



REVIEW

Foods of the Mediterranean diet: citrus, cucumber and grape

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Summary

Fruit and vegetables are excellent sources of health-promoting bioactive compounds and nutraceuticals. Regular consumption of fruit and vegetables helps prevent the onset and progression of many non-communicable diseases. The Mediterranean diet envisages consumption of healthy vegetables and fruit on a daily basis for maximum health benefits. Traditional use envisages vegetable-based and fruit-based diets, and many studies scientifically proved the beneficial effects of Mediterranean vegetables and fruits. Rich in bioactive phytochemicals, citrus, cucumbers and grapes have antioxidant, anti-inflammatory, antimicrobial, cardioprotective, anti-ageing and anti-cancer properties. Studies indicate that intake of citrus, cucumbers and grapes reduces hypertension,

hyperlipidemia, skin problems and infections and improves the health of the cardiovascular and nervous systems. These beneficial effects are mediated by several bioactive molecules present in Mediterranean diet vegetables and fruits, such as citrus, cucumbers and grapes. Indeed, they contain flavones, isoflavones, tannins, polyphenols and many beneficial natural molecules. This review focuses on the bioactive ingredients in citrus fruit, cucumbers and grapes, all components of the Mediterranean diet, and their health effects. A deep understanding of Mediterranean diet's components, as well as clinical trials to test natural molecules beneficial effects, will permit to further explore the therapeutic potential of the Mediterranean diet in several pathological conditions.

Introduction

The Mediterranean diet is widely accepted to be a very healthy diet. Whole grains, legumes, fruit, vegetables, white meat, fish, nuts and olive oil are all essential components. This diet is beneficial for human health and wellbeing because of its abundance of antioxidants, fibre, vitamins, minerals, phytosterols, probiotics, omega 3 and omega 6 fatty acids and phytosterols.

Citrus fruit is popular in the Mediterranean region. Though not native to the region, it has become an important commodity because of its place in the Mediterranean diet. Various citrus fruits have been used traditionally to treat illnesses in many Asian countries. Due to their medicinal qualities, citrus secondary metabolites such flavonoids, alkaloids, limonoids, coumarins, carotenoids, phenolic acids and essential oils are precious for maintaining human health. Their qualities include cardiovascular and neuroprotective properties and antioxidant, anti-inflammatory and anti-cancer effects [1-15]. The cucumber *Cucumis sativus* L. (family Cucurbitaceae) is a vegetable widely consumed throughout the world. It has a high water content and relatively few calories, as well as strong antioxidant, lipid-lowering and anti-diabetic effects. By eliminating pockets of toxins and old debris, cucumber has a purifying effect on the body. The skin is nourished by application fresh cucumber juice, which has a calming effect on irritation and reduces edema. Cucumber can also calm the body and

reduce the pain of sunburn. The fruit is cooling, hemostatic, tonic and effective against excessive thirst and heat stroke. The seeds are used to treat constipation and have a cooling effect on the body. Cucumber is a source of cucurbitacins, cucumerin A and B, cucumegastigmanes I and II, vitexin, orientin, isoscoparin 2''-O-(6'''-(E)-p-coumaroyl) glucoside and apigenin 7-O-(6''-O-p-coumaroyl glucoside) [16-32].

Grapes are rich in primary and secondary metabolites such as polyphenols. Polyphenols and phenolic acids have strong anti-inflammatory and anti-cancer effects and immunomodulatory properties. Although their distribution varies greatly in the different tissues, the pericarp and seeds of grapes are rich in polyphenols and phenolic acids. The leaves and seeds of the grapevine are tasty and healthy ingredients of Mediterranean cooking.

Citrus phytochemicals and their health-promoting effects

Citrus fruit is a distinctive component of the Mediterranean diet and adds richness and variety and to its health-promoting effects. It has many nutritional and healthy properties. It has been used for centuries to treat illnesses, such as bronchitis, tuberculosis, coughs, colds and menstrual disorders [1]. Citrus fruit is rich in vitamins, minerals and fibre and without sodium, fat and cholesterol. It also contains secondary phytochemicals, such as carotenoids and

polyphenols, that prevent non-communicable diseases such as cardiovascular disease and cancer. Citrus fruit is rich in vitamin C which plays a key role in the absorption of inorganic iron, thus helping to alleviate anemia if administered with appropriate medicines [2, 3]. Vitamin C also promotes formation of collagen. Although citrus is not an excellent source of iron or zinc, its vitamin C content mediates release of iron and zinc from other foods, thereby maintaining iron status [2]. Citrus contains cellulose, hemicellulose and pectin which make up 60 to 70% of its total fibre content. Together with lignin, this form of fibre may decrease absorption of glucose after consumption of carbohydrates and reduce reabsorption of bile acids, lowering plasma levels of cholesterol [1-3].

Citrus fruit contains many important secondary metabolites in its peel, pulp, seeds, pressed oil and juice (Tab. I). Their concentrations vary between citrus species and in the various parts of the fruit [1-3]. Hesperidin and flavonoids have been linked to the anti-inflammatory and antioxidant activities of phenolic acids, such as caffeic, chlorogenic and ferulic acids [2]. The compounds responsible for these benefits include coumarins, essential oils (limonene) and flavonoids such naringin, naringenin, hesperidin and nobiletin (auraptene, imperatorin) [1]. Citrus also contains triterpene compounds like limonoids that have been remarked for their anti-cancer properties in animal models (stomach, skin, colon and lung) and in human colon adenocarcinoma cells and human breast cancer cells. Flavonoids extracted from citrus can also lower blood sugar, triglycerides and cholesterol levels. The flavanones hesperidin, naringenin, naringin and neohesperidin, as well as polyethoxylated flavonoids (nobiletin, tangeretin) are responsible for these qualities [1, 2].

Cucumbers (*Cucumis sativus* L.) belong to the Cucurbitaceae family and are widely cultivated all over the world. They are eaten raw in salads, fermented (pickled) or cooked [17]. *C. sativus*, one of the 30 species of cucumbers, has the highest commercial value [18, 19]. The therapeutic potential of *C. sativus* leaves, fruits and seeds is extensively mentioned in ayurvedic medicine for management of ageing [20, 21]. The cucumber is of-

Cucumber phytochemicals and their health-promoting effects

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Tab. I. Phytochemicals in the citrus family and their bioactivity.

Components	Bioactivity	References
Folate (Folic acid / folacin)	Promotes cell proliferation and red blood cell synthesis, prevents neural tube defects, stabilizes genetic material and may protect against cancer and heart disease.	[4,5]
Potassium	Minerals and sodium can retain biological fluids. Low sodium and high potassium levels may lower blood pressure.	[4,5]
Dietary fibre	Includes resistant starch, soluble and insoluble polysaccharides, pectin and certain other components. Boosts intestinal flora and shortens the time food spends in the gut. Some types of fibre help lower blood fat levels. May lower risk of certain malignancies, heart disease and digestive issues including constipation.	[5]
Non-nutrient phytochemicals		
Coumarins Polymethoxyflavones	Anti-obesity effects. Citrus peels are rich in coumarins, a class of polyphenols. Auraptene, the most prevalent coumarin in citrus, is found in grapefruit, trifoliolate oranges, sour oranges and particularly <i>Citrus natsudaikai</i> . Products made from citrus fruits like marmalade and grapefruit juice maintain auraptene activity. Prevent formation of lipid droplets	[6]
Polyphenols	Anti-microbial, anti-viral, anti-allergic, anti-inflammatory, anti-proliferative and anti-carcinogenic activity; astringent flavors. Anthocyanins are responsible for many of the colors of fruit and vegetables.	[5, 7-10]
Flavonoids		
Nobiletin Citromitin Tangeretin	Hepatoprotective, anti-obesity and anti-hyperglycemic effects. Prevent D-galactosamine-induced liver damage	[11]
Kaempferol Quercetin Apigenin Naringenin	Anti-microbial effects Cell-cell signaling antagonists, biofilm formation suppressors	[12]
Hesperidin	Anti-allergic effects Reduces granulocytes degranulation and allergic symptoms	[13]
Limonin Nomilin	Hepatoprotective, anti-obesity and anti-hyperglycemic effects Improves indicators of liver injury and inflammation	[14]
Essential oils	Anti-microbial effects Inhibit pathogens and microorganisms of decomposition	[15]
Chimpi	Anti-anxiety effects Strong anxiolytic effect equivalent to fluoxetine.	[16]

ten used to treat skin problems such as sunburn and eye inflammation. It is thought to revive, cool, heal, soothe and soften irritated skin and to prevent itching. Bioactive substances in several chemical classes have been isolated from this plant. A distinguishing feature of this species are cucurbitacins. Cucumber fruits are 96.4% water, 0.4% protein, 0.1% fat, 2.8% carbohydrate, 0.3% minerals, 0.01% calcium, 0.03% phosphorus, 1.5 mg/100 g iron and 30 IU/100 g vitamin B. They also contain enzymes such as proteases, ascorbate oxidases, succinic dehydrogenase and malic dehydrogenase [19]. They have a significant amount of ascorbic acid [20] while pulp and peel extracts contain lactic acid (7-8% w/w), which has demonstrated antioxidant properties [17]. The tetracyclic cucurbitane nuclear skeleton of cucurbitacins is arbitrarily split into twelve groups that form many cucurbitacins with antiproliferative properties [22].

PHYTOCHEMICALS OF CUCUMBER SEEDS

Cucumber seeds contain compounds such flavonoids, tannins, saponins and steroids [23]. Indeed, ethanol extract of cucumber seeds contained flavonoids, terpenoids, tannins, cardiac glycosides, phenols and carbohydrates [24]. Moreover, methanol extract of cucumber pulp contained tannins, alkaloids, saponins, glycosides, terpenes, phenolics and glycosides [25, 26]. The cotyledons of various varieties of *C. sativus* seedlings contained cucurbitacins A B, C, D, E and I [27] that have cytotoxic, antitumor, hepatoprotective, anti-inflammatory, antibacterial, anti-helminthic, cardiovascular and anti-diabetic properties [28]. Finally, cucumber contains two newly discovered primary C-glycosyl flavonoid compounds: cucumerin A and cucumerin B. Cucumber leaves and fruits contain many flavonoids, such as vitexin, isovitexin, and orientin, and carotenoids [29-33]. Table II summarized the main phytochemicals present in cucumber plant.

PHARMACOLOGICAL ACTIVITY OF CUCUMBER PHYTOCHEMICALS

Antioxidant activity

Cucumber (*Cucumis sativus* L.) contains several free radical scavenging compounds that reduce oxidative stress by reducing superoxide mutase, guaiacol peroxidase, glutathione reductases and ascorbic acid peroxidases [20, 34]. Other antioxidants include butylated hydroxyl anisole (BHA) which is a more effective free radical scavenger than ascorbic acid. Tannins, polyphenols and flavonoids in cucumber also show radical-scavenging effects [34].

Anti-cancer activity

Cucumber contains many compounds with anti-cancer properties [35]. For instance, methanol and acetone extracts of cucumber has shown cytotoxicity against cancer cell lines HeLa and Michigan Cancer Foundation-7. Ethanol extract of cucumber leaves is rich in glycosides, alkaloids, tannins, proteins, amino acids, phytosterols, steroids, terpenoids and saponins; it inhibited the growth of HeLa and HepaG2 cancer cell lines in the MTT assay. Significant anticancer activity was seen at doses of 62.5, 125, 250 and 500 mg. Ethanol extract was more effective against HepG2 than against HeLa. According to the authors, the triterpenoids in the extract were responsible for the anti-cancer activity [35].

Antibacterial and antifungal properties

Ethyl acetate and methanol extracts of cucumber fruit have been reported to have antimicrobial activities, while methanol extract of cucumber seeds is reported to inhibit entero-pathogens *S. aureus*, *P. aeruginosa* and *E. coli*. Volatile cucumber oil has shown antibacterial and antifungal properties against gram-negative and gram-positive bacterial strains [36]. The research demonstrated an effect of *C.s.* against two major fungi. The authors concluded that *C.s.* seeds may have antifungal potential [37]. The study showed that ethanol extract of *Cucumis sativus* Linn. screened positively for antifungal activity against six fungi compared to reference griseofulvin [37].

Cytotoxicity

Ethanol extracts of *Cucumis sativus* showed cytotoxicity against brine shrimp nauplii in a brine shrimp toxicity assay. Toxicity rates were concentration-dependent. The LC50 and LC90 of the extract against brine shrimp nauplii were 75 µg/ml and 120 µg/ml, respectively [37].

Hepatoprotective activity

Cucumis sativus has been demonstrated to protect against oxidative stress caused by cumene hydroperoxide. Antioxidant and radical-scavenging compounds of *Cucumis sativus* fruit extract readily cross the cell membrane and protect against intracellular generation of reactive oxygen species. Aqueous extract of *Cucumis sativus* fruit acts as a hepatoprotective and antioxidant against cumene hydroperoxide-induced hepatotoxicity [38].

Hypoglycemic and hypolipidemic activity

Animal models such as alloxan-induced diabetic rats (AIDRs) have been used to test the hypoglycemic and hypolipidemic effects of cucumber. For instance, ethanol extracts of fruits of the Cucurbitaceae family, in-

Tab. II. Phytochemicals in cucumber plant.

Plant	Part of plant	Class of compounds	References
Cucumber	Seed	Tannins, saponins, terpenoids and steroids	[23, 24]
	Pulp	Tannins, alkaloids, saponins, glycosides, terpenes, phenolics and glycosides	[25, 26]
	Cotyledons	Cucurbitacins A B, C, D, E and I	[27]
	Leaves and fruits	Flavonoids, carotenoids	[29-33]

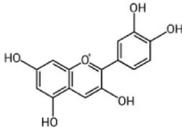
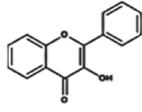
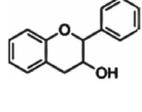
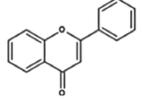
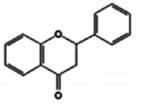
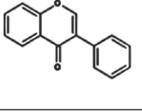
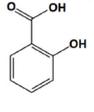
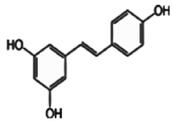
cluding cucumber, white pumpkin and ridge gourd, significantly reduced blood sugar levels in AIDRs. They also lowered the high lipid profiles of these rats. Ridge gourd was shown to significantly improve liver glycogen levels in AIDRs. The study suggested that cucumber fruit extracts may prove beneficial as supplements in the treatment of hyperglycemia and hyperlipidemia, which frequently coexist in diabetic patients. However, additional research is required to screen individual chemical

compounds, identify antidiabetic lead compounds and determine their mechanisms of action [39].

Grape phytochemicals and their health-promoting effects

Grapes are grown in many parts of the world but are perhaps best known in California in the United States and in the Mediterranean from Portugal to Lebanon and Syria.

Tab. III. Health benefits of phytochemicals present in grapevine and other sources.

Grapevine phytochemicals	Other sources	Health benefits	References
Anthocyanin: natural non-toxic water-soluble flavonoid pigments 	Mulberries, black currants, red currants, sweet cherries, blue berries, strawberries, plums, red onion, red raspberries, black chokeberries	<ul style="list-style-type: none"> • Antimicrobial effects • UV protection • Weight loss • Protection against type 2 diabetes • Decreased risk of cancer • Improved cognitive function • Reduce inflammation 	[54-57]
Flavanols 	Onions, kale, red wine, tea, peaches, berries, tomatoes, lettuce, scallions, broccoli	<ul style="list-style-type: none"> • Reduce blood pressure • Improve blood flow to the brain and heart • Prevent blood clots fight cell damage 	[57-59]
Flavan-3-ols 	White, green, oolong and black tea, apples, purple and red apples, blue berries, strawberries, chocolate	<ul style="list-style-type: none"> • Antioxidant • Anticarcinogen • Antimicrobial • Cardiovascular preventive • Antiviral • Neuroprotective 	[57, 58, 60]
Flavones 	Parsley, red peppers, celery, chamomile, peppermint	<ul style="list-style-type: none"> • Antioxidant • Anti-inflammatory • Antimicrobial • Anticancer 	[57, 58, 61]
Flavanones 	Limes, lemons, oranges	<ul style="list-style-type: none"> • Inhibit apoptosis • Induce peripheral and cerebral vascular blood flow • Improve cognitive performance 	[57, 58, 62]
Isoflavones 	Soy, red clover, green tea, split peas, pigeon peas, peanuts, chickpeas, lima beans	<ul style="list-style-type: none"> • Prevent cardiovascular disease, osteoporosis, hormone-dependent malignancy and cognitive decline 	[57, 58, 63]
Phenolic acids 	Berries, herbs, spices, cocoa, flax seeds, vegetables, olives, coffee, tea	<ul style="list-style-type: none"> • Antioxidant preventing cell damage • Anti-inflammatory 	[64]
Resveratrol 	Peanuts, berries, cocoa, blueberries, bilberries, cranberries	<ul style="list-style-type: none"> • Antibacterial • Antifungal • Antioxidant • Anti-inflammatory for arthritis and skin • Prevents cancer, diabetes, Alzheimer's disease 	[65-69]

Many Mediterranean sites produce magnificent wines, famous for their flavor and bouquet [40, 41]. Grapes contain high concentrations of phenolic acids, flavanols, flavon-3-ols [42], myricetin, peonidin, flavonoids, resveratrol, quercetin, tannins, anthocyanins, cyanidin, ellagic acid and proanthocyanins [41-49]. Besides the phytochemicals in the fruit, pulp, seeds and leaves of the grapevine, the wine derived from grapes also contains polyphenols and antioxidants [49]. The primary polyphenols in wine are resveratrol, anthocyanins, catechins and tannins (proanthocyanidins and ellagitannins) [50, 53]. Red wine and white wine are an integral part of the Mediterranean diet; they have alcohol concentrations of 14% and 11%, respectively, significantly lower than 35%, the alcohol content of spirits [51-53]. The polyphenol component of wine can have great health-protective effects [50-52], whereas white wine has fewer bioactive compounds than red wine; distilled drinks like liquor and spirits have virtually no bioactive compounds [46]. Different health effects are anticipated for alcoholic beverages due to their different chemical compositions.

Like wine, other bioactive elements of the Mediterranean diet, including nuts, fruit and vegetables (which mostly contain flavonoids) and olive oil (mainly hydroxytyrosol, tyrosol and oleocanthal), can also have cardioprotective effects through various synergistic pathways [53]. Besides containing many potential health-promoting phytochemicals (Tab. II), grapes are also rich in potassium, a mineral that maintains the body's fluid balance and can help lower high blood pressure and reduce the probability of developing heart disease and stroke. Grape seeds are rich in vitamin E, which helps keep the skin supple and moisturized. Grapes contain other components that may help prevent acne and improve the hair by boosting blood flow to the scalp. Resveratrol in grapes can strengthen the immune system, promote wound healing and prevent bacterial infections. Grape resveratrol slows the normal aging process by inhibiting cell death and reducing age-dependent deterioration of cells. Antioxidants such as flavan-3-ols and resveratrol in grapes have been observed to be effective against cancer of the mouth, throat, pancreas, prostate and colon, among others [68, 69]. Being rich in water and fibre, grapes help bowel movements, thus maintaining a healthy digestive system. Grape seed extract has been shown to play an important role in combating irritable bowel syndrome [70], while grape skin is rich in melatonin that plays a role in circadian rhythms [71]. The consumption of certain varieties of grapes, rich in polyphenols and fibre, has been shown to reduce the onset and incidence of cardiovascular disorders [72]. For instance, a randomized, parallel-group, controlled trial with 34 non-smoking adults (13 hypercholesterolemic and 21 normocholesterolemic) who were given supplements of 7.5 g/day grape antioxidant fibre containing 1400 mg polyphenols and 5.25 g dietary fibre for 16 weeks showed a significant reduction in blood pressure and normalisation of lipid profile [73]. Other studies have indicated that grapes and their phytochemical constituents have cardioprotective effects by lowering blood pressure, lipids, platelet function and thrombosis [74].

Conclusions

Vegetable- and fruit-based nutraceuticals have become popular for many pathophysiological conditions and cosmetic uses at traditional and commercial scale. Although the bioactive phytochemicals of these essential ingredients of the Mediterranean diet are backed by much evidence of traditional use, carefully designed clinical trials are required to further explore their therapeutic potential in different pathophysiological conditions.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; ZN, Kristjana D, Kevin D, BA, VV, GM, AI: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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