human prostate cancer cells, and this same cell line adapted to selenium over 6 months to compare acute versus chronic effects of sodium selenite, the latter most closely resembling human clinical trials on the effects of selenium in cancer prevention and therapy. Our results demonstrated that oxidative stress was induced by sodium selenite at high concentrations in both acute and chronic treatments, but outcomes were different. After acute exposure to selenite, cells exhibited mitochondrial injury and cell death, mainly apoptosis. After chronic exposure to selenite, cells showed growth inhibition caused by cell cycle arrest, increased numbers of mitochondria and levels of mitochondrial enzymes, and only minimal induction of apoptosis. Immunoblotting analysis revealed that multiple proteins were up-regulated by chronic exposure to selenite. Among them, only up-regulation of manganese superoxide dismutase and the cyclin-dependent kinase inhibitor p21(Waf1/Cip1), proteins known to be redox sensitive and to have cell cycle regulatory functions, correlated with cell growth inhibition. Our results in selenite-adapted cells suggest that selenium may exert its effects in human prostate cancer cells by altering intracellular redox state, which subsequently results in cell cycle block.
PMID: 11585738 [PubMed - indexed for MEDLINE]

1: Biofactors 2001;14(1-4):127-33
Selenium and signal transduction: roads to cell death and anti-tumour activity.
Ghose A, Fleming J, Harrison PR.
CRC Beatson Laboratories, The Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow, G61 1BD, UK.
Accumulated evidence from prospective studies, intervention trials and studies on animal models of cancer have suggested a strong inverse correlation between selenium intake and cancer incidence. Several putative mechanisms have been suggested to mediate the chemopreventive activities of selenium: of these, the inhibition of cellular proliferation and the induction of apoptosis are particularly attractive. The mitogen activated protein kinase (MAPK) pathways are known to be important regulators of cell death and our recent work has focused on the involvement of these pathways in selenium-induced apoptosis in primary cultures of oral cancers and corresponding normal mucosa derived from biopsy material. Using this system, the oral carcinoma cells were found to have enhanced sensitivity to apoptosis when treated with certain selenium compounds compared to normal oral mucosa. Induction of Fas ligand was associated with selenium-induced apoptosis. Signal transduction studies suggests that selenium induces several changes in the MAPK signalling pathways but functional intervention/inhibitor studies indicate that activation of the JNK pathway seems to be most important.
PMID: 11568449 [PubMed - indexed for MEDLINE]
Liposomal Delivery System

1: J Pharm Pharm Sci. 2001 May-Aug;4(2):138-58.

Potential of polysaccharide anchored liposomes in drug delivery, targeting and immunization.

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PURPOSE: Recently the emphasis has been laid upon the carbohydrate mediated liposomal interactions with the target cells. Among the various carbohydrate ligands, such as glycoproteins, glycolipids, viral proteins, polysaccharides, lipo-polysaccharides and other oligosaccharides, this review deals with the polysaccharide anchored liposomal system for their potential in drug delivery, targeting and immunization. Over the years, various strategies have been developed which include coating of the liposomal surface with natural or hydrophobized polysaccharides, namely mannan, pullulan, amylopectin, dextran etc., or their palmitoyl or cholesteroyl derivatives. The polysaccharide(s) coat tends vesicular constructs physicochemically stable in bio-environments and site-specific. The aim of improving the physical and biochemical stability of liposomes and the ability to target liposomes to specific organs and cells, were the major attributes of the polysaccharide anchored liposomes. In this review the authors attempted to overview various applications of polysaccharide bearing liposomes, including lung therapeutics, targeted chemotherapy, cellular targeting, cellular or mucosal immunity and macrophage activation. Future prospects of the delivery module are also discussed. The review in general explores the concepts, options and opportunities of polysaccharide anchored liposomes with newer perspectives.

1: Reg Immunol. 1990-91;3(6):289-96.

Mucosal and systemic responses to an oral liposome-Streptococcus mutans carbohydrate vaccine in humans.

Childers NK, Michalek SM, Pritchard DG, McGhee JR.

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Purified polysaccharide antigens are often poorly immunogenic, especially when given by the oral route. However, it has been shown in experimental animals that liposomes can greatly increase the immunogenicity of certain polysaccharide antigens. Here we report the induction of immune responses in humans to an oral vaccine consisting of liposomes containing purified serotype carbohydrate antigen of Streptococcus mutans, the primary etiological agent of dental caries. Four volunteer subjects swallowed enteric coated gelatin capsules containing liposomal-antigen for seven consecutive days. Pre- and post-immunization samples of saliva and plasma were analyzed for antibody activity to S.

mutans carbohydrate by ELISA. Salivary anticarbohydrate IgA responses were detected in all four subjects between day 21 and day 32. Upon second and third immunizations, subjects experienced salivary responses earlier than following the first immunization. Early (day 4-7) plasma IgA responses to the carbohydrate were found in three subjects which consisted of both polymeric and monomeric forms. Variable levels of plasma IgG anti-carbohydrate antibody activity were seen in three individuals. These results show that orally administered liposomal-S. mutans serotype carbohydrate antigen induces a salivary IgA response in humans and provides evidence for the efficacy of liposomal antigen delivery system in the induction of a protective mucosal immune response against microbial pathogens.

1: Infect Immun. 1998 Sep;66(9):4299-304.

Effectiveness of liposomes possessing surface-linked recombinant B subunit of cholera toxin as an oral antigen delivery system.

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Departments of Microbiology and Oral Biology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.

Liposomes appear to be a promising oral antigen delivery system for the development of vaccines against infectious diseases, although their uptake efficiency by Peyer's patches in the gut and the subsequent induction of mucosal immunoglobulin A (IgA) responses remain a major concern. Aiming at targeted delivery of liposomal immunogens, we have previously reported the conjugation via a thioether bond of the GM1 ganglioside-binding subunit of cholera toxin (CTB) to the liposomal outer surface. In the present study, we have investigated the effectiveness of liposomes containing the saliva-binding region (SBR) of Streptococcus mutans AgI/II adhesin and possessing surface-linked recombinant CTB (rCTB) in generating mucosal (salivary, vaginal, and intestinal) IgA as well as serum IgG responses to the parent molecule, AgI/II. Responses in mice given a single oral dose of the rCTB-conjugated liposomes were compared to those in mice given one of the following unconjugated liposome preparations: (i) empty liposomes, (ii) liposomes containing SBR, (iii) liposomes containing SBR and coadministered with rCTB, and (iv) liposomes containing SBR plus rCTB. Three weeks after the primary immunization, significantly higher levels of mucosal IgA and serum IgG antibodies to AgI/II were observed in the rCTB-conjugated group than in mice given the unconjugated liposome preparations, although the latter mice received a booster dose at week 9. The antibody responses in mice immunized with rCTB-conjugated liposomes persisted at high levels for at least 6 months, at which time (week 26) a recall immunization significantly augmented the responses. In general, mice given unconjugated liposome preparations required one or two booster immunizations to develop a substantial anti-AgI/II antibody response, which was more prominent in the group given coencapsulated SBR and rCTB. These data indicate that conjugation of rCTB to liposomes greatly enhances their effectiveness as an antigen delivery system. This oral immunization strategy should be

applicable for the development of vaccines against oral, intestinal, or sexually transmitted diseases.