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Cancer chemoprevention by nuts: evidence and promises

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1. ABSTRACT

Chemoprevention is the use of chemical compounds to interfere with the early precancerous stages of carcinogenesis and thereby reverse tumor formation. Many chemopreventive agents, either natural or synthetic, have been identified. Some of the most promising compounds are found in vegetables and fruits. There are numerous mechanisms of action by which these components can intervene in the prevention of cancer, although they have not been fully elucidated. It is worth to note that some foods contain different bioactive compounds. Therefore the possibility exists that combinations of compounds, naturally occurring in those foods, may have a cumulative or even synergistic effect. Nuts are very rich in different bioactive compounds whose anti-cancer properties have already been described. Epidemiologic studies have already suggested that nuts consumption may be potentially beneficial in the incidence of other diseases, such as coronary heart disease and diabetes. Although the results are not conclusive, recent studies show possible cancer protective effects of nuts. This review will focus on the laboratory and clinical evidence of nuts chemopreventive and therapeutic properties.

2. INTRODUCTION

Nuts have played a key role in human diet, since our ancestors relied largely on hunting and picking to satisfy their feeding needs and their diet was largely vegetarian (fruit, whole cereals, seeds, roots and nuts). Even nowadays, the few primitive cultures still existing consume essentially foods from vegetal origin (50-70%). Some anthropologists recently suggested that the traditional Paleolithic diet composed of cereals, roots, legumes, nuts, tubers, fruit and game, very likely had a protective effect against cardiovascular and other degenerative diseases (1), even though, because of the adverse living conditions, diseases and dangers, the average lifetime of humans in those days was obviously much lower than the expected length we have today. For centuries nuts consumption has been a constant habit on people's tables, also because it was a cheap, energetic, proteic, alternative food, easily available during difficult times. Later on, following the prosperity of the west modern society, attention started to be paid to the importance of food in human's health. In 1970, the USDA (US Department of Agriculture) published guidelines advising to consume alcohol, sweets and fat foods with moderation. As a consequence nuts, which are

known to be very rich in total fat, were considered for some decades food to avoid. On the contrary, according to epidemiological studies and clinical trials, not only there is not any association between nuts consumption and weight gain (2), but there is evidence that omega 3 fatty acids may prevent obesity (3,4). Still in 1992, the first food guide pyramid made a number of misleading claims including the "all fats are bad" one, which became quickly common knowledge. In this pyramid, nuts were included in the fat proteic food section along with meat, eggs, fish, poultry and dry beans, which had to be limited to 2-3 servings per week. Only in the last 10-15 years, thanks to the scientists' interest in nuts and to the numerous studies in this field, there has been a revaluation of the role of nuts in human nutrition. A neat distinction between saturated and unsaturated fats has emerged. Saturated fats, contained in fatty meats, meats products, processed food and dairy aliments, are believed to raise low density lipoproteins (LDL) cholesterol and so to be partly responsible for cardiovascular diseases; they should not exceed 10% of our diet. On the contrary, mono and poly unsaturated fats, with a few exceptions, have the ability to diminish LDL cholesterol, helping to prevent cardiovascular diseases. Nuts, together with seeds, avocados, olive oil and oily fish such as salmon, fresh tuna and mackerel, are very rich in unsaturated fatty acids. In the new food pyramid, launched by USDA in 2005 and called MyPyramid, importance was put particularly on physical activity, and nuts, together with beans, peas and seeds, were considerate food alternative to low fat and lean meat such as fish, recommended 3-5 portions per week. Recently, there have been a large number of studies related to diets high in nuts and peanuts (although peanuts are classified as legumes they may be considered nuts from a nutritional point of view), particularly regarding their role in protecting against cardiovascular disease. As a consequence, there are sufficient evidence to indicate that nuts and nut-containing products help cardiovascular health, as claimed by the United State Food and Drug Administration (5). Therefore, both epidemiological studies and controlled clinical trials demonstrate the beneficial effect of nuts consumption on cardiovascular disease. On the contrary, only a few studies have been currently conducted to investigate the role of nuts in cancer prevention and the attention has been focused mainly on colorectal, breast, prostate, liver and lung cancer. The aim of this review is to discuss the existing evidence about chemopreventive properties of nuts and to support the hypothesis that different bioactive compounds contained in nuts can act in synergy preventing tumor development. For this purpose, we examine the phytochemicals composition of nuts and their possible chemiopreventive mechanisms of action and we review the main epidemiological and experimental studies concerning the effect of nuts on different types of cancers.

3. EFFECT OF NUTS ON CARDIOVASCULAR AND OTHER DISEASES

The role of nuts in protecting against coronary hearth disease (CHD) is widely recognized. Four major epidemiological studies have shown an average of 37% reduction of CHD deaths as a result of the introduction of nuts consumption in the diet (6). This benefic effect is mainly attributed to the fatty acid profile of nuts, which is made by more than 75% of monounsaturated fatty acids (MUFA). This is thought to be able to improve blood lipid levels (6), lowering CHD risk. Moreover, nuts provide additional non-lipid bioactive compounds that have been recently considered to contribute to the reduction of CHD risk, such as tocopherol, squalene and phytosterol (7). Scientific evidence of a positive effect of nuts on a number of other chronic diseases has been reported. Nuts intake has been proved to be inversely related to body mass index and adiposity (8), while frequent nuts consumption does not induce weight gain (9,10). Similarly, epidemiological studies have demonstrated that a Mediterranean diet enriched with nuts supplements have a positive effect on Metabolic Syndrome (11), which includes symptoms such as abdominal obesity, high blood pressure, hyperglycemia and dyslipidemia that are known to cause cardiovascular disease. Some studies have also shown the potential beneficial antioxidant effect of nuts (12) and their potential protective effect against inflammation, insulin resistance and type 2 diabetes in women (13,14,15). Since increasing evidence is emerging that links most chronic diseases and cancer to oxidative stress and incorrect inflammatory response, bioactive compounds contained in nuts are similarly good candidates in the prevention of such diseases.

4. CANCER AND CHEMOPREVENTION

During the last century, along with a rise in life expectancy and a shift in the major cause of death from infectious and preventable conditions to the degenerative diseases of old age (16), we have witnessed an increasing growth of cancer as a global health problem. The World Health Organization has recently estimated that there are more than 10 million cases of cancer around the world every year (17). On the other hand, in the last decades, there has been a decrease in the mortality rate for cancer in European countries (18,19) and, more interestingly, in the incidence of this disease in the population, clearly due to the introduction of some preventive actions. Lifestyle has been proven to have a big impact in human cancer occurrence, together with diet, that it is believed to be responsible for 10-70% of cancer mortality (20). While the existence of many dietary substances capable to increase the risk of developing cancer (carcinogens) is well known, it has also been claimed that other dietary constituents have a positive impact in prevention of specific cancers. There are three stages that can be recognized in cancer development: a first stage of "initiation", when a single cancer cell or multiple individual cells appear in a tissue exposed to a carcinogen; a second stage called "modification", during which cancer cells multiply; and a third stage of "progression" in which it is believed that further genetic changes leading to malignancy occur (21). Cancer chemoprevention is defined as the use of natural or synthetic compounds to prevent or delay the early precancerous stages of carcinogenesis (17). These compounds include for instance anti estrogen drugs such as tamoxifen, which has been shown to reduce the incidence of breast cancer. Other examples comprise dithiothiones,

which are potential chemopreventive agents naturally occurring in broccoli and cauliflower (22). Furthermore, a number of epidemiological studies confirmed that phytochemicals such as carotenoids and flavonoids, decrease the risk of colon cancer (23,24). Curcumin is under investigation in pancreatic cancer and it has already shown some positive results as coadjuvant of standard chemotherapy (25). Three different types of chemoprevention have been proposed (16). Primary prevention, which is addressed to healthy individuals, aims at the inhibition of cancer initiation and mutation by activating protective mechanisms. Secondary prevention, when a premalignant lesion has been detected, aims at the inhibition of tumor progression via protective mechanism, and by affecting the hormonal status, the immune system and the tumor angiogenesis. Tertiary prevention, which is addressed to cancer patients after therapy, aims at the inhibition of cancer spread and metastasis formation (16). According to this, chemopreventive agents can be divided into two main categories: blocking agents, that inhibit tumor initiation, and suppressive agents, that prevent the progression of cancer (26). Many phytochemicals contained in food and nuts can act either as blocking agents (ellagic acid, flavonoids, indole-3-carbinol, sulphoraphane), or suppressing agents (betacarotene, curcumin, resveratrol, inositol pentakiphosphate and inositol hexakisphosphate, genistein, epigallocatechin 3-gallate, [6]-gingerol, capsaicin), against cancer.

5. PHYTOCHEMICAL COMPOSITION OF NUTS AND POSSIBLE CHEMOPREVENTIVE MECHANISMS OF NUTS COMPONENTS

Phytochemicals are 'non-nutritive' substances which are found in plants (27). There are more than 5000 different phythochemicals contained in vegetables, fruit and grain already identified and it is believed that a higher number of them is still unknown (28). Dietary phytochemicals are classified as: carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulfur compounds, the first two groups being the most studied. Carotenoids are pigments contained in plants, microorganisms and animals and in a wide range of orange vegetables and fruits. They have a provitamin and antioxidant effect. Phenolics are substances derived from plants' secondary metabolism and they can be divided into phenolic acids, flavonoids, stilbenes, coumarins and tannins. They are found mainly in cranberry and broccoli, but also in apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, grapefruit (29), spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery and cucumber (30). Epidemiological studies have shown that phytochemicals play strong part in reducing not only cancer and cardiovascular diseases, but also other chronic diseases (31-33). However, it is likely that the balanced combination of phytochemicals naturally present in fruit and vegetables is responsible for these preventive effects (28,34-37). Trials conducted on single antioxidant did not result in the same positive outcome. As an example, in clinical studies, B-carotene supplement given to patients did not affect the incidence of malignant neoplasms such as non-melanoma skin cancer and lung cancer (38), although cancer risk was proven to be inversely related to consumption of B-carotene containing fruit and vegetables. It should be also considered that the dose used in studies on animal models is so high that it is very unlikely that humans would eat these amounts of compounds within a regular diet (39). For these reasons, it is widely recommended to rely on the contribution of a large variety of foods, which contain a balance combination of phytochemicals, to improve nutrition and health, and not on expensive dietary supplement. Furthermore, when considering the potential beneficial properties of a compound it is necessary to take into account its absorption and bioavailability. For this reason, before transfer results obtained from in vitro and in vivo studies to humans, it should be carefully considered the dosage used and the fact that compounds are purified. For instance several data are now available on resveratrol bioavailability and toxicity in humans, but the conclusions are discordant (40). Indeed, it is yet to be clarified the exact nature of endogenous metabolite and their biological properties, as well as the precise distribution of resveratrol within tissues and cells (40). Previous attempts to measure resveratrol bioavailability have used resveratrol contained in wine or other metabolites as biomarker of wine consumption. This approach does not consider the concomitant absorption of other polyphenols and alcohol that may interact with resveratrol action, making difficult the identification of resveratrol-specific effect.

5.1. Phytochemicals composition of nuts

Nuts are a peculiar, complex food group containing a high percentage of total fat (from 44 to 72 g/100g), most of which are monosaturated, mainly oleic acid and palmitoleic acid, and polyunsaturated fatty acids, the most common being linoleic acid and linolenic acid (7,41). In addition, they are rich in different macro and micronutrients and others bioactive components such as vitamins and minerals, selenium, magnesium, folic acid, tocopherol, squalene, fibers, proteins, and antioxidants. But what appears to be more interesting is their phytochemical composition and the antioxidant, antinflammatory and anticarcinogenic role that these bioactive compounds may play, in synergy with the others constituents, in the prevention of chronic diseases and cancer (7,42,43). The most common phytochemicals present in nuts are from the families of phytosterols, carotenoids, phenols and inositol polyphosphates (Figure 1). Phytosterols, contained in the fatty part of nuts, are sterols similar to cholesterol. Their concentration (in mg/100g) is: 280 in pistachios, 198 in pine nuts and macadamias, 187 in almonds, 150 in pecans, 138 in cashews, 120 in hazelnuts, 113 in walnuts and 95 in Brazil nuts (44). Phytosterols are believed to inhibit inflammation processes, to prevent the absorption of dietary cholesterol and therefore decrease serum cholesterol (45,46). Carotenoids, mostly contained in colorful fruit and vegetables and widely investigated for their anticancer properties, are present in some nuts only in low concentrations, i.e. in pistachios. Plant foods are a great source of phenols, including stilbenes, phenolic acids and flavonoids. In nuts, the highest content of phenols is found in walnuts (16.3 mg Gallic Acid Equivalent /g), pecans (12.8 mg/100g) and pistachios (8.7 mg/100g) (44).

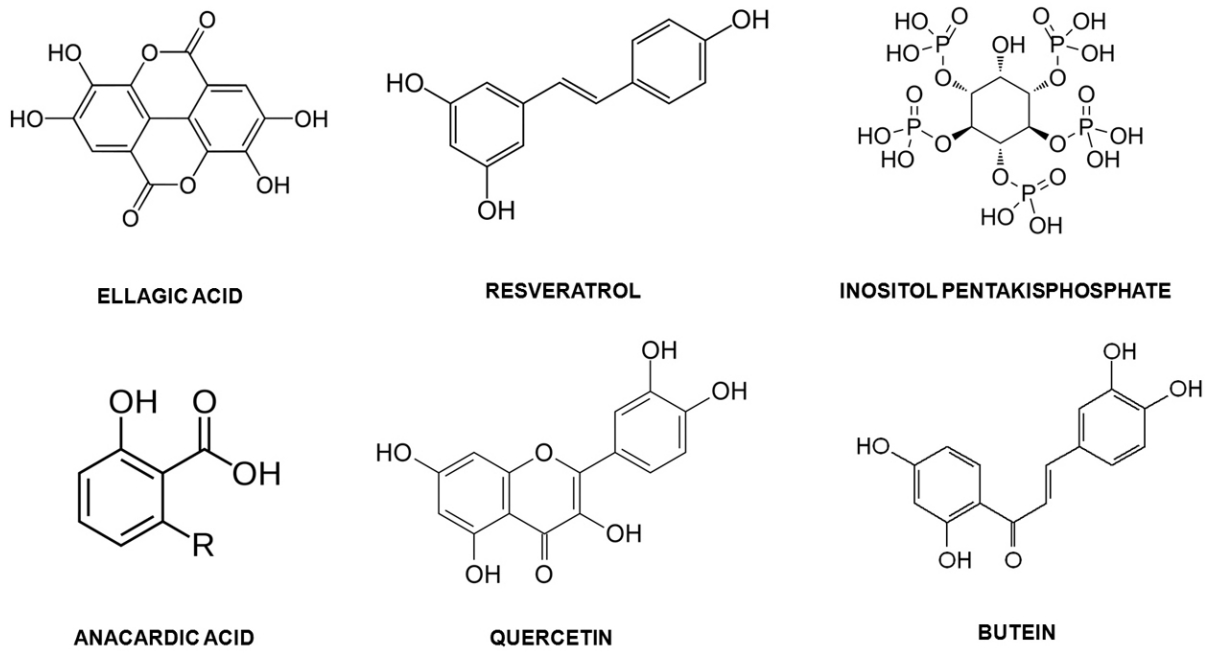

Figure 1. Chemical structures of main bioactive compounds contained in nuts.

Among stilbenes, resveratrol is one of the most studied. It is contained in grapes, berries, red wine, peanuts, pistachios and pine nuts. In addition to its capacity to prolong yeast and mice life span (47), it is considered to lower the incidence of hearth disease through red wine consumption, thanks to a phenomenon known as the "French Paradox" (48) and to have antinflammatory and anticarcinogenic properties. Flavonoids are polyphenols which can be divided into different subclasses: flavanols, flavanones, flavones, isoflavones, flavonols and anthocyanidins. They are contained in the vast majority of nuts, some of them (i.e. almonds), having the same amount as some fruit and vegetables. Pecans have 34 mg/100 g, almonds 15, pistachios and hazelnuts 12, while red delicious apples 15 and apricots 13 (49). Proanthocyanidins are found in high concentration in hazelnuts (501 mg/100g), pecans (494 mg/100g), pistachios (237 mg/100g), almonds (184 mg/100g) and walnuts (67 mg/100g) (50). They have been proven to be chemopreventive agents, as well as to reduce urinary tract infections and increase vascular reactivity. A new interesting class of bioactive compounds, also contained in nuts, is represented by inositol polyphosphates. Inositol hexakisphosphate (IP_6), also known as phytic acid, has anti-cancer action, although it requires very high concentration to be active (51). IP_6 and inositol pentakisphosphate (IP_5) have been reported to be present in several foods including cereals (52), beans and nuts at very high concentration (53). High levels of IP_5 have been found in cashews (150 mg/100g) and peanuts (60 mg/100g) (53). This is a large amount if we consider that resveratrol content in nuts is 0.002-0.179 mg/100gr (14) and 0.6-8 mg/L in red wines and still the beneficial effect of such foods are ascribed essentially to this compound. Furthermore, nuts contain IP_6 as well and its content is usually 4 to 10 times higher than IP_5. Interestingly, it has been reported that roasting decreased IP_6 concentration in nuts with a parallel increase in IP_5 levels (52).

5.2. Possible chemopreventive mechanisms of nuts components

The abnormal cell growth leading to tumor development can be affected by genetic, environmental and dietary factors. Unlike the vast majority of healthy cells, cancer cells develop many strategies that block or reduce the body ability to eliminate them. Moreover, they spread to sites distant to the primary tumor through a process called metastasis by invading the circulatory system, entering a new organ and subsequently creating a net of new blood vessels supporting the secondary tumor in a process called angiogenesis (54). These processes are regulated by cellular signals whose deregulation leads to abnormal cell cycle progression, altered cell motility and adhesion properties, induction of angiogenesis and inhibition of the process of programmed cell death (apoptosis) in cancer cells (54,55). One of the key pathways involved in these processes is the phosphoinositide 3-kinase (PI3K)/Akt pathway (56). Another key protein is the transcription factor nuclear factor kappaB (NF-kB), which activation can be stimulated by inflammation and several other factors (57). As a consequence, the possibility to modulate the activity of proteins involved in these pathways is probably crucial in the prevention of degenerative disorders including cancer. Although we know that many components of vegetables plants and nuts have anticancer properties, their mechanisms of action are still not completely understood. Some of the main potential cancer preventive mechanisms are listed below (Table 1).

Table 1. Bioactive compounds contained in nuts and potential mechanisms of action

Compound	Mechanism of action	Sources and concentration (mg/100g)
Phytosterols	Anti-inflammatory	Pistachios (280), pine nuts and macadamias (198), almonds (187), pecans (150), cashew (138), hazelnuts (120), walnuts (113), Brazil nuts (42)
Betacarotene	Anti-oxidant, anti-inflammatory, anti-angiogenic, pro-apoptotic, anti-metastatic	Pistachios (0.21)
Quercetin	Anti-inflammatory, pro-apoptotic, anti-metastatic	Almonds (NA), pine nuts (NA)
Ellagic acid	Pro-apoptotic	Walnuts (59), pecans (3.3)
Resveratrol	Anti-oxidant, anti-inflammatory, pro-apoptotic, anti-metastatic	Pistachios (0.115), peanuts (0.084)
roanthocyanidins	Anti-oxidant, anti-inflammatory	Hazelnuts (501), pecans (494), pistachios (237), almonds (184), walnuts (67)
Phytoestrogens	Anti-hormone	Hazelnuts (0.107), pistachios (0.382), chestnuts (0.21), walnuts (0.14), cashew (0.13),
IP_5,	Anti-angiogenic, pro-apoptotic	Cashew (150), peanuts (60), almonds, pecans, pistachios, pine nuts, macadamias, walnuts, Brazil nuts (NA)
Tocopherol α-γ	Anti-oxidant	Almonds (452), hazelnuts (371.3), walnuts (321.1), peanuts (148.2), macadamias (122.3) μg/g oil
Squalene	Anti-oxidant	Hazelnuts (186.4), macadamias (185), peanuts (98.3), walnuts (9.4), almonds (95) μg/g oil
Anacardic acid	Pro-apoptotic	Cashew (NA)
Folic acid	Anti-DNA damage	Chestnuts (0.11), hazelnuts (0.113), almonds (0.050), Brazil nuts (0.022), cashew (0.025), pistachios (0.051), pine nuts (0.034), walnuts (0.031), pecans (0.022), macadamias (0.011)
Selenium	Anti-oxidant	Brazil nuts (1.917), cashew (0.020), walnuts (0.017), pistachios (0.007), pecans (0.038), macadamias (0.036), almonds (0.025), hazelnuts (0.024)
Caffeic acid	Anti-proliferative, anti-metastatic	Cashew (NA), walnuts (NA)

5.2.1. Anti-oxidant action

It is well known that oxidative stress causes cellular alteration leading to carcinogenesis in animals and humans (58). Antioxidant compounds present in plants and nuts can inhibit cancer development probably because of the combined action of multiple agents contained in these foods (59). Antioxidant substances present in nuts are: selenium (a component of antioxidant enzymes), quercitin, resveratrol (60), tocopherols and squalene (7).

5.2.2. Anti-inflammatory action

It has been proved that inflammatory states are a cause of cancer development in humans (61-63). Some compounds found in nuts, such as quercitin and resveratrol, can reduce the inflammatory process (43,64), thus preventing inflammation-induced tumors (i.e. colorectal, stomach, pancreas and cervix).

5.2.3. Anti-hormone action

Natural compounds contained in plants with the ability to modify hormonal activity are called phytoestrogens. Isoflavonoids are phytoestrogens present in nuts, although their content is higher in soy. Since high level of some hormones have been shown to be a risk factor for certain types of tumor, such as breast, ovarian and prostate cancer (65,66) high consumption of phytoestrogens may reduce the risk of these tumors, according to epidemiological studies conducted on Asian population (67). Nevertheless more recent studies showed controversial results, some of which suggesting the hypothesis of an inverse relationship between soyfoods intake and breast cancer recurrence (68).

5.2.4. Anti-angiogenic action

Angiogenesis is the formation of new vessels from existing vasculature, a key process in tumor development. Preventing the formation of these newly formed blood vessels may be very important to inhibit tumor proliferation. An anti-angiogenic agent present in nuts, IP_5, has been recently demonstrated to be active both *in vitro* and *in vivo* (69-71). Similarly, resveratrol can inhibit new blood vessels growth in animals (72).

5.2.5. Anti-proliferation and pro-apoptotic action

Some nuts components, such as flavonoids (quercetin) and stilbenes (resveratrol and ellagic acid), are believed to modify molecular events in the early stages of cell tumor growth. In some *in vitro* studies these polyphenols have been shown to promote apoptosis in cancerous cells, to decrease carcinogenesis and stop cancer cell growth (73). Many phytochemicals, including anacardic acid and butein contained in cashew and IP_5 (70-74), have been found to promote apoptosis in cancer cells.

5.2.6. Anti-DNA damage action

Folic acid is an important component in the DNA process of synthesis and repair, and is found in nuts. Since it has been proved that a folate deficiency in the diet can increase the possibility of developing colorectal and possibly cervical tumor (59,67), a diet rich in folic acid may protect against diseases associated with DNA damage inducing cancer.

5.2.7. Anti-metastatic action

Tumor cell invasion is a key process in cancer development, strictly linked to metastasis formation and therefore to cancer progression (55). Among the many phytochemicals from natural origins, Beta-carotene, quercitin and resveratrol, all contained in nuts, have shown an anti tumor cell invasion action and the ability to inhibit metastasis (75,76).

6. STUDIES ON CANCER PROTECTIVE EFFECTS OF NUTS

One of the processes responsible for carcinogenesis is cell exposure to oxidant substances. These oxidant agents, which are found in the environment or are produced inside cells, are normally balanced by other antioxidants substances. In some circumstances,

disequilibrium can

Table 2. Epidemiological studies

Type of cancer	Results	Population	References
Colon	Benefits	European	81
Colorectal	Benefits (on female)	Taiwan	82
Endometrial	Reduced risk	Greek women	83
Prostate	Negative correlation Mild protective effect 31% reduction	59 countries Adventist men Canadian	84 85 86
Stomach	Protective effect Increased risk	Japanese Greek	87 88
Lung	Benefits	Multicentric	89
Skin	Benefits	Multicentric	90

Table 3. Experimental studies

Nut or phytochemical	Type of cancer	Results	References
Walnuts	Breast	< tumor growth	91
Resveratrol	Hepatocellular	< tumor cells proliferation > apoptosis	96
Caffeic acid	Hepatocellular	< tumor cells proliferation < tumor growth and metastases	97, 98
Ellacic acid	Hepatocellular Prostate	< tumor growth < tumor incidence	99 100
Quercetin	Lung Hepatocellular	< tumor growth < tumor growth	102 101, 103, 104
Squalene	Colon Lung Skin	< tumor growth < tumor growth < tumor growth	105
IP6	Mammary	< tumor cells proliferation > apoptosis < tumor cells proliferation	106, 107
IP5	Ovarian, Lung cancer,	> apoptosis, <angiogenesis, < tumor growth	69-71, 108
Butein	Bladder	<cell invasion	29, 110
Anacardic acid	Multiple	< tumor cells proliferation	33, 111

occur leading to oxidative stress which can damage lipids, proteins and DNA, increasing the risk of developing chronic diseases and cancer (58,77). Some dietary compounds are known to be carcinogens, including benzo[a]pyrene, found in charred meat and in cigarettes smoke (78). The introduction of dietary compounds, such as phytochemicals with antioxidant properties (29,79), can be helpful in preventing the effects of oxidant substances. As far as nut consumption is concerned, there are only few epidemiological studies on the anticarcinogenic effects of nuts intake (80). This is partly due to the fact that in the past twenty years studies have been mostly concentrated on colorectal cancer, and also because of difficulties in the interpretation of epidemiological data, since most of the studies on nuts were often associated with legumes and seeds (80).

6.1. Epidemiological studies

Recent prospective studies about the effects of nuts on colorectal and endometrial cancers have shown anticarcinogenic benefits in colon cancer (81) and colorectal cancer (82), but only in female population. There appear to be also a correlation between nuts intake and a reduced risk of endometrial cancer, according to a study on Greek women (83), although this study involved a low risk population for this type of cancer and nuts were associated with legumes and seeds. Three studies have analyzed the correlation between nuts intake and prostate cancer with promising although not conclusive results: the first study found a negative correlation (84), the second only a very moderate protective effect (85), whereas the third study discovered a 31% reduction of prostate cancer in a Canadian population, although nuts are once again mixed with legumes and seed (86). A study carried out in Japan in 1992 found a protective dose response effect against stomach cancer (87), while another study in a Greek population observed an increased risk, probably due to the habit of eating salted nuts in this country (88). Even though carotenoids are present only in small amount in nuts, they also possess anti-cancer properties in epidemiological studies (89,90) (Table 2). There are currently not sufficient data available to draw any conclusion on potential protective effects of nuts on other types tumor. Further epidemiological studies in this field are eagerly needed.

6.2. Experimental studies

Evidence of the chemopreventive role of components of nuts has been also shown in *in vivo* and *in vitro* studies (Table 3). A pilot study conducted on mice implanted with human breast cancer cells and fed with an 18% of dietary calories from walnuts, demonstrated a significantly slowing of the tumor growth (91). Several phythochemicals have been proved to have potential anti-cancer properties in hepatocellular carcinoma (HCC) such as resveratrol, caffeic acid and ellagic acid, contained in peanuts and nuts (92). Resveratrol has been widely investigated for its preventive role in cardiovascular diseases. Moreover, resveratrol is thought to be able to have a positive effect on a vast number of diseases related to inflammation, neurodegenerative illnesses, ischemic injuries, viral infections and cancer (93-95). Data emerging from numerous studies clearly show that this compound has a potential anticarcinogenic effect against HCC by

decreasing the tumor cells proliferation and increasing apoptosis, suggesting that it may be very effective both in prevention and in treatment of liver cancer (96). The polyphones caffeic acid and its derivate caffeic acid phenethyl ester (CAPE), have been demonstrated to decrease cell proliferation and viability in HCC in some *in vitro* studies (97-98) and to block invasion of HCC cells. In animal models, these compounds have revealed potential chemiopreventive role by stopping HCC and metastases growth in mice and rats (97). A potential antitumoral activity for another polyphenol, ellagic acid, has also been found in animal models. Indeed, ellagic acid has been found to have an inhibitory effect on N-2-fluorenylacetamide-induced liver carcinogenesis in rats and to decrease the incidence of prostate cancer in mice (99,100). Among flavonoids, quercetin, which is the most common dietary flavonoid and is found in nuts and many other foods, have been demonstrated to have an anticancer activity in animal models, by inhibiting lung cancer and HCC in mice (101,102). In some *in vitro* studies, quercetin has been shown to have an anticancer effect in human HCC cells (101,103,104). Squalene, which is a steroid precursor with antioxidant properties, is contained in olive oil, soybean oil and nuts (7). There is evidence that this compound can act as a chemiopreventive agent against chemically induced colon, lung and skin cancer in rodents (105). IP_6, is a phytochemical found in grains, seeds, beans and nuts. Together with its antioxidant action, IP_6 is known to decrease mammary cancer growth in animal models by inhibits proliferation and promoting apoptosis (106). In some *in vitro* studies IP_6 has been demonstrated to stop breast cancer cell proliferation in human cell lines (107). Another very interesting bioactive compound present in wheat bran, legumes and nuts at very high concentration (108), is IP_5. It has been recently proved that this substance plays a role as anti-tumor agent in mice and that it enhances the effect of cytotoxic drugs in ovarian and cancer cells (69-71,108). For these reasons IP_5 may be useful as a coadjuvant to the action of commonly used anti-cancer drugs. Indeed among the different inositol polyphosphates tested, IP5 specifically showed pro-apoptotic properties and was more active than IP_6 (69-71). More recently, by using a Kinase profiling assays on almost 60 different kinases, it has been reported that IP5 potently and specifically inhibits a key enzyme in the PI3K/Akt pathway 3-phosphoinositide-dependent protein kinase 1 (PDK1) *in vitro* and the PDK1-dependent phosphorylation of Thr308 Akt in cell lines and *in vivo* (109). Taking into consideration the amount of IP_5 present in food and their regular partake, it appears that this phytochemical has a potential as a chemopreventive agent. Therefore the consumption of IP5–containing food may have cancer chemopreventive effects in human cancer. Another interesting bioactive compound is Butein (3,4,2',4'-tetrahydroxychalone), a plant polyphenol, that has potent effects against various types of cancer cells (29). Butein is able to inhibit migration and invasion in human bladder cancer cell through NF-kB signaling pathways (110). Anacardic acid (2-hydroxy-6-alkylbenzoic acid), is a dietary and medicinal phytochemical contained in cashew nuts with established anticancer activity in cell and animal models (33, 111). The mechanisms by which anacardic acid inhibits cancer cell proliferation remain undefined. Recently, it has been shown that anacardic acid inhibits cell proliferation, cell cycle progression, and apoptosis in an estrogen receptor (ER)-dependent manner by reducing ER-DNA interaction and inhibiting ER-mediated transcriptional responses (112).

7. PERSPECTIVE

Despite the important advances in our understanding of the mechanisms responsible for the malignant transformation during the last few years, only little progress has been achieved in decreasing the risk to develop cancer. Nevertheless, new strategies have been developed to limit the appearance or the development of cancers through respectively the chemoprevention and the chemosensitization to conventional therapies. Among the different molecules able to act both as chemopreventive and chemosensitizer there are several phytochemicals contained in nuts. The association between nuts consumption and cancer risk is poorly understood and remains controversial. It is well recognized that phytochemicals contained in nuts possess biological effects. Moreover, nuts are a good source of healthy fats, vitamins, antioxidants and minerals**.** Nevertheless the potential of nuts consumption associated with health benefit has been often disregarded. Several factors have contributed to this negative view on nuts consumption, above all the mainstream advice to follow a "low-fat diet", and therefore that nuts consumption should be limited because of their high fat and caloric content. Other factors have contributed to the unhealthy image of nuts such as insurgence of allergies and toxins contamination associated with nuts consumption. Despite this "negative image", experimental evidence underlines the health benefit associated with their consumption, above all data showing that they can lower risk of heart disease by as much as 35%. Although experimental evidences suggest that nuts may have also chemopreventive action, especially on colorectal and prostate cancer, at present there are not sufficient data corroborating their anticancer properties. Therefore, further research is warranted to accurately assess the relationship between nuts consumption and cancer risk.

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