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Chemopreventive Activity of Mediterranean Medicinal Plants

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1. Introduction

Generally, the use of plants, herbs or other natural products in medicines is since humans inhabited earth. It was "since ever" when humans were trying to find out which plants might be useful to fight several pains and aches, fever, dyspepsia, or wounds. Through the ages, humans learned which plants would cure different illnesses, or might be poisonous and cause even death, and those that could be part of their diet. There are too many examples and references in the pharmaceutical, knowledge that passed from generation to generation. There is ample historical evidence for different usages of herbs by our ancestors. Herbs are the oldest drugs in the world. The initial use was primarily experimental similar to what applied to animals, e.g. against poisonous plants. The first record of the valuable properties of medicinal plants was by the Sumerians (6000 BC), followed by Chinese and Greek. The first book written about herbal plants was by Chinese (4000 BC). However, Greeks were these who spread the use of medicinal plants in West using the knowledge written down by Theophrastus (300 BC). Apollonios wrote about their uses in cosmetology and in religious ceremonies. Hippocrates recommended Pimbinella anisum, of the Umbelliferae family for sneezing and Theophrastus indicated the usefulness of 600 aromatic and medicinal plants in several pathologies. In ancient Rome, Galenus who was the personal physician to Roman emperors and is nowadays considered as "The Father of Pharmacy" was most devoted to aromatherapy. Reports about the uses of essential oils occur even in the Bible, and it was approximately during the 8th century AD when the Arabs improved the methods of extracting the essential oils from natural products and creating novel elixirs and medicines. During the Middle Ages, the essential oils producers were not affected by cholera and plague. During the Renaissance, the use of plants, essential oils, herbs and several other natural products was progressively neglected. The revolution of Chemistry and the synthesis of drugs resulted in almost complete abandonment. However, the impressive results of treating traumas with different botanical products during the two World Wars motivated scientists to further deal the potential of natural products in disease treatment. Aspirin (acetylsalicylic acid), perhaps the most popular painkiller, has a very long history and its medical use stretches back to antiquity. Medicines made from willow and other salicylate-rich plants date back at least to 400 BC. Willow bark extract became recognized for its specific effects on fever, pain and inflammation in the mid-

eighteenth century. Lewis and Clark allegedly used willow bark tea in 1803-1806 as a remedy for fever for members of the famous expedition. By the nineteenth century pharmacists were experimenting with and prescribing a variety of chemicals related to salicylic acid, the active component of willow extract. Chemist Charles Frédéric Gerhardt and many other chemists established the compound's chemical structure and devised efficient methods of synthesis of acetylsalicylic acid. Aspirin's popularity grew over and it is now accepted as one of the most efficient drugs in many health problems.

The NCI (National Cancer Institute) has examined more than 30,000 plants with anticancer activity (Ipek, 2005). However, the use of plants as a means treatment is still very limited. From 250,000 to 500,000 species plants, a small percentage has been examined for its medicinal properties. The World Health Organization estimates that 80% of the inhabitants of the earth choose traditional medicine for primary health needs, much of which relies on the use of essential oils from plants. The main aromatic plants belong to the families Labiatae, Umbelliferae, Lauracae, Myrtacae and Compositae.

Today, various types of consumer products based on natural products may appear with different names, which are:

- Neutraceuticals
- Dietary supplements
- Herbal remedies
- Herbal teas and infusions

All the Mediterranean countries are extremely rich in native plants, many of which are cultivated systematically.

For several decades the majority of drug substances were either natural products or compounds. However, in the last century, synthetic chemistry and biotechnology techniques have offered alternatives to natural sources (Harvey, 2009). The past few decades have witnessed a renewed interest in the field and nowadays although to a lesser extent, the field still continues to produce new drugs; half of the drugs approved since 1994 have been based on natural products (Harvey, 2008). Contemporary Western science supports the right use of traditional medicinal plants, which have become a part of many modern therapies after thorough investigations on their quality and safety. There are of course certain steps to take before introducing medicinal plants into disease prevention or treatment. In most cases, research starts when there is knowledge of use of plants by native people for disease treatment within folk medicine. Accurate identification, phytochemical analysis, pharmacological screening, in vitro, animal model and human interventions, further identification of the most bioactive fraction or component and of the exact mechanism underlying the activity, and finally toxicity tests are steps to be taken prior consideration of the candidate medicinal plant or component to be administered in disease. To this end, collaboration among specialists in ethnobotany, ethnopharmacy, ethnopharmacology ethnomedicine, phytochemists, analytical and organic chemists is essential. Depending on the activity investigated other specialists, e.g. in microbiology or in cancer, might be required.

Ethnobotany is the study of the relationships that exist between people and plants. Ethnobotanists aim to document, describe and explain complex relationships between

cultures and plants; explore how plants are used for food, medicine, clothing, hunting, and religious ceremonies.

Ethnopharmacology differs from ethnopharmacy in that it is the biological evaluation of how effective traditional medicines are, whereas ethnopharmacy deals instead with much broader considerations of drug use. These considerations are related to the perception, use, and management of pharmaceuticals within a given human society.

Ethnomedicine is the comparative study of how different cultures view disease and how they treat or prevent it; also, the medical beliefs and practices of local cultures, those that have relevant written sources, as well as knowledge and practices that have been orally transmitted over the centuries.

Phytochemistry is the study of phytochemicals that includes techniques such as extraction, isolation and structural elucidation (MS, NMR) of natural products, as well as various chromatography techniques (HPLC, LC-MS).

Although very few people nowadays would abandon the benefits of modern pharmaceutical science or the convenience of technology, a growing interest in medicinal plants and their uses occurs which began in early 1980s. It has been reported that almost 80% of the global population in developing countries use plant materials for health care (Farnsworth et al., 1985). Plants are a good source of chemical compounds many drugs originate from a natural compound isolated from a medicinal plant. Nevertheless, this extended medicinal use reported does not incorporate or result in respective drug discovery. According to estimates only 20% of all plant species have been chemically or biologically evaluated (Cordell, 2003) and therefore the evaluation of a natural product seems to be a great prospect in the seek out for new drugs. Fabricant and Farnsworth (2001) showed that 94 species of plant are utilized for the production of the 122 single agent natural products that are used as single agent drugs around the world. Of these, 72% were used clinically for the same or a related ethnomedical purpose.

This 80% of medicinal plants not yet chemically or biologically evaluated is a major challenge (Cordell & Colvard, 2005). The evidence to date with natural products is intriguing and guarantees greater attention. More research is indicated to bring about the biological effects and how susceptibility factors including nutrient–nutrient interactions and genetics influence the response. Automation, nanotechnology and proteomics, will have an increasingly important impact and thus we must be prepared to use them appropriately (Cordell & Colvard, 2005). Microarray assay systems based on the enhanced knowledge of the human genome will be brought to the level of the routine evaluation of extracts and compounds in order to assess genetic impact.

2. Mediterranean medicinal plants and cancer chemoprevention

Carcinogenesis is generally recognized as a complex and multistep process in which oxidative stress and inflammation plays a crucial role, and distinct molecular and cellular alterations occur (Franco et al., 2008; Kryston et al., 2011). Cancer chemoprevention attempts to interfere in the progress of the disease by using natural or synthetic substances. In the term of chemoprevention, many food components of the Mediterranean diet, gained the "food-borne anticarcinogens" title due to their content on components with

chemopreventive properties. Those chemical compounds have proved that they may interrupt or reverse the carcinogenesis process by acting on intracellular signalling network molecules involved in the initiation and/or promotion, but also may arrest or reverse the progression stage of cancer (Ramos, 2008). Those "food-borne anticarcinogens" can be define as either "blocking agents" which act immediately before or during the initiation of carcinogenesis by chemical carcinogens, or "suppressing agents, which act after initiation during the prolonged stages of promotion and progression (I.T. Johnson, 2007). Blocking agents scavenge Reactive Oxygen Species by potentiate the antioxidant enzyme system, or prevent genotoxic carcinogens, from forming adducts with DNA, either by inhibiting their activation from carcinogens or by enhancing their detoxification and excretion (Nelson et al., 1993). Suppressing agents act after initiation, during the prolonged stages of promotion and progression. They may prevent further DNA damage, induce cell-cycle arrest or apoptosis, as well as inhibit inflammation, invasion or angiogenesis (Fig. 1).

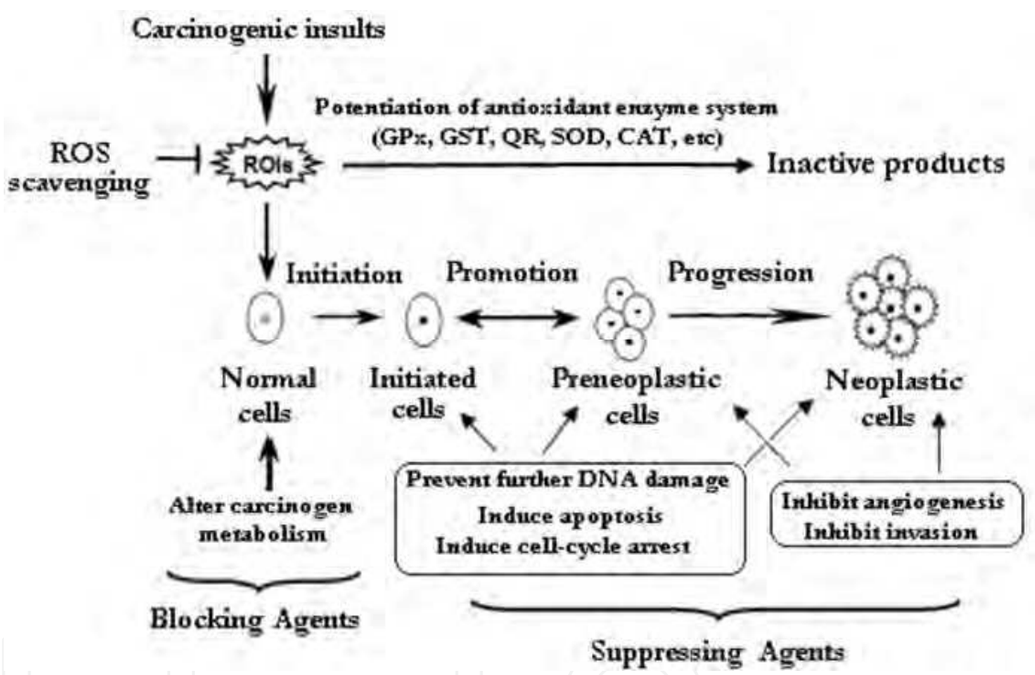

Fig. 1. Mechanism of cancer chemoprevention.

The present chapter aimed to assess the chemoprevention activity of plants derived from Mediterranean basin. Original research studies that were published in English until August 2011, were selected through a computer-assisted literature search (i.e., PubMed and Sciencedirect). We focused on the anticancer properties of phytochemicals from Chios mastic gum (Pistacia Lentiscus var. Chia) and Mediterranean herbs, derived mainly from family *Lamiaceae (*e.c. genous Origanum, Rosmarinus, Satureja, Thymus, Sideritis, Salvia, Mentha).

2.1 Chios mastic (*Pistacia lentiscus L.*) and cancer chemoprevention

Chios Mastic is the name of a resinous sap produced from the mastic tree (*Pistacia lentiscus* var. *chia*) (Fig. 2A). It is a natural, aromatic resin in teardrop shape, falling on the ground in

drops from superficial scratches induced by cultivators on the tree's trunk and main branches with sharp tools (Fig. 2B). As it drips, it appears as a sticky and translucent liquid which, 15-20 days later, is solidified into irregular shapes influenced by the area's weather conditions in summertime that is intense drought and sunlight. After being solidified, it has a crystal form (Fig. 2C), while its rather bitter taste quickly subsides to leave a distinctive aroma that really makes it unique. That solid product is then harvested and washed by mastic growers, giving us finally the natural Chios mastic. Soil and climatic characteristics allow the development of mastic trees just south of the island of Chios in the Aegean Sea, Greece. Its color is initially ivory-like but as time goes by, that shade is lost and 12 to 18 months later it changes into yellowish due to oxidation. It is made of hundreds of components; such multitude probably justifies the multiple uses of Chios mastic, in the fields of food industry, health and cosmetic care, worldwide.

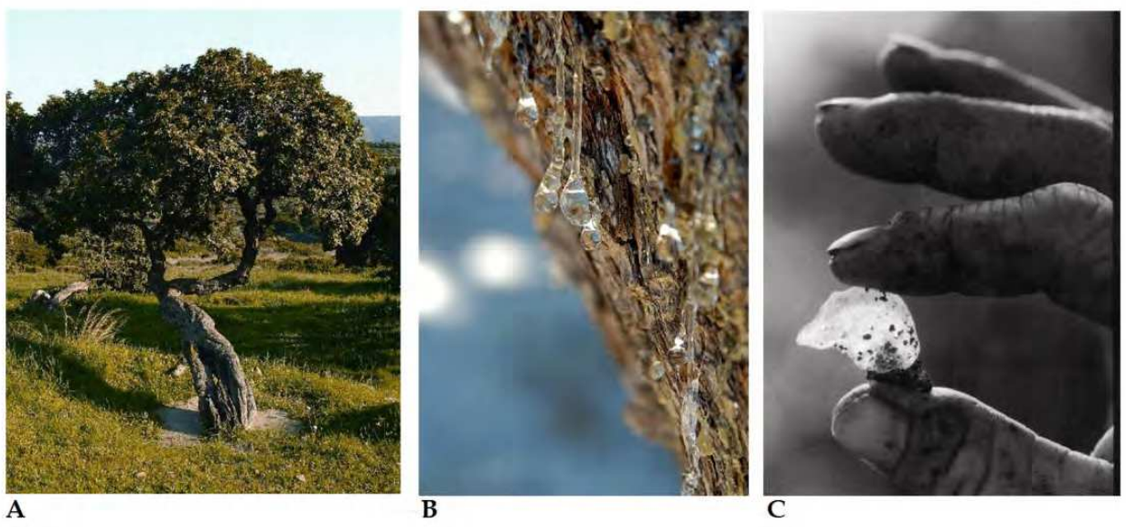

Fig. 2. **A:** Mastiha Tree, **B:** Mastiha tree trunk and **C:** Mastiha drop.

Chios mastic has been recognized since ancient times both for its distinctive aroma and its healing properties. It has been recorded as the first natural chewing gum in the ancient world. The mastic is known since antiquity for its organoleptic characteristics, but also for its beneficial properties. The first recorded promoter mastic was Dioscorides who wrote that Chios produced the best and greatest quantity of mastic, noting that it was indicated for coughing and stomach ailments, to sweeten the breath, and for facial masks. Several years later, Galen, the most important Greek physician after Hippocrates, extolled mastic's styptic and lenitive properties and recommended it for inflammations of the stomach, intestines and liver. Aretaeus, a physician from Cappadocia who lived in the second half of the 2nd century CE, left many formulas for poultices using mastic. A poultice of apple pulverized with mastic and meliloto (a species of aromatic clover) remedied delirium. A poultice of dates pulverized in wine together with mastic and aloe helped the patient regain strength after a cardiac episode. A poultice of quince, dates, nardo (valeriana) and mastic treated an upset stomach. Monk Antonio Menzani di Cuna in the pharmacy of the Franciscan Monastery of Saint Savior in Jerusalem created a most effective balsam named "The Jerusalem Balsam" using four ingredients: aloe, frankincense, myrrh, and mastic, dissolved

in ethanol. The philosopher and physician al-Razi (868-932 CE) who was considered the Hippocrates of Islam, prescribed a mixture of alum and mastic to fill decayed teeth and the chewing of mastic as an appetite stimulant for pregnant women. Abu Yusuf Ya'qub ibn Ishaq al-Kindi, a physician in 9th century Baghdad, provided a medical formula "that makes those who drink happy"; it fortified the stomach, sweetened the breath, and aided the liver. It was administered before or after food and contained rose oil, clove, valeriana, cinnamon, saffron, cardamom, hazel nuts, and mastic. Abu Marwan'Abd al-Malik, born in Seville in 1091, was one of the most eminent clinicians of his time who prescribed a preparation of licorice, raisins and mastic for liver problems. The healing action of mastic was explained by the Swiss physician and alchemist Paracelsus, in his Der grossen Wundartzney (Great Surgery Book). "The biological nature of man is such that it enables him to self-heal, to re-balance and re-fill. Wounds are not healed by the balsam. Mastic, resins and other healing agents are unable to create even a fiber of flesh. They have, however, the property that enables nature to work unimpeded to heal the wound."

The first research studies on the health effects of mastic were in the mid 1980s regarding peptic ulcers (Al-Habbal et al., 1984; Al-Said et al., 1986; Huwez & Al-Habbal, 1986). Since then, more and more studies have been carried out in order to highlight the pharmaceutical effects of mastic in a number of diseases.

The research on the anticancer effects of mastic is most recent. First, Balan et al. (2005) showed that hexanoic gum extract caused apoptosis in HCT116 colon cancer cells. Although the mechanism of action was not elucidated, the resin appeared to trigger a cascade of reactions catalyzed by a family of proteases, caspases, resulting in DNA degradation and apoptosis of cancer cells. The ethanol extract of mastic gum exhibited similar properties, while the observation that cell death continued even when gum treatment stopped indicated that apoptosis was programmed (Balan et al., 2007). Also, in a study of Kaliora et al., (2010), different solvent extracts from 500 μg dried product suppressed cell proliferation, significantly ($p<0.05$) in AGS cells. In the same study, FACS indicated that extracts significantly induced cell death ($p<0.05$). All extracts statistically decreased protein and mRNA ICAM-1 levels ($p<0.05$), while IL-8 protein and mRNA levels showed no significant difference. They concluded that the ethanol-terpene-rich extract was the most effective. A similar mechanism was observed in prostate cancer cells (He et al., 2006; He et al. 2007a, 2007b).

The study of Moulos et al. (2009) was the first to investigate the effect of mastic essential oil in the expression of the whole genome (genome-wide expression analysis). This study provided novel evidence on the molecular basis of tumor growth inhibition mediated by mastic oil and set a rational basis for application of genomics and bioinformatic methodologies in the screening of natural compounds with potential cancer chemopreventive activities Microarray expression profiling was performed using Illumina mouse-6 v1 beadchips, followed by computational analysis. For a number of selected genes, RT-PCR validation was performed in Lewis lung carcinomas, cells as well as in three human cancer cell lines of different origin A549 alveolar epithelial cell, colon cancer HCT116 and K562 myelogenous leukaemic cells. DNA microarray applied in this study allows for the measurement of the expression of complete genome, including identification of functions, metabolic pathways and regulatory mechanisms in diseases such as cancer. The method of the microarray is a milestone in the science of genetics. In the study of Moulos al. the

cultivation of LLC with mastic oli (0.01% v/v) resulted in regulation of the expression of 925 genes. Among them, modifications on cell cycle/proliferation, survival and NF-kappaB cascade in conjunction with concomitant regulation of genes encoding for PTEN, E2F7, HMOX1 (up-regulation) and NOD1 (down-regulation) indicated some important mechanistic links underlying the anti-proliferative, pro-apoptotic and anti-inflammatory effects of mastic oil. The expression profiles of Hmox1, Pten and E2f7 genes were similarly altered by mastic oil in the majority of test cancer cell lines. Inhibition of PTEN partially reversed mastic oil effects on tumor cell growth, indicating a multi-target mechanism of action.

A recent study in mice with colon cancer confirmed the antineoplastic role of mastic (Dimas et al., 2009). The intraperitoneal injection of hexane extract of gum at a dose equal to 200 mg/kg body weight resulted in significant suppression of tumor growth in a human colon cancer/immunodeficient mouse model. However, the schedule of administration seemed to play a key role in toxicity. When the extract given for a whole month applying 5 day administration-2 day interval, the size of tumors was significantly reduced, but none of the animals survived the intervention. Conversely, when the schedule was 4 day administration-3 day interval, tumor size was significantly decreased and all animals survived.

In none of the above studies was the bioactive compound in mastic determined. Essential oils and resins, including mastic essential oil and resin, contain a wide variety of terpenes. Specifically, essential oils consist of volatile, low molecular weight terpenes, and resins consist of a mixture of volatile and non volatile terpenes. Terpenes are hydrocarbons of plant origin with carbonate skeleton of 2-methyl-1,3-butadiene or isoprene a common organic compound with the formula $CH_2=C(CH_3)CH=CH_2$. The terpenes identified in Chios mastic are over 80 structures (Papageorgiou et al., 1997; Assimopoulou & Papagerogiou, 2005; Paraschos et al., 2007).

Numerous studies have shown the beneficial role of several terpenes known to be contained in Pistacia species against several cancers; pancreas, breast, colon, liver, and skin (Crowell, 1999). The main monoterpenes are perillyl alcohol, limonene, geraniol and α-pinene and the major triterpenes oleanolic acid and isomer ursolic acid (Fig. 3).

The chemotherapeutic action of perillyl-alcohol is established. In the study by Stark et al. (1995) Perillyl alcohol significantly reduced the growth of hamster pancreatic tumors to less than half that of controls. A percentage of 16% of perillyl alcohol-treated pancreatic tumors completely regressed whereas no control tumors regressed. Perillyl alcohol induced contact inhibition in cultured human pancreatic carcinoma cells and inhibited their anchorage-independent growth ($P<0.001$). Thus, perillyl alcohol has antitumor activity against pancreatic carcinomas at non-toxic doses, and may be an effective chemotherapeutic agent for human pancreatic cancer. As regards the mechanism of action, the perillyl alcohol has been shown to inhibit the proliferation of B12/13 adenocarcinoma pancreatic cells and also to induce apoptosis (Stayrook et al., 1997). Also, the expression of the pro-apoptotic Bak protein was multiplied up to 8 times, which was not observed in normal pancreatic D27 cells. It is rather that the antitumor activity of perillyl alcohol toward pancreatic cancers may be due to preferential stimulation of Bak-induced apoptosis in malignant versus normal cells. Bak may, therefore, be a useful biomarker for the chemopreventive and therapeutic effects of perillyl alcohol, indicative of a Bak-dependent apoptotic pathway.

In 1994, Haag and Gould examined the effect of perillyl alcohol in Wistar-Furth rats with DMBA initiated breast cancer. When tumor diameter reached 3mm, their diet was enriched with 2.5% perillyl alcohol. Three weeks later, the tumors in 22 out of 27 rats (81%) disappeared completely. This observation lead the researchers to examine the effect of different concentrations of the monoterpene in tumors already reached 10mm. After 15 weeks of 2% perillyl-alcohol intervention, 10 of the 20 animals showed complete tumor decrease and additional 5 showed some improvement. However, diet enrichment with 3% perillyl alcohol resulted to toxicity and death in some animals. On the contrary, Stark et al. (1995) have sown that 3% perillyl alcohol in the diet is absolutely secure. The results are conflicting and this is due to methodological weaknesses. Food intake depends on body weight and the number of animals present in each cell. It is noteworthy that the rats maintain a kind of hierarchy with the obvious presence of the "stronger" and more "weak". The more animals form a group, the more difficult it is to calculate food intake. In the study by Haag and Gould (1994) in each cage housed only two animals, while that of Stark et al. (1995) not listed. The choice of the strain should also be chosen with strict criteria for the purposes of the study. Thus, limonene appears to reduce the incidence of kidney cancer in F344 rats, but not in NCI-Black-Reiter rats in the absence of α2-globulin in liver cells (Dietrich & Swenberg, 1991).

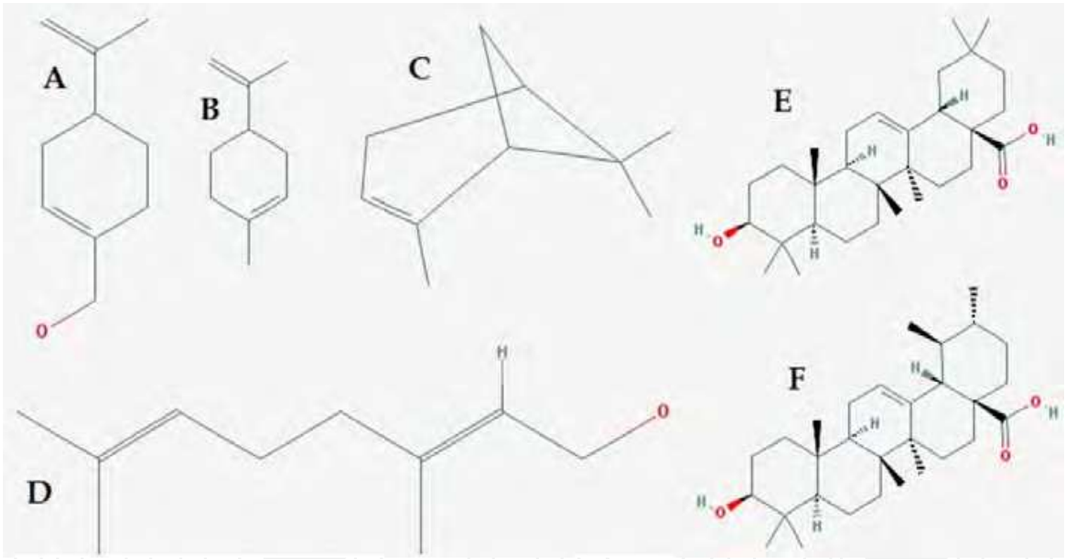

Fig. 3. Chemical structure of the main monoterpenes **A:** perillyl alcohol, **B:** limonene, **C:** geraniol and **D:** α-pinene and major triterpenes **E:** oleanolic acid and **F:** isomer ursolic acid of Chios mastic.

After 19 weeks incorporating 1% perillyl-alcohol in the diet of rats with DEN-liver cancer, the mean liver tumor weight was 10-fold less than that for the untreated animals. The monoterpene did not influence tumor cell proliferation but increased the apoptotic index approximately 10-fold. The mRNA levels for the mannose 6-phosphate/insulin-like growth factor II receptor and the transforming growth factor beta type I, II, and III receptors were also significantly increased in the liver tumors from the terpene-treated animals when compared to the corresponding receptor mRNA levels in the normal tissue surrounding the tumors and in the tumors of untreated animals. The results demonstrated that perillyl-

alcohol does not promote the formation of liver tumors, but rather inhibits their growth by enhancing tumor cell loss through apoptosis (Mills et al., 1995).

Angiogenesis is essential for the progression of solid tumors and hematological malignancies. Thus, antiangiogenic therapy is one of the most promising approaches to control cancer. When Loutrari et al., (2004) examined the ability of perillyl alcohol to interfere with the process of angiogenesis, they observed prevention of new blood vessel growth in the in vivo chicken embryo chorioallantoic membrane assay and inhibition of the morphogenic differentiation of cultured endothelial cells into capillary-like networks. In addition, perillyl alcohol inhibited proliferation and induced apoptosis of endothelial cells via the caspase-3 activity and DNA fragmentation. Consistent with the observed antisurvival effect, perillyl alcohol treatment resulted in a significant inhibition of Akt phosphorylation in endothelial cells. Finally, it differentially modulated the release of two important angiogenic regulators: vascular endothelial growth factor and angiopoietin 2. A recent study in the effects of ursolic and oleanolic acid administration on the formation of 1,2-dimethyl-hydrazine (DMH)-induced aberrant crypt foci in the colon of the male Wistar rat. When either individually or as a mixturewere administered in rats, a significant reduction in the frequency of aberrant crypt foci in the group treated with the triterpenoid compounds plus DMH was recorded compared to those treated with DMH alone, suggesting that triterpenes have a protective effect against colon carcinogenesis (Furtado et al., 2008). In the study by Yamai et al. (2009) the triterpenes enhanced conventional therapy in esophageal cancer and anti-tumor activity attribted to the powerful antioxidanteffects (Ovesná et al., 2006) and their ability to block angiogenesis (Sogno et al., 2009).

Perillyl alcohol at the 1 g/kg level significantly inhibited the incidence (percentage of animals with tumors) and multiplicity (tumors/ animals) of invasive adenocarcinomas of the colon, whereas perillyl alcohol at 2 g/kg diet inhibited the incidence of total adenocarcinomas of the colon and small intestine as compared to the control diet (Reddy et al., 1997). The study indicated that the colon tumors of azoxymethane-induced colon carcinogenesis animals fed perillyl alcohol exhibited increased apoptosis as compared to those fed the control diet. These results demonstrate the potential chemopreventive activity of perillyl alcohol against colon carcinogenesis.

When investigating whether the addition of d-limonene to the diets of rats would modify the process of mammary tumor induction, diets containing 1,000 or 10,000 p.p.m. of d-limonene were fed to rats one week prior to DMBA induced tumor formation. A significant reduction in mammary carcinogenesis was observed at each level. The inhibition of carcinogenesis was mainly due to an increase in latency; however, major differences in incidence could be seen during the follow-up period. For example, rats fed 10,000 p.p.m. of d-limonene had a 72% reduction in mammary tumors when compared to controls at 18 weeks post DMBA treatment. In addition to inhibiting the appearance of mammary tumors, d-limonene was also found to cause the regression of frank mammary tumors. No toxicity was evident in these rats even at the highest d-limonene dose (Elegbede et al., 1984). Maltzman et al. (1991) observed that limonene inhibited the toxicity of DMBA, increasing the urinary excretion of DMBA and its metabolites, reducing the formation of DMBA-DNA complexes affecting the liver detoxification pathway.

Topical perillyl alcohol significantly inhibited tumor incidence and multiplicity, average tumor size, and the average tumor burden/mouse without any apparent toxicity in a

nonmelanoma model of mouse skin carcinogenesis. It inhibited UVB-induced AP-1 transactivation in both cultured human keratinocytes and transgenic mice that stably express a luciferase reporter driven by AP-1 elements. The results suggested that perillyl alcohol might be used for chemoprevention of human skin cancer. (Batherlman et al., 1998).

However, clinical trials in cancer patients are intimidating. The 20 patients, of whom 15 were evaluable in the study of Bailey et al. (2008), received perillyl alcohol in doses between 1,200 and 2,000 mg/m^2 for a total of 43 courses. The most common observed toxicities were nausea, gastrointestinal distress, and fatigue. Other toxicities included diarrhea or constipation, hypokalemia, and one incidence of acute pancreatitis. Due to these toxicities, four of the patients declined further treatment either during or after the second course. While perillyl alcohol was not detected in plasma, perillic acid and dihydroperillic acid were detected in plasma, and the peak levels at 2,000 mg/m^2 per dose were approximately 600 μM perillic acid and 50 μM dihydroperillic acid. There was no evidence that levels of TGF-b plasma and the expression of Ras proteins were affected, indicative of the non significant advantages of perillyl alcohol In adults with advanced malignancies. No significant difference occurred between lesions appearing on the perillyl alcohol treated forearm vs. the placebo-treated forearm in healthy non skin cancer subjects under UV radiation (Stratton et al., 2008), indicative that most probably perillyl alcohol cream has no chemopreventive activity in skin cancer. Finally, intake of 55 mg-perillyl alcohol daily for six months, reduced 50% the size of tumors in 3.4% of adults with malignant gliomas (da Fonseca et al., 2008a, 2008b).

Conclusively, although sometimes inconsistent, the naturally occurring Chios mastic or individual terpenic components are many hoped for application as chemotherapeutic agents. The first report to display a promotion potential of Chios Mastic Gum on the formation of preneoplastic lesions comes from Doi et al., (2009). In a rat liver medium-term carcinogenesis bioassay, orally administered mastic of 1% apparently promoted GST-P foci yield after DEN-initiation but the 0.1% dose (48.3 mg/kg/day) was concluded as non-promoting dose. This 0.1% dose is almost equivalent to 2.9 g/day/person with the average human body weight regarded as 60 kg. Most Chios mastic doses previously reported in human studies were around this level, e.g. 5 g/day/person (Triantafyllou et al., 2007), 4 g/day/person (Bebb et al.,2003), 2.2 g/day/parson (Kaliora et al., 2007a, 2007b), or 1 g/day/person (Al-Habbal et al., 1984). Favorable effects of mastic such as anticarcinogenic potential could be achieved at relatively low doses without any toxicity (He et al., 2006). Further studies must elucidate the mechanisms underlying and determine safety levels in humans.

2.2 Mediterranean herbs and cancer chemoprevention

In herbal medicine the term herbs is used to refer not only to herbaceous plants but also to bark, roots, leaves, seeds, flowers and fruit of trees, shrubs, and woody vines, and extracts of the same that are valued for their savory, aromatic, or medicinal qualities. The botanical term herb refers to seed-producing plants with non-woody stems that die down at the end of the growing season (Craig, 1999).

Herbs have been grown and used for culinary and medicinal purposes since antiquity. The Mediterranean basin has been distinguished throughout the generations with a rich

inventory of natural medicinal herbs and it is the place in which the sience of botany was born. Oregano (*Origanum vulgare*), Sage (*Salvia officinalis*), Thyme (*Thyumus vulgaris*), Saffron (*Crocus sativus*), Rosemary (*Rosmarinus officinalis*), Savory (*Satureja hortensis*), Bay Laurel (*Laurus nobilis*), Basil (*Ocimum basilicum L.*), Chamomile (*Marticaria chamomilla*), Dittany of Crete (*Origanum dictamnus*), Marjoram (Origanum *majorana),* Rosemary (Rosmarinus *officinalis),* Sideritis (Sideritis *syriaca),* Hypericum (*Hypericum perforatum),* Pennyroyal *(Mentha pulegium),* Olive (*Olea europaea*), Anise (*Pimpinella anisum*), Coriander (*Coriandrum sativum*), Garlic (*Allium sativum*), Fennel (*Foeniculum vulgare*), Garden cress (*Lepidium sativum*), Lavender (*Lavandula angustifolia*), Myrtle (*Myrtus communis*), Nigella (*Nigella sativa*), Sumac (*Rhus coriaria*) are some of the generally considered as native Mediterranean herbs. Herbs are used as flavorings and seasonings, for the preservation and storage of various foods and help to maintain their organoleptic properties. In most of these herbs, the flavor is provided by the aromatic ingredients in their essential oils and oleoresins (Craig, 1999). They are also used for the treatment of headaches, neuralgia, gingivitis, toothaches, tonsillitis, sore throat, common cold and against cough. Cultures throughout history have practiced the art of pain management through remedies such as oral ingestion of herbs.

Hereby are cited indicative examples of some herbs and some of the healing properties attributed to them:
Basil (*Ocimum basilicum L.*): antispasmodic, diuretic, laxative, auxiliary for memory
Bay Laurel (*Laurus nobilis*): tonic, appetizer
Rosemary (*Rosmarinus officinalis*): antiseptic, antirheumatic, tonic
Dittany (*Origanum dictamnus*): emmenagogue, tonic, healing
Thyme (*Thymus vulgaris L.*): antispasmodic, antiseptic, antirheumatic
Oregano (*Origanum vulgare)*: expectorant, antispasmodic, disinfectant
Sage (*Salvia officinalis L.*): against hypotension and anemia, antidiabetic
Chamomile (*Marticaria chamomilla*): soothing, anti-insomnia, against flu

In the past it was not known the exact way of activity of herbs and their healing properties recorded empirically. Those properties provoked the interest of researchers to conduct numerous studies in order to verify these observations and to ascertain the responsible substance for these properties. Today it is known that the properties of medicinal plants owned to chemical compounds that they contain, termed phytochemicals, with antioxidant, anti-inflammatory, anti-bacterial, anticancer and cardioprotective properties. Today much of scientific research has been focused on investigating the possible use of medicinal plants for prevention, cure and/or adjunctive treatment of chronic diseases such as cancer.

Several commonly used herbs have been identified by the National Cancer Institute as possessing cancer-preventive properties (Caragay, 1992). Many studies showed that many phytochemical compounds of herbs of the Mediterranean basin, gained the "food-borne anticarcinogens" title. These beneficial substances act as antioxidants and electrophile scavengers, stimulate the immune system, inhibit nitrosation and the formation of DNA adducts with carcinogens, induce phase I or II detoxification enzymes, act on intracellular signalling network molecules involved in the initiation and/or promotion of cancer, interrupting thus or reversing the carcinogenesis process (Bisset, 1994; Robbers et al., 1994; Cuvelier et al., 1994; Armata et al., 2008; Saddiqe et al., 2010; Lee et al., 2011).

Thyme (*Thymus vulgaris*), Rosemary (*Rosmarinus officinalis*) and Sage (*Salvia officinalis L.*) have phenolic compounds (phenolic diterpenes, flavonoids and phenolic acids) that are able

to inhibit cancer, through inhibiting the initiation, as well as tumor progression (Craig 1999; Ho et al., 2000). Sideritis or "mountain tea" (*Sideritis syriaca, Sideritis clandestina*), Hypericum (*Hypericum perforatum*) and sage (*Salvia officinalis L.)* contain polyphenols (chlorogenic acid, apigenin, protocatechuic acid, caffeic acid, rosmaric acid, carnosol, qerqetin, luteolin, apigenin, p-coumaric acid, hypericine, geraniol, α-pinene, β-pinene) with anti-inflammatory and antioxidant properties (Saddiqe et al., 2010; Armata et al., 2008; Lu & Foo, 2001; Thorsen & Hildenbrandt, 2003). Carnosol has been evaluated for anti-cancer properties in prostate, breast, skin, leukemia, and colon cancer with promising results (Jonhson, 2011).

Fig. 4. **A:** Oregano (Origanum vulgare), **B:** Dittany of Crete (Origanum dictamnus), **C:** Vogel (Origanum microphilum), **D:** Thyme (Thymus vulgaris), **E:** Pennyroyal **(**Mentha pulegium), **F:** Hypericum (Hypericum perforatum).

Methanol extract of Olives (*Olea europaea*), rich in phenolic compounds, exhibits gastric cancer preventive efficacy by limiting cell proliferation, inducing cell death and suppressing inflammation in AGS cancer cells (Kountouri et al., 2009). Chamomile (*Marticaria chamomill*) and Oregano (*Origanum vulgare*) show antimicrobial activity against Helicobacter pylori, a Gram-negative bacteria that infects the stomach and strengthens the chances of stomach cancer (Stamatis et al., 2003; Bampidis et al., 2006; Couladis et al., 2003).

Many studies have been reported to that phytochemicals from herbs interfere at the initiation of cancer. In vitro studies with cancer cell lines, showed that oregano extract protect against oxidative stress and DNA damage from radiation (Rao et al., 2006; Bakkali et

al., 2006). Additionally, oregano extract was found to have strong antioxidant activity, through the capture free radicals, suppression of fat oxidation, inhibition of NOS and protection of DNA from H_2O_2-induced oxidative damage (Zheng & Wang, 2001; Aherne et al., 2007; Tsai et al., 2007). The components which are responsible for this activity are carvacrol, the terpene rosmarinic acid, glycosides of protocatechuic acid and thymol (Karioti et al., 2006; Braga et al., 2006). Several phytochemicals inhibit tumor formation by stimulating the protective phase II enzyme, glutathione transferase. GT is a detoxifying enzyme that catalyzes the reaction of glutathione with electrophiles to form compounds that are less toxic, more water-soluble, and can be excreted easily. Mice fed with a diet containing thyme (*Thymus vulgaris L*, 0.5% or 2.0%) or treated orally with thymol (50-200 mg/kg) or carvacrol (50-200 mg/kg) once a day for 7 successive days, showed a significantly increased in GT protein levels (Sasaki et al., 2005). Similar results were observed when rosemary extract or carnosol alone were administered in female rats (Singletary, 1996). Limonene, geraniol, menthol, and carvone found in commonly used herbs stimulate also glutathione transferase activity (Craig, 1999).

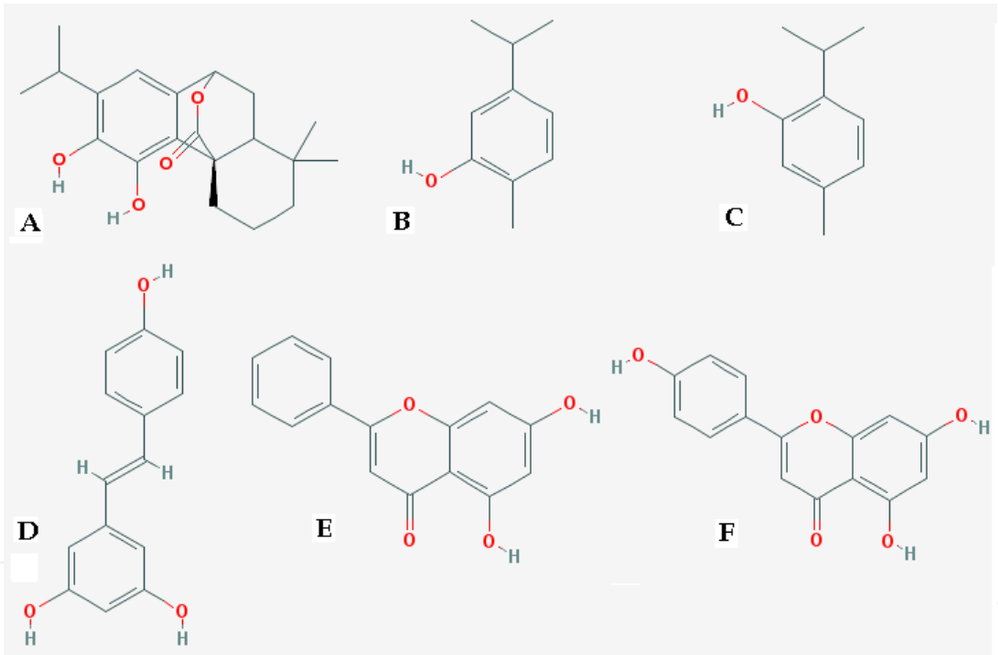

Fig. 5. Chemical structure of the terpenes **A:** carnosol, **B:** carvacrol, **C:** thymol and polyphenols **D:** resveratrol, **E:** chrysin and **F:** apigenin founds in many herbs.

Herbs phytochemicals have gained also the "suppressing agents" title. Inhibition of tumor cells proliferation has been highlighted in several studies that have been done on herbs, or on isolated components of them; nevertheless, the precise mechanism of action is not fully defined. Carnosol and thymol from oregano can inhibit the proliferation of cancerous cells or cells with active oncogenes (Sasaki et al., 2005; Slamenova et al., 2007; Mezzoug et al., 2007). Carnosol, also found in large quantities in dittany and in thyme, can inhibit the proliferation of breast cancer cells by 50% after incubation for 48h in a concentration of 100μM, by inducing apoptosis (Arunasree, 2010). An in vivo study of Moran et al. (2005) showed that dietary carnosol (0.1%) decreased APC associated adenoma formation by 46%

in the C57BL/6J/Min/+ (Min/+) mouse when compared to controls. Also, carnosol induces G2/M cell cycle arrest that targets cyclin A and cyclin B1 with an IC50 of 23 μM in Caco-2 colon adenocarcinoma cells which are representative of precancerous lesions (Visanji et al., 2006). Additional in vitro work has shown that carnosol significantly inhibited the highly metastatic mouse melanoma B16 cells through down regulation of matrix metalloproteinase 2, c-jun, as well as the redox sensitive transcription factor nuclear factor-kappa B (Nf-κB) (J.J. Johnson et al., 2008). Also, J.J. Johnson et al. (2008) shows that carnosol promoted G2 cell cycle arrest of PC3 cell line, with inhibition of cyclins A, D1, D2 and cdks 2 and 6, and targets multiple signaling pathways that include the AMPK and PI3K/Akt pathway. Resveratrol and chrysin can inhibit the proliferation of Caco-2 cells after 72h incubation when administered in combination at concentrations of 20 mM and 32 mM, respectively (Iwuchukwu et al., 2011). The effect of resveratrol to inhibit cell proliferation, has been reported previously and found to be associated with the remaining cell cycle arrest at phases S and G2/M through inhibition of Cdk7 and p34Cdc2 (Joe et al., 2002; Estrov et l., 2003; Liang et al., 2003). Similar results were reported by Jin et al. (2010) on the activity of total polyphenols from tea in cell lines of colon (IT29, LoVo, SW480, HCT116). The inhibition of cancer cell proliferation from those phytochemicals was positive correlated with the incubation time (24h-1w) and the dose administered (50-300 mg). Farnesol and geraniol, and to a lesser extent perillyl alcohol, found in spearmint (*Mentha spicata*), substantially suppressed the growth of pancreatic, colon, murine leukemia, hepatoma and melanoma tumor cells (Burke et al., 1997; Carnesecchi et al., 2001). Polyphenolics in green tea (Camellia sinensis) are known to possess antimutagenic and anticancer activity. Some evidence suggests that tea has a protective effect against stomach and colon cancers (Dreosti, 1996). The way of which tea polyphenols inhibit cell proliferation has been elucidated. More specifically, EGCG reduces cell proliferation by inhibiting enzymes that catalyze reactions of DNA replication. EGCG inhibit proteasome be forming ester bonds with it, resulting in accumulation of p27KIP1 and arrest of cell cycle in G1 phase. Additionally, EGCG induces the cyclin kinase inhibitor WAF1/p21 resulting cells arrest in phase G0/G1 (Syed et al., 2007). Also, a recent study found that genistein inhibits the proliferation of prostate cancer cells after incubation for 72h at three different concentrations (5 mg/mL, 10 mg/mL, 20 mg/mL) (Peternac et al., 2008). The essential oil of Rosemary, caused 50% inhibition of tumor cells proliferation, at breast and prostate cancer, after 24h incubation at concentrations of 190 and 180 mg/mL respectively (Hussain et al., 2010). The petroleum ether extract of Hypericum adenotrichum Spach (called "kantaron" in Turkey), a member of Hypericum perforatum genus that grows to Western Turkey, showed antiproliferative effects in HL-60 promyeloic leukaemia cells, which correlated with cyclin D1 suppression and p21 induction (Ozmen et al., 2009). Also, methanol extract of Malva Silvestris rich in phenolic compounds, inhibited cell proliferation of B16 and A375 melanoma cell lines (Danilea et al., 2007).

Many studies shows that extracts of oregano and its components have anti-inflammatory properties, as they suppress inflammation in vivo and in vitro. Braga et al. (2006) found that thymol at a concentration of 2.5-20 mg / mL inhibits the release of elastase, a marker of inflammation, by human neutrophils after stimulation with a chemotactic peptide. Resveratrol can inhibit in vitro the expression of IL-8 in monocytes stimulated with PMA (Shen et al., 2003). Additionally, resveratrol and quercetin, found that they can inhibit the secretion of IL- 8 in stimulated with IL-1 tumor cells in the liver (Gauliard et al., 2008). The

apigenin, a flavone, also displays the ability to reduce secretion of IL-1b, IL-8 and TNf-α in monocytes stimulated with LPS (Nicholas et al., 2007). Zhou et al. (2004), studying the effect of hyperforins, one of the phytochemicals contained in the sedge, found that it induce gene expression of IL-8 in intestinal epithelial cells and in leukemia cells by a mechanism independent of the NF-κB. The ability of polyphenols to inhibit the secretion of IL-8 was confirmed in another study which found that ellagic acid, chrysin, genistein and EGCG can reduce significant levels of secretion of IL-8 cell line of bowel cancer (Romier et al., 2008). Carnosol can inhibit enzymes involved in the development of inflammation (5-LOX, COX-2, NOS, etc.) affecting various signaling pathways. The anticancer action has been studied in various cancers (eg prostate, breast, skin, leukemia, etc.) with encouraging results (J.J. Johnson, 2011). Apigenin, chrysin and kaempferol can suppress COX-2 transcription by mechanisms including activation of the PPARg transcription factor (Liang et al., 2001). Curcumin inhibited COX-2 activities through suppression of NF-κB activity via control of the NIK/IKK signaling complex in colon cancer cells (Plummer et al., 1999). Phenylethyl isothiocyanate in winter cress (*Barbarea vulgaris*) showed a strong anti-inflammatory activity by reducing the level of iNOS mRNA in LPS-stimulated mouse RAW264.7 macrophages (Ippoushi et al., 2003). Gingerol inhibited nitric oxide synthesis in activated J774.1 mouse macrophages and prevented peroxynitrite- induced oxidation and nitration reactions in macrophages (Chen et al., 2003). Polyphenols from green tea inhibit STAT3 expression, a transcriptional factor, and prostate cancer growth and subsequently induce apoptosis of prostate cancer cells (Siddiqui et al., 2008). Resveratrol modulates IL-6-induced intercellular adhesion molecule-1 (ICAM-1) gene expression by suppressing STAT3 phosphorylation (Wung et al., 2005). Some of the phenolic components containing herbs have been evaluated on their ability to affect the activation of NF-KB, and its commitment to the positions 'target' in DNA. More specifically, the chrysin and ellagic acid reduce the activation of NF-KB in Caco-2, which had previously stimulated with either LPS, IL-1, or with TNF-a (Romier et al., 2008). Additionally, chrysin (3 mmol/L) was found to reduce the activation of NF-KB in stimulated by TNF-a A549 human lung adenocarcinoma epithelial cell line. In contrast to the above, the chrysin caused increased binding capacity of this transcription factor to DNA, but also led to increased activation when administered to mouse macrophages that had undergone stimulation with LPS (Woo et al., 2005). Conflicting results were also studying the action of two other phenolic compounds, genistein and resveratrol. Both compounds appear to induce the activation of NF-KB in stimulated either with LPS, IL-1, or TNF- a Caco-2 colon cells (Romier et al., 2008). However, regarding genistein, Li et al. (2005) demonstrated the ability to reduce the activation of NF-KB in PC3. Also, resveratrol was found to reduce the activation of this molecule in U937, HeLa, and H4 (Holmes-McNary et al., 2000; Manna et al., 2000). Moreover, a study of the effect of resveratrol on TNF-a stimulated MCF7 cells, showed that it prevents the binding of NF-KB to DNA (Banerjee et al., 2002). Another phenolic molecule has been extensively studied is EGCG, which was found to inhibit the activation of NF-KB in cancer cell lines A431 (Gupta et al., 2004) and LNCaP (Hastak et al., 2003). One interpretation proposed to explain the contradictory results of the effect of polyphenols on levels of activation of NF-KB in cell lines of colon balances have studied is that there are probably different signaling pathways responsible for activation of NF-KB as response to various phenolic compounds. This diversity of cells in the intestinal epithelium may be associated with prolonged exposure to high concentrations of polyphenolic components in relation to blood cells and other organs are exposed to comparatively lower concentrations (Romier et al., 2008).

Historical and current studies and surveys indicate, that the region of the Mediterranean has been distinguished throughout generations with a rich inventory of natural medicinal herbs. By expanding upon the wisdom of the Greeks over the centuries, indigenous medicine has contributed greatly to the development of modern medicine in Europe and remains one of the closest forms of original European medicine. A diet in which culinary herbs are used generously to flavor food, provides a variety of active phytochemicals that promote health and protect against chronic diseases such as cancer. Charlemagne was correct when he said "a herb is a friend of physicians and the praise of cooks". Nevertheless, whereas some herbal products may be safe and may contain active constituents that have beneficial physiologic effects, others may be unsafe to use. The Food and Drug Administration has classified several herbs as unsafe, even in small amounts, and hence they should not be used in either foods or beverages (Craig, 1999). Some herbs are safe in modest amounts but they may become toxic at higher doses. Overall, when herbs are prescribed appropriately, the safety of traditional herbal medications is high. Any plant parts used or prescribed by ethnopharmacologists should be tested for safety before being recommended for human use.

3. Conclusion

Although there is a lack of definitive evidence for the association of Mediterranean diet with various types of cancer and whatever the final assessment of the overall contribution of such diets to cancer prevention turns out to be, there is no doubt that the phytochemicals they contain do exert a range of fascinating and potentially important biological effects on human health. Over the last decade, a broad spectrum of plant natural compounds, that have gained much attention for consideration as cancer chemopreventive or therapeutic agents, has been isolated from traditional herbal medicines, spices, fruits, and vegetables. These plant secondary metabolites as medicines, dietary supplements or "health food" ingredients may exhibit considerable benefits over synthetic drug approaches, as they offer an inexpensive, convenient, readily applicable and accessible health-care approach for prevention, control and management of diseases such as cancer. The continued emergence of new evidence for the multifunctional effects of these products has certainly provided much impetus for future research into their modes of action and their application in cancer prevention and treatment. Advances in cellular, biochemical and molecular biology techniques and experimental approaches using transcriptome, proteome, metabolome and bioinformatics analyses have provided useful new insights into cancer therapeutics.

One obvious weakness of the current state of research, is that much of it has been conducted in vitro, with little regard for the bioavailability of the compounds studied. In most cases the small proportion of any compound that is absorbed undergoes extensive metabolism before reaching target organs, and the products are readily excreted. In the future, long-term systematic intervention trials, that will take into consideration the bioavailability and metabolism of those phytochemicals, will be essential to gather good evidence of their anticancer potential. Such strategies will contribute to a full risk–benefit analysis, based on a thorough understanding of their overall biological effects. With the expected advances in our understanding of the specific signaling pathways, transcription factors and molecular target genes affected by chemopreventive plant compounds, these natural products will offer a great promise as anticancer therapeutics or chemopreventive agents. Moreover,

further development of these potent natural products will improve the efficacy of targeted therapeutic strategies to win the long run battle against cancer.

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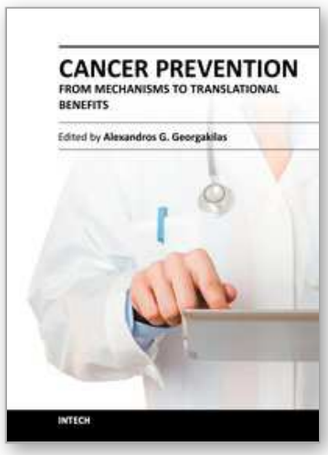

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