Original Article

Therapeutic role of olive leaves and hyperthermia on nitrosodiethylamine induced hepatocarcinogenesis in rats

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ABSTRACT

Aim of the study

The present investigation was carried out to evaluate the effects of ethanolic olive leaves extract (OLE) alone or with whole body hyperthermia(WBH) in rat models of liver carcinogenesis, initiated by nitrosodiethylamine (NDEA) and promoted by phenobarbital(PB).

Methods

Liver cancer was induced by daily intraperitoneal injection of NDEA (200mg/kg) for three weeks. Two weeks after the last day of treatment with NDEA, PB was used with the aim to promote the carcinogenic effects for up to 6 weeks. OLE (200mg/kg) was administered intraperitoneally for 3 weeks either during or after the period of PB administration to hepatocellular carcinoma-bearing rats. After the experimental period, serum and liver samples were collected for biochemical and histopathological analysis.

Results

On administration of the carcinogens, the levels of serum tumor markers and liver enzymes increased markedly, but were significantly lowered in the groups of OLE treatment, especially when OLE was administered during the period of PB administration. On the contrary, the albumin serum levels were decreased in the carcinogen-administered animals, which was improved up to normal levels in the OLE groups alone or with hyperthermia. The results were dependent on the stage of carcinogenesis, rather than the duration of the protective treatment. The histopathological observations of liver tissues were corresponding with the biochemical results and confirmed the difference between control and treated groups.

Conclusions

OLE may efficiently prevent the initiation step of carcinogenesis and modulate the development of NDEA-induced and PB-promoted hepatocellular carcinogenesis in rats.

Keywords: Olive tree, hyperthermia, hepatocarcinogenesis, nitrosodiethylamine, oleuropein, rats.

Introduction

The olive leaf is the first botanical mentioned in the Bible. Through the history of civilization, the olive plant has been an important source of nutrition and was used for medical reasons. The olive leaf extract contains compounds with potent antimicrobial activities against bacteria, fungi and mycoplasma.[1] Several epidemiological studies have shown that the incidence of coronary heart diseases and certain cancers, e.g., breast and colon cancers, are rarer in the Mediterranean basin where the diet is rich in olives and olive products.[2] In addition, the olive leaves are considered a source of several antioxidants[3] and of substances with anti-inflammatory activities.[4]

There is an increasing interest in the phenolic compounds of olive by-products, due to their biological properties. Oleuropein is the most abundant biophenol in olive leaves and has been used in a number of medical treatments since its first reference in the literature[5]; oleuropein prevents cardiac diseases by protecting membrane lipid oxidation acting on coronary dilation and by its antiarrythmic action[6] improves lipid metabolism and prevents obesity, protects vital enzymes and hypertensive cell death in colon cancer patients[7] and finally presents antiviral properties.[8] Recently, AIDS patients have begun to use olive leaf extract for a variety of indications, among them as a drug for the support of immune system, to relieve chronic fatigue, to boost the effects of anti-HIV medications, and to treat HIV-associated Kaposi's sarcoma and HSV infections.[3] All these effects represent the antioxidant and nutraceutical capacities of olive leaf extracts in which by-products show a synergistic effect.[10]

Hyperthermia has been used as a cancer treatment in which body tissues are exposed to high temperatures. High temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. It has been proposed that with killing cancer cells and damaging proteins and structures within the cells, hyperthermia may shrink tumors[11] Preliminary data suggest that heat may be especially destructive to two types of tumor cells: those that are making DNA in preparation for division and those that are acidic and poorly oxygenated. These cell types tend to be resistant to radiation. It has been suggested by proponents that heat also appears to be make cells more sensitive to radiation by preventing radiation-damaged cells from repairing themselves.[12] When used as an adjunct to chemotherapy, hyperthermia may potentiate the effects of some chemotherapeutic agents.[13]

Primary liver cancer has been classified as the fifth most common cause of cancer and the fourth most cause of cancer mortality in the world.[14] The major risk factors of this disease include N- nitrosodiethylamine (NDEA) which is one of the most important environmental hepatocarcinogens that has been reported to generate free radicals to exert its carcinogenic effects.[15] It has been widely used in the field of experimental hepatocarcinogenesis.[16] Foodstuffs such as milk and meat products, salted fish, alcoholic beverages and a few varieties of vegetables are the principal sources of nitroso-compounds.[16] In rats, NDEA has been shown to be metabolized to its active ethyl radical metabolite, and the reactive product interacts with nuclear enzymes involved in DNA repair/replication causing mutation, which would lead to carcinogenesis.[17]