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Prevention and therapy of cancer by dietary monoterpenes.

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Monoterpenes are nonnutritive dietary components found in the essential oils of citrus fruits and other plants. A number of these dietary monoterpenes have antitumor activity. For example, d-limonene, which comprises >90% of orange peel oil, has chemopreventive activity against rodent mammary, skin, liver, lung and forestomach cancers. Similarly, other dietary monoterpenes have chemopreventive activity against rat mammary, lung and forestomach cancers when fed during the initiation phase. In addition, perillyl alcohol has promotion phase chemopreventive activity against rat liver cancer, and geraniol has in vivo antitumor activity against murine leukemia cells. Perillyl alcohol and d-limonene also have chemotherapeutic activity against rodent mammary and pancreatic tumors. As a result, their cancer chemotherapeutic activities are under evaluation in Phase I clinical trials. Several mechanisms of action may account for the antitumor activities of monoterpenes. The blocking chemopreventive effects of limonene and other monoterpenes during the initiation phase of mammary carcinogenesis are likely due to the induction of Phase II carcinogen-metabolizing enzymes, resulting in carcinogen detoxification. The post-initiation phase, tumor suppressive chemopreventive activity of monoterpenes may be due to the induction of apoptosis and/or to inhibition of the post-translational isoprenylation of cell growth-regulating proteins. Chemotherapy of chemically induced mammary tumors with monoterpenes results in tumor redifferentiation concomitant with increased expression of the mannose-6-phosphate/insulin-like growth factor II receptor and transforming growth factor beta1. Thus, monoterpenes would appear to act through multiple mechanisms in the chemoprevention and chemotherapy of cancer.

Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer.

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Perillyl alcohol is a natural product from cherries and other edible plants. Perillyl alcohol and d-limonene, a closely related dietary monoterpene, have chemotherapeutic activity against pancreatic, mammary, and prostatic tumors. In addition, perillyl alcohol, limonene, and other dietary monoterpenes have chemopreventive activity. Several mechanisms may account for the antitumorigenic effects of monoterpenes. For example, many monoterpenes inhibit the post-translational isoprenylation of cell growth-regulatory proteins such as Ras. Perillyl alcohol induces apoptosis without affecting the rate of DNA synthesis in both liver and pancreatic tumor cells. In addition, monoterpene-treated, regressing rat mammary tumors exhibit increased expression of transforming growth factor beta concomitant with tumor remodeling/redifferentiation to a more benign phenotype. Monoterpenes are effective, nontoxic dietary antitumor agents which act through a variety of mechanisms of action and hold promise as a novel class of antitumor drugs for human cancer.

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Prevention & therapy of mammary cancer by monoterpenes

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Monoterpenes, found in a wide variety of plants, are a major component of plant essential oils. The unsubstituted monocyclic monoterpene limonene has been shown to prevent carcinogen-induced mammary cancer at both the initiation and the promotion/progression stages. This terpene also causes the complete regression of the majority of advanced rat mammary cancer when added to the diet. Modification of limonene by hydroxylation at various positions increases both its chemopreventive and therapeutic efficacy. For example, the naturally occurring hydroxylated limonene analog perillyl alcohol is 5-10 times more potent than limonene and has a similar therapeutic index. Several cellular, metabolic and molecular activities are associated with terpene exposure. These include induction of phase I and II hepatic detoxification enzymes, selective inhibition of protein isoprenylation, inhibition of CoQ synthesis, and induction of the mannose 6-phosphate/IGFII receptor and TGF beta. Due to the therapeutic efficacy of monoterpenes in experimental model systems, clinical evaluation of this class of compounds has begun in advanced cancer patients. We feel that the results of these therapeutic trials, will facilitate the development of current terpenes and more potent analogs for future chemoprevention trials.

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Cancer chemoprevention and therapy by monoterpenes.

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Monoterpenes are found in the essential oils of many plants including fruits, vegetables, and herbs. They prevent the carcinogenesis process at both the initiation and promotion/progression stages. In addition, monoterpenes are effective in treating early and advanced cancers. Monoterpenes such as limonene and perillyl alcohol have been shown to prevent mammary, liver, lung, and other cancers. These compounds have also been used to treat a variety of rodent cancers, including breast and pancreatic carcinomas. In addition, in vitro data suggest that they may be effective in treating neuroblastomas and leukemias. Both limonene and perillyl alcohol are currently being evaluated in phase I clinical trials in advanced cancer patients. The monoterpenes have several cellular and molecular activities that could potentially underlie their positive therapeutic index. The monoterpenes inhibit the isoprenylation of small G proteins. Such inhibitions could alter signal transduction and result in altered gene expression. The results of a new gene expression screen-subtractive display-have identified or confirmed several up- or downregulated genes in regressing mammary carcinomas. For example, these regressing tumors overexpress the mannose 6-phosphate/IGF II receptor. The product of the gene both degrades the mammary tumor mitogen IGF II and activates the cytostatic factor TGF-beta. These and other alterations in the gene expression of mammary carcinomas lead to a G1 cell cycle block, followed by apoptosis, redifferentiation, and finally complete tumor regression in which tumor parenchyma is replaced by stromal elements. It is likely that monoterpenes prevent mammary cancer during their progression stage by mechanisms similar to those that occur during therapy.

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