Chapter 6
Beneficial Herbs and Spices

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Keywords Chronic diseases · Food applications · Functional food · Health claims · Herbs · Spices Therapeutic properties

Abbreviations

8-OHdG	8-hydroxy-2'-deoxyguanosine
BHT	Butylated hydroxytoluene
CAT	Catalase
CCSCH	Codex Committee on Spices and Culinary Herbs
CVDs	Cardiovascular diseases
DSLD	Dietary Supplement Label Database
EFSA	European Food Safety Authority
EU	European Union
FDA	Food and Drug Administration
$GABA_A$	γ-aminobutyric acid
GAE	Gallic acid equivalent
GMP	Good Manufacturing Practices
GPx	Glutathione peroxidase
GT	Green tea
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LPO	Lipid peroxidation
MPO	Myeloperoxidase
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
US	United States
VLDL	Very-low-density lipoprotein

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Key Points
- Herbs and spices have been widely used from ancient times for both food and medicinal purposes.
- Some of the health claims for herbs and spices may not have been fully demonstrated, and more regulations are needed to regulate these claims.
- Trial evidence for the use of herbs and spices has uniformly demonstrated safety, but the efficacy data are limited by small subject size and short duration trials.
- Efficacy evidence is most robust for the herb green tea and the turmeric spice.

Introduction

Diet and nutrition are important elements in the promotion and maintenance of good health [96]. The World Health Organization recommends regular consumption of fruits and vegetables, including herbs and spices, because of their potential to decrease the incidence of several chronic diseases [98]. The Codex Committee on Spices and Culinary Herbs (CCSCH) is responsible for establishing worldwide standards for spices and culinary herbs in their dried and dehydrated state in whole, ground, and cracked or crushed form and consulting, as necessary, with other international organizations in the standard development process to avoid duplication. According to CODEX [22], herbs come from plant leaves or flowering parts either fresh or dried, and spices come from other parts of the plant such as roots, stem, bark, seeds, and bulb [94]. They are also usually dried before used. In some cases, herbs and spices may come from the same plant but from different parts. Herbs and spices have been widely used for both food and medicinal purposes (Fig. 6.1). In culinary practices, they are employed as preservatives (antioxidants or antimicrobials), flavor enhancers, colorants, and ingredient substitution of salt and sugar. Efforts to assess dietary intake of spices and herbs are complicated because their use is varied and they are consumed in trace amounts together with other foods.

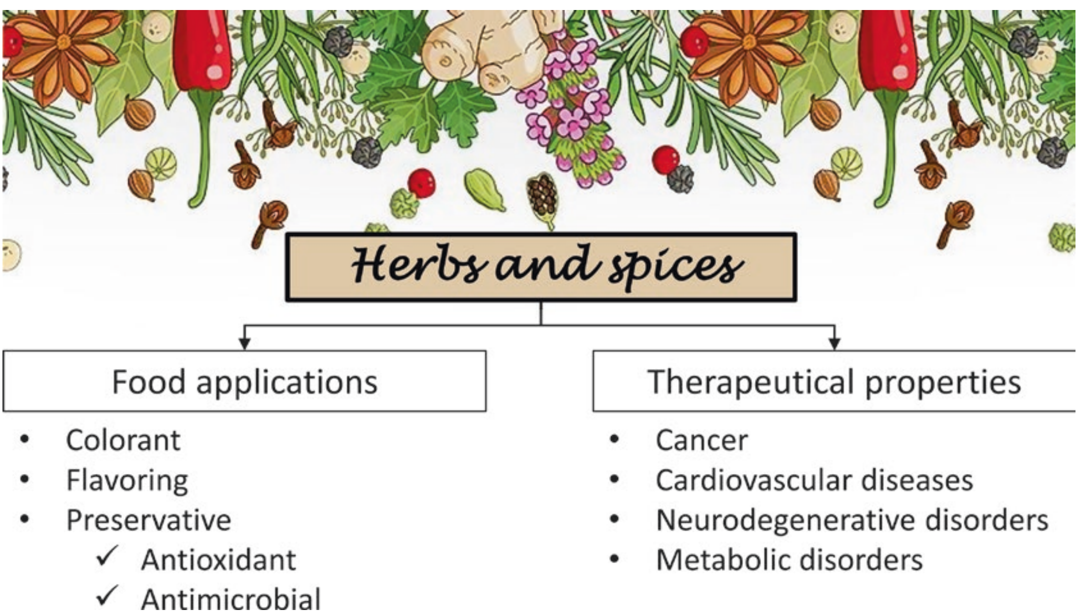

Fig. 6.1 Food applications and therapeutic uses of herbs and spices

Concentrations of herbs and spices in finished foods frequently fall within the range of 0.5–1% [49]. In medicine, they are used to reduce the risk or treat noncommunicable chronic diseases associated with oxidative stress and inflammation [76]. Herbs and spices are rich sources of bioactive phytochemicals such as phenolic compounds, carotenoids, sterols, terpenes, alkaloids, glucosinolates, and other sulfur-containing compounds, the majority of which have powerful antioxidant capacity. These phytochemicals seem to be responsible for the therapeutic effect of herbs and spices, and they provide a variety of health benefits [73] such as anticancer [49], anti-inflammatory [12], antibacterial [87], antiviral [47], and antioxidant effects [94]. The above statement accounts for the increasing interest in the health-promoting and protective properties of culinary herbs and spices.

The use of plant ingredients in food products is well established as vegetables and fruits, herbs and spices, herbal teas and infusions, beverages, and plant food supplements and has steadily increased in the last decade [17]. Health claims are increasingly appearing on our food, but the food industry is not allowed to make medicinal claims about food. In the European Union (EU), the discrepancy between the assessment of medical claims and health claims regarding the use of traditional data made the Commission of the European Food Safety Authority (EFSA) in September 2010 decide not to continue with the assessment of health claims for plant and herbal substances, the so-called "botanical" substances. The Scientific Committee decided alternatively to focus its work first on the safety assessment of botanicals and botanical preparations used as ingredients in food supplements. Since the Commission and member countries need more time to decide how to assess safety, evaluation of health claims was deferred. However, there are a few authoritative recommendations regarding the intake of herbs and spices in existing national dietary guidelines.

Research has begun to identify not only culinary uses but also other potential benefits of spices and herbs in human health according to that described in Fig. 6.2. Authorized health claims in food labeling are claims that have been reviewed by the Food and Drug Administration (FDA) or EFSA

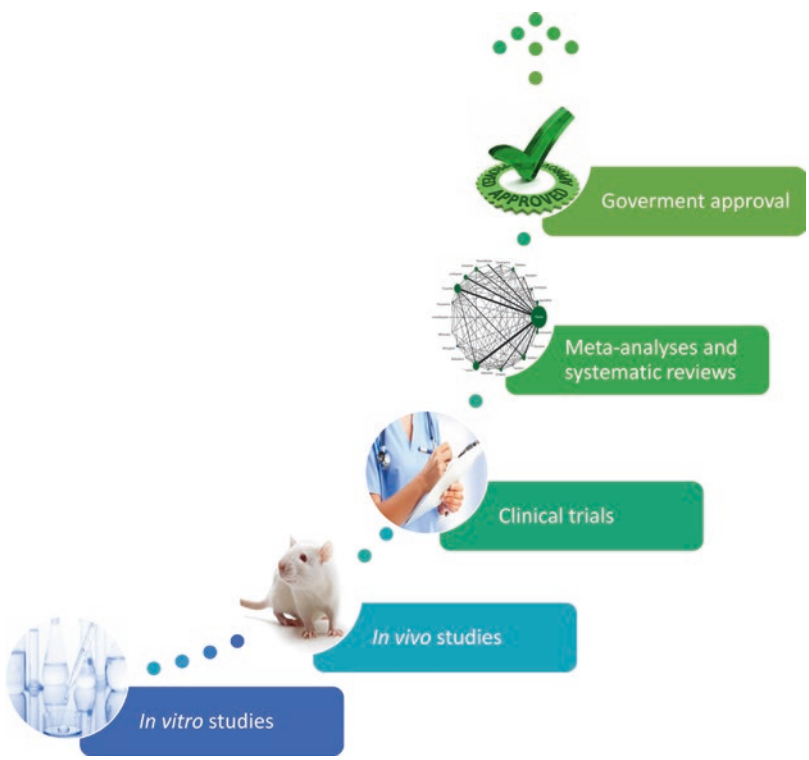

Fig. 6.2 Research steps for the approval of a health claim of herbs or spices

and are allowed on food products or dietary supplements to show that a food or food component may reduce the risk of a disease or a health-related condition. Health claims are truthful, clear, reliable, and useful to the consumer. Permitted health claims must provide scientific evidence on the relationship existing between a food category, a food or one of its constituents, and health benefit.

In the past decade, the number of clinical trials involving spices and herbs has increased sixfold [27]. Clinical trials aim to evaluate a medical intervention in human populations. Before the clinical trial, in vitro laboratory tests and in vivo studies in animals to test potential therapy's safety and efficacy are performed. After the success of a clinical trial, the FDA or EFSA may approve the drug for clinical use and continues to monitor its effects [70]. If a health claim is rejected, further research and an appeal for resubmission should be conducted. In addition, if a cause-effect relationship cannot be demonstrated, in some cases a nutrition claim can be included in the label. Nutrition claims state that a food has particular beneficial nutritional properties in terms of energy amount, nutrients, or other substances, for instance, "reduced salt" or "high in fiber." If neither a health nor a nutrition claim is approved, the herb or spice can still be used as a food ingredient or additive, but it would not have the corresponding claim indicated on its label. The declaration of the ingredient on its food label will depend on the legislation in the country in which the product will be commercialized.

In order to increase our understanding on the mechanisms of action of the potential health-promoting properties, phytochemicals, their bioactivity, and impact in human health and disease, the use of the term "phytochemomics" has been proposed as an advanced analytical approach. This multidisciplinary research field is essential for establishing a cause-effect relationship and authorizing or rejecting nutrition and health claims made on foods, herbs, and botanicals enriched in phytochemicals [15]. Therefore, the aim of the present chapter is to review the most significant findings related to the food applications and therapeutic properties of herbs and spices, focusing on the beneficial effects reported in clinical trials.

Herbs

Herbs may be defined as the dried leaves of aromatic plants used to impart flavor and odor to foods with, sometimes, the addition of color [74]. Table 6.1 shows the information regarding the food applications and therapeutic properties of the 25 most commonly consumed herbs.

Herbs can be consumed in different forms as a condiment in cooking, as beverages, or as essential oils due to their characteristic chemical composition. Beverages composed from herbs can be separated into tea or herbal infusions. The common tea is made from leaves of the plant *Camellia sinensis*, and four types are produced: white tea, green tea (both unfermented), Oolong tea (semi-fermented), and black tea (fermented) [42]. Nevertheless, the term herbal infusion usually refers to infusions made with other herbs, for instance, boldo, feverfew, linden, lemon verbena, lovage, senna, St. John's wort, hibiscus, and thyme. Other difference between these beverages is the temperature of water; in the case of tea, it is usually prepared with boiling water, while herbal infusions are made with hot water (without reaching boiling point). In general, herbal beverages constitute an important part of the food culture in countries where traditional medicines are widely used such as some Asian countries, although their interest and consumption have increased exponentially in nontraditional regions, such as in many European countries. Due to the potential beneficial health effects related to tea drinking, there are studies that have determined and compared the chemical composition of different teas and herbal infusions [40]. Furthermore, herbs can be used fresh, where their highly delicate aromatic character is best preserved, but the vast majority of the trade is based on dried herbs. In this sense, herbs are used as natural preservatives (antioxidant or antimicrobial), colorants, and flavorings in the food industry.

Table 6.1 Food applications and therapeutic properties of the most consumed herbs

Herbs	Scientific name	Family	Tissue	Food applications	Therapeutic properties	Registered clinical trials (*n*)
Basil	*Ocimum basilicum* L.	Lamiaceae	Leaves	Flavoring, antimicrobial	Cancer[a], metabolic disorders[b]	2
Bay	*Laurus nobilis*	Lauraceae	Leaves	Flavoring, colorant	Metabolic disorders[a, b]	1
Boldo	*Peumus boldus molina*	Monimiaceae	Leaves	Beverage	–	0
Borage	*Borago officinalis* L.	Boraginaceae	Leaves	Antioxidant	Cardiovascular diseases[b], metabolic disorders[b]	10
Calendula	*Calendula officinalis* L.	Asteraceae	Flowers	Flavoring, Colorant	Cardiovascular diseases[b], neurodegeneratives disorders[b]	8
Chamomile	*Matricaria chamomilla* L.	Asteraceae	Flowers	Colorant	Cardiovascular diseases[b]	23
Chervil	*Anthriscus cerefolium*	Apiaceae	Leaves	Flavoring	–	0
Chives	*Allium schoenosprasum*	Amaryllidaceae	Leaves	Flavoring	–	0
Feverfew	*Tanacetum parthenium* L.	Asteraceae	Leaves	Beverage	Migraine[b]	1
Lemon balm	*Melissa officinalis* L.	Lamiaceae	Leaves	Flavoring, Antioxidant	Neurodegeneratives disorders[a, b], metabolic disorders[a, b], cancer[b], cardiovascular diseases[b]	2
Lemon grass	*Cymbopogon citratus*	Poaceae	Leaves	Flavoring, beverage	Cancer[a]	0
Lemon verbena	*Aloysia citrodora*	Verbenaceae	Leaves	Beverage	Neuromuscular diseases[b]	1
Linden	*Tilia americana* L.	Malvaceae	Leaves	Beverage	Neurodegeneratives disorders[b]	1
Lovage	*Levisticum officinale*	Apiaceae	Leaves	Beverage	Urologic diseases[b]	1
Marjoram	*Origanum majorana*	Lamiaceae	Leaves	Flavoring, antioxidant	Respiratory disorders[b]	1
Oregano	*Origanum vulgare*	Lamiaceae	Leaves	Flavoring, antioxidant, antimicrobial	Metabolic disorders[a, b], cardiovascular diseases[b], sleep desorders[b], respiratory disorders[b]	10
Parsley	*Petroselinum crispum*	Apiaceae	Leaves	Flavoring	Metabolic disorders[b], urinary disorders[b]	5
Pennyroyal	*Mentha pulegium* L.	Lamiaceae	Leaves	Flavoring, beverage		0
Rosemary	*Rosmarinus officinalis*	Lamiaceae	Leaves	Flavoring, antioxidant, antimicrobial	Cancer[a], metobolic disorders[a, b], cardiovascular diseases[b], respiratory disorders[b], urinary disorders[b]	26

(continued)

Table 6.1 (continued)

Herbs	Scientific name	Family	Tissue	Food applications	Therapeutic properties	Registered clinical trials (*n*)
Sage	*Salvia officinalis*	Lamiaceae	Leaves	Flavoring, antioxidant, antimicrobial	Metabolic disorders[a, b], cardiovascular diseases[b]	10
Senna plant	*Cassia angustifolia*	Fabaceae	Leaves, flowers	Beverage		0
St. John's wort	*Hypericum perforatum* L.	Clusiaceae	Flowers	Beverage	Cancer[b], metobolic disorders[b], cardiovascular diseases[b], anxiety disroders[b]	38
Tea	*Camellia sinensis* L.	Theaceae	Leaves	Antioxidant, beverage	Metabolic disorders[a, b], cancer[a, b], cardiovascular diseases[b], neurodegenerative diseases[b], urinary disorders[b]	396
Thyme	*Thymus vulgaris*	Lamiaceae	Leaves	Antioxidant, antimicrobial	Metabolic disorders[b], respiratory disorders[b]	13

Number of clinical trials registered in ClinicalTrials.gov in November 2018
[a]Published human studies of the therapeutic properties of herbs
[b]Currently ongoing clinical trials studying therapeutic properties herbs

Food Applications

Flavorings

A culinary herb is an edible plant that when consumed in small quantities, provides substantial flavor and aroma. Fresh or dried leaves from different types of herbs (Table 6.1) can be often used as a food ingredient in many dishes such as salads, pasta, sausages, soups, marinades, meat, egg, vinegar, even in desserts, biscuits, and some alcoholic beverages such as liqueurs and wine [13, 94]. Aromatic compounds in herbs are either phenolic or terpene-based compounds. Some important chemical compounds for the flavoring potential of herbs are carvacrol, thymol (in oregano and thyme), and linalool (in sage and rosemary) [74].

Colorants

Colorants are food additives that add or restore color in foods [71]. They are used to improve the appearance of foods and to maintain their natural color during processing and storage [60]. Plant-derived pigments are divided in four groups: green chlorophylls, yellow-orange-red carotenoids, red-blue-purple anthocyanins, and red betanin. Nowadays, there is increasing interest in the development of colorants from natural sources, especially in food industries. Color and freshness are the main criteria favored essentially by the social trend toward the consumption of natural products instead of synthetic ones because of their side effects, toxicity, and allergic reactions [85]. In herbs, the principal compounds responsible for color are flavonoids which dye in colors from pale yellow (isoflavones) through deep yellow (chalcones, flavones, flavonols, aurones), orange (aurones) to reds and blues (anthocyanins) [74].

Some herbs have been described as natural colorants. Bay leaf has been employed as a food colorant due to the presence of anthocyanins [61]. The flower of *Calendula* is normally used as a food colorant to bring a yellow color due to the presence of carotenoids. The stability of these compounds during commercial shelf life is very important if the final products have to be attractive and acceptable [82]. In addition, essential oils obtained from fresh or dried flower heads of chamomile have coloring properties [28]. However, spices are more commonly used as a source of natural colorants than herbs.

Preservatives: Antioxidants

The Codex General Standard for Food Additives defines antioxidants as food additives that prolong the shelf life of foods by protecting against deterioration caused by oxidation [35]. Several studies have proven the excellent preservative capacity of different plant extracts in different food matrices. Antioxidants, even in low amounts, significantly delay or prevent oxidation reactions of susceptible ingredients such as lipids [34]. Many herbs are excellent sources of natural antioxidants, and their antioxidant properties are associated to flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins, and isocatechins [5].

Rosemary, oregano, sage, marjoram, thyme, borage, balm, and tea, among others, are natural sources of antioxidants (Table 6.1) and are considered as free radical scavengers [30]. Kumar et al. reviewed the use of herbs in meat and meat products [56]. In this sense, rosemary and oregano extracts were used in raw pork batters to identify the main antioxidant compounds and their effect on color and oxidation. Results showed that rosemary extracts had a high antioxidant activity, even more than the phenol compounds separately. These extracts also showed the highest antioxidant capacity, possibly due to the presence of high concentrations of carnosic acid and carnosol, among other compounds. However, ethanol oregano extracts containing high concentrations of phenols, mainly rosmarinic acid, efficiently prevented color deterioration [38]. Borage has also been added as an antioxidant in fermented sausages [20] and balm in meat products [21]. Sage was effective in controlling lipid and cholesterol oxidation, minimizing the prooxidant effects of salt, cooking, and storage in chicken meat [63]. Green tea extract has also been used to protect Turkish dry-fermented sausage (sucuk) against oxidation during the ripening periods, and it showed more effectiveness than butylated hydroxytoluene (BHT). Green tea extract has shown capacity to scavenge oxygen radicals and to chelate metal ions [14].

Rosemary extract (E-392) has been classified as a food additive in the EU and in the USA, and it is the only herb commercially available for its use as an antioxidant. Carnosic acid and its derivative carnosol are also used and regulated as key antioxidant compounds in rosemary extracts by the European Commission [10, 32]. Rosemary leaf extract antioxidant is prepared by solvent extraction (ethanol, acetone, or ethanol followed by hexane) or supercritical carbon dioxide extraction, which are then deodorized, decolorized, and standardized. According to the EU regulation, only deodorized rosemary extracts containing carnosic acid and carnosol are considered additives. Application areas are food matrices, including oils, animal fats, sauces, and bakery wares, and meat and fish products [10]. Rosemary is known to be a superoxide radical scavenger, lipid antioxidant, and metal chelator [30].

Preservatives: Antimicrobials

There is increasing interest in the antimicrobial properties of herbs and their products to reduce the occurrence of microbial (bacteria, yeast, fungi) contamination in foods caused by undesirable pathogenic microorganisms such as *Listeria monocytogenes*, *Escherichia coli* O157:H7, *Salmonella typhimurium*, *Bacillus cereus*, and *Staphylococcus aureus*. Antimicrobial compounds and extracts improve shelf life of foods and generally minimize pathogens and toxins produced by microorganisms. However, these compounds or their extracts act as antimicrobials in vitro, and to achieve the same effect in foods, a greater concentration is needed. Only a few food preservatives possessing antioxidant and antimicrobial properties containing essential oils from rosemary, sage, thyme, oregano, and basil are already commercially available. They have been used successfully alone or in combination with other preservation methods. Rosemary hydroalcoholic extract has been effective against *Streptococcus mitis*, *Streptococcus sanguinis*, *Streptococcus mutans*, *Streptococcus sobrinus*, and *Lactobacillus casei* standard strains, and its antimicrobial activity has been proved in all tests, except against *Streptococcus mitis* [89]. Costa et al. [23] have studied the antibacterial activity of essential oils from oregano against multiresistant bacteria (including *Escherichia coli*, *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Saccharomyces cerevisiae*) [23]. Essential oils from oregano, thyme, marjoram, and basil were also active against strains of *Listeria monocytogenes* and *Salmonella enteritidis* in meat products but were more active against gram-positive bacteria [90].

Therapeutic Properties

In order to overcome the difficulties of applying the pharmaceutical regulation to herbal medicinal products in a uniform manner, specific provisions for traditional herbal medicinal products have been introduced in the EU relating to medicinal products for human use (Directive 2001/83/EC). Bibliographical or expert evidence to the effect that the medicinal product in question has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the community, is required for assessing the safety of the medicinal product [33]. The following section reviews all the clinical trials studying the health-promoting properties of herbs in metabolic disorders, cardiovascular diseases, cancer, and neurodegenerative disorders.

Metabolic Disorders

Several in vitro studies show antidiabetic properties of herbs, but only a few clinical trials investigating the effect of herbs on metabolic disorders have been conducted. In a parallel randomized double-blind clinical trial with 82 patients with borderline hyperlipidemia, the consumption of 3 g of lemon balm leaf powder per day for 2 months was associated with a significant decrease in mean serum LDL cholesterol [46].

The effect of bay leaf ingestion for 30 days in men and women over the age of 40 showed reduced fasting serum glucose, total cholesterol, LDL, and triglycerides compared to the placebo group [53]. Similarly, males and females over 40 years old with controlled type I diabetes consuming 3 g of bay leaf per day for 4 weeks had reduced serum total cholesterol, LDL, triglycerides and fasting glucose and had greater serum HDL compared to baseline [3]. These results suggest that bay leaf consumption may help manage hyperlipidemia.

The potential hypolipidemic effect of consuming oregano extract has also been studied in humans. Forty-five non-smoking men were divided in three groups: placebo group (mango-orange juice, $n = 15$); low phenolic group (mango-orange juice enriched with oregano extract, in which daily dosage of total phenolic compounds from the extract was 300 mg gallic acid equivalent (GAE), $n = 15$); and high phenolic group (mango-orange juice enriched with oregano extract, in which daily dosage of total phenolic compounds from the extract was 600 mg GAE, $n = 15$). Results after 90 min of juice ingestion showed a significant reduction in LDL oxidation in the low phenolic group [72].

Sage extract also has beneficial effects on blood lipid profile in humans. In a randomized double-blind placebo-controlled clinical study, newly diagnosed primary hyperlipidemia patients consumed a capsule containing 500 mg of sage extract every 8 hours for 2 months. At the end of the study, subjects had lower serum total cholesterol, triglycerides, LDL, and VLDL and increased HDL compared to both baseline and placebo groups [54]. In another study on healthy female subjects between the ages of 40 and 50, consumption of sage aqueous infusion twice a day for 2 weeks was associated with lower plasma LDL, total cholesterol, and greater plasma HDL [83]. In a double-blind, placebo-controlled trial, 56 obese, hypertensive subjects were randomized to receive a daily supplement of 1 capsule that contained either 379 mg of green tea extract or a matching placebo, for 3 months. Results showed that a daily supplementation with 379 mg of green tea extract favorably influences blood pressure, insulin resistance, inflammation, oxidative stress, and lipid profile in patients with obesity-related hypertension [11].

Cardiovascular Diseases

Herbs have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia [81]. A study regarding the effect of lemon balm infusion drunk twice a day for 30 days in 55 radiology staff showed that the activity of superoxide dismutase (SOD), catalase (CAT), and guttation peroxidase (GPx) increased significantly, but the level of lipid peroxidation (LPO), 8-hydroxy-2′-deoxyguanosine (8-OHdG), and the activity of myeloperoxidase (MPO) significantly decreased. Hence, it decreases radiation-induced oxidative stress biomarkers, and since oxidative stress is related to cardiovascular diseases (CVDs), lemon balm may have potential in the prevention or treatment of these diseases [103]. The antioxidant potential of lemon balm infusion may be due to its phenolic compounds, especially phenolic acids (rosmarinic acid, gallic acid, and ferulic acid), flavonoids (luteolin 7-O-glucoside, quercetin 3-rutinoside, and quercetin 3-O galactoside), and their antioxidant capacity [55]. In another clinical trial, participants with hypercholesterolemia who consumed 140 mg of lemon grass oil daily experienced a significant drop in mean cholesterol concentrations up to 38 mg/dL, but this trial had no control group [29]. Hawthorn is an herb used for improving blood flow. The leaves, fruit, and flowers of hawthorn are widely used in Europe for improving the pumping capacity of the heart and for treating angina. The major activity of hawthorn is thought to be mediated by various flavonoids. Patients with congestive heart failure (NY Heart Association class II) who were given 600 mg/day of a hawthorn extract had significantly lower blood pressure, heart rates, and less shortness of breath when exercising compared with subjects not receiving hawthorn [86]. Studies have suggested that green tea may lower blood cholesterol concentrations and blood pressure and may be effective for the treatment of hypertension and hyperlipidemia in both patients on medications and healthy subjects [68]. A double-blind, randomized, placebo-controlled, parallel-group trial studied the effect of daily intake of a capsule containing 75 mg theaflavin, 150 mg of green tea catechins, and 150 mg of other tea polyphenols for 12 weeks on subjects with mild-to-moderate hypercholesterolemia already consuming a low-fat diet. Results showed that the extract decreased mean serum total cholesterol and LDL by 11.3% and 16.4%, respectively, in treated volunteers compared to the placebo group [64]. Similar results were recently described in a randomized, double-blind trial with 115 women with central obesity. A high-dose of green tea extract with epigallocatechin gallate (EGCG) at a daily dosage of 856.8 mg resulted in significant weight loss, reduced waist circumference, and a consistent decrease in total cholesterol and LDL plasma levels without any side effects [18].

Hibiscus tea has demonstrated antihypertensive properties in several clinical trials studies. Anthocyanin compounds (delphinidin-3-sambubioside and cyanidin-3-sambubioside) were involved in these effects [41]. Previous studies conducted in hypertensive patients used a higher dose of hibiscus tea to compare its effects with that of either black tea, for instance, in a sequential randomized controlled clinical trial, 60 diabetic patients with mild hypertension were randomly allocated in 2 groups, hibiscus tea and black tea. In each group, they consumed their corresponding infusion two times per day for one month. Results showed a significant decrease from 134.4 to 112.7 mm Hg for hibiscus tea consumers group, and so consuming hibiscus tea had positive effects on blood pressure in type 2 diabetic (T2DM) patients with mild hypertension [69]. In addition, the first reported placebo-controlled clinical trial in order to examine the effect of hibiscus tea on blood pressure was described by McKey et al. [66]. In a randomized study, double-blind, placebo-controlled clinical trial, 65 pre- and mildly hypertensive adults were distributed in 2 groups, hibiscus tea and placebo group. For 6 weeks, participants consumed daily a bag of hibiscus tea or placebo (which contain artificial hibiscus flavor). Results showed at 6 weeks of treatment, hibiscus tea lowered systolic (−7.2 ± 11.4 mm Hg) and diastolic (−3.1 ± 7.0 mm Hg) blood pressure compared with placebo, although in the last case this change did not differ from placebo group. Results suggest daily consumption of hibiscus tea, in an amount readily incorporated into the diet, lowers blood pressure in pre- and mildly hypertensive adults and may be an effective component of the dietary changes recommended for people with these conditions [66].

Chamomile, rosemary, sage, and thyme have high flavonoid contents, and therefore they have an important role in dietary flavonoid intake, but there is little evidence to support a direct cardiovascular health benefit from these herbs apart from some epidemiological studies [94].

Cancer

Worldwide, more than 3000 plants have been reported to have anticancer properties. There are several in vitro studies and rodent in vivo studies suggesting that certain herbs may have a chemopreventive effect against the early initiating stages of cancer. Herbs containing known anticarcinogenic effects in animal models of cancer include basil, rosemary, mint, and lemon grass [94]. Nevertheless, limited data are available concerning the effectiveness of herbal extracts as anticarcinogenic agents in humans [4]. Experimentally, several medicinal plants and herbal ingredients have been reported to have anticancer effects. Herbs may be able to inhibit carcinogen bioactivation, decrease free radical formation, suppress cell division, and promote apoptosis in cancerous cells [50].

Green tea is the only herb that has shown clinical evidence for supporting its anticancer effects [43]. A double-blind placebo-controlled study showed that green tea catechins were safe and effective for treating premalignant prostate cancer [8]. In contrast, other studies showed that green tea has minimal clinical activity against prostate cancer [19, 48]. Catechins (phenolic compounds) have been identified as the main active constituents responsible for most of the biological properties of green tea.

Bioactive compounds present in herbs with cancer-preventive properties include terpenes (basil, marjoram, mint, rosemary, oregano, sage, and thyme), polyphenols, mainly flavonoids compounds (basil, marjoram, mint, rosemary, oregano, sage, parsley and thyme), and epigallocatechin gallate and other catechins (green tea) [7, 44, 100, 101].

Neurodegenerative Disorders

Lemon balm has been used traditionally for the treatment of dementia and amnesia, two disorders that are closely associated with Alzheimer's disease. A clinical trial of 42 patients during 16 weeks demonstrated reduction of agitation and improvement in cognitive and behavioral functions after administration of hydroalcoholic extract of lemon balm (60 drops/day) standardized to contain 500 μg citral/mL (terpenoid compound) [1]. Based on limited data, a proposed mechanism for the memory-enhancing effects of lemon balm may be attributed to the inhibition of acetylcholinesterase activity, the stimulation of acetylcholine (nicotinic and muscarinic receptors), and γ-aminobutyric acid ($GABA_A$) receptors, as well as the inhibition of matrix metalloproteinase-2 (MMP-2).

Spices

According to the FDA, spices are defined as "aromatic vegetable substances, in the whole, broken, or ground form, whose significant function in food is seasoning rather than nutrition." Table 6.2 shows the food applications and therapeutic properties of the most consumed spices.

Table 6.2 Food applications and therapeutic properties of the most consumed spices

Spices	Scientific name	Family	Tissue	Food applications	Therapeutical properties	Registered clinical trials (*n*)
Anise	*Pimpinella anisum*	Apiaceae	Fruit	Flavoring	Metabolic disorders[a, b]	6
Caraway	*Carum carvi*	Apiaceae	Fruit	Antioxidant	Metabolic disorders[b], back pain[b]	12
Cardamom	*Elettaria cardamomum*	Zingiberaceae	Fruit	Flavoring, antioxidant	Cancer[b], cardiovascular disease[b]	5
Celery	*Apium graveolens*	Apiaceae	Fruit	Flavoring	Cardiovascular disease[b], neurodegenerative disorders[b]	10
Cinnamon	*Cinnamomum zeylanicum*	Lauraceae	Bark	Flavoring, antioxidant, antimicrobial	Cardiovascular disease[a, b], metabolic disorders[a, b], neurodegenerative disorders[b], dental caries[b]	58
Cloves	*Eugenia aromaticum*	Myrtaceae	Flower bud	Flavoring, antioxidant, antimicrobial	Cardiovascular disease[a], metabolic disorders[a], cancer[b], dental caries[b]	15
Coriander	*Coriandrum sativum*	Apiaceae	Fruit	Flavoring, antioxidant	Cardiovascular disease[b], metabolic disorders[a]	7
Cumin	*Cuminum cyminum*	Apiaceae	Fruit	Flavoring, antioxidant, antimicrobial	Metabolic disorders[a, b], fungal infection[b]	20
Dill	*Anethum graveolens*	Apiaceae	Fruit	Flavoring	Cancer[b], kidney injury[b]	16
Fennel	*Foeniculum vulgare*	Apiaceae	Fruit	Flavoring, antioxidant	Chronic constipation[b]	4
Fenugreek	*Trigonella foenum-graecum*	Fabaceae	Fruit	Flavoring	Metabolic disorders[a, b], hypogonadism[b]	19
Garlic	*Allium sativum*	Liliaceae	Bulb	Flavoring	Cancer[a, b], cardiovascular disease[a, b], metabolic disorders[a, b]	54
Ginger	*Zingiber officinale*	Zingiberaceae	Rhizome	Flavoring, antioxidant	Cardiovascular disease[a], metabolic disorders[a, b], anxiety[b], psoriasis[b]	144
Horseradish	*Armoracia lapathifolia*	Brassicaceae	Root	Flavoring	Metabolic disorders[b]	10

(continued)

Table 6.2 (continued)

Spices	Scientific name	Family	Tissue	Food applications	Therapeutical properties	Registered clinical trials (*n*)
Mustard seed	*Brassica nigra, Brassica juncea, Brassica hirta*	Brassicaceae	Seed	Flavoring, antimicrobial	Cancer[b], metabolic disorders[b]	5
Nutmeg	*Myristica fragrans*	Myristicaceae	Kernel of the seed	Flavoring, antioxidant	–	0
Onion	*Allium cepa*	Liliaceae	Bulb	Flavoring	Cardiovascular disease[b], metabolic disorders[a, b]	29
Paprika	*Capsicum annum*	Solanaceae	Fruit	Flavoring, colorant	Cardiovascular disease[a], headache[b]	2
Pepper, black/white	*Piper nigrum*	Piperaceae	Fruit	Flavoring, antioxidant	Cardiovascular disease[a, b], metabolic disorders[b]	119
Pepper, red	*Capsicum frutescens*	Piperaceae	Fruit	Flavoring	Metabolic disorders[b], neurodegenerative disorders[b]	41
Saffron	*Crocus sativus*	Iridaceae	Stigma	Colorant	Metabolic disorders[b], macular degeneration[b]	4
Star anise	*Illicium verum*	Illiciaceae	Fruit	Antioxidant	–	0
Turmeric	*Curcuma longa*	Zingiberaceae	Rhizome	Colorant, antimicrobial	Cancer[a, b], cardiovascular disease[a, b], neurodegenerative disorders[a, b], metabolic disorders[a, b] skin inflammation[b], osteoarthritis[b]	117
Vanilla	*Vanilla tahitensis*	Orchidaceae	Fruit	Flavoring	Metabolic disorders[b], osteoporosis[b]	57

Number of clinical trials registered in ClinicalTrials.gov in November 2018
[a]Published human studies of the therapeutic properties of spices
[b]Currently ongoing clinical trials studying therapeutic properties spices

Food Applications

Flavorings

Flavoring food is one of the most common uses of spices. There is a conventional classification of spices based on the degree of taste [74]:

- Hot spices: Black, red, and white pepper, ginger, and mustard
- Mild spices: Paprika and coriander
- Aromatic spices: Allspice, cardamom, celery, cinnamon, clove, cumin, dill, fennel, fenugreek, onion, garlic, and nutmeg

The most important flavor compounds found in culinary spices are eugenol (allspice, cinnamon, and clove), piperine (black pepper), gingerol (ginger), myristicin (nutmeg), and turmerone (turmeric) [74].

Colorants

Paprika (E160c) and curcumin (E100) are the two natural colorants obtained from spices allowed as food additives in the EU and in the USA [31, 58]. Paprika extract (E160c) is a natural dark red dye obtained by solvent extraction from the ground fruit pods, with or without seeds, of *Capsicum annuum*, and it contains capsanthin and capsorubin as the principle coloring compounds [32]. In both the EU and the USA, paprika extract (E 160c) is permitted *quantum satis*, which means that no maximum numerical level is specified and it shall be used in accordance with good manufacturing practice, at a level not higher than is necessary to achieve the intended purpose and provided the consumer is not misled [31]. However, for meat preparations and processed meat, there is an established limit by the European Commission of 10 mg/kg product [58]. Curcumin (E100) is obtained by solvent extraction of turmeric, the ground rhizomes of *Curcuma longa*. Curcumin, which represents about 2–8% of most turmeric preparations, gives turmeric its distinct color and flavor. A concentrated curcumin powder is obtained by crystallization. The orange-yellow powder consists essentially of curcumins, the coloring principle (1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-dien-3,5-dione), and its two desmethoxy derivatives in varying proportions [32]. The EU has established an acceptable daily intake of curcumin of 3 mg/kg; however, the USA limits the amount of turmeric used in foods by the good manufacturing practices (GMP) where manufacturers use only the amount of an additive necessary to achieve the desired result [58].

Preservatives: Antioxidants

Different spices have been studied to preserve different food matrixes. For instance, coriander has been proven to be efficient as an antioxidant in the control of lipid oxidation in white hake fish meatballs during frozen storage [84]. Dwivedi et al. [26] have studied Chinese five-spice ingredients composed of cinnamon, cloves, fennel, pepper, and star anise alone and in combination in cooked ground beef. Results showed that all spices and blends reduced rancid odor/flavor in cooked ground beef. However, the spices did not mask rancid off-flavors but had antioxidant effects [26]. Cooked ground beef has also been used as a food matrix to study the antioxidant effect and sensory attributes of individual ingredients (black pepper, caraway, cardamom, chili powder, cinnamon, cloves, coriander, cumin, fennel, ginger, nutmeg, salt, star anise) of an Indian spice blend (garam masala). All individual spices of garam masala were effective in maintaining low rancidity levels in cooked beef during refrigeration in addition to significant reduction of perception of rancid odor and rancid flavor [97]. The antioxidant properties of spices are due to their chemical composition, especially to phenolic compounds. In fact, there is a linear relationship between the phenolic and flavonoid content and the antioxidant capacity of a spice [99]. Most of the antioxidants from spices act by reacting with free radicals created during the initiation stage of autoxidation or by forming complexes with metal ions [30].

Preservatives: Antimicrobials

The use of spices as preservatives has been assessed in multiple foods such as meat, fish, dairy products, vegetables, rice, fruit, and animal food. Spices can exert antimicrobial activity in two ways: by preventing the growth of spoilage microorganisms (food preservation) and by inhibiting the growth of those pathogenic (food safety) [36]. Many extracts obtained from spices possess antimicrobial activity against a wide range of bacteria, yeast, molds, and viruses due to the presence of high levels of phenolic compounds. Cumin and clove essential oils inhibited the growth of total bacteria on meat samples for 15 days at 2 °C [39]. In addition, treatment of raw chicken meat with extracts of clove, oregano, cinnamon, and black mustard was effective against microbial growth [78]. The addition of turmeric extract (1.5%) to whole gutted rainbow trout can also retard microbial growth, delay the chemical changes, maintain sensory attributes (texture, odor, color, and overall acceptance), and extend the shelf life during refrigerated storage [75]. Although the antimicrobial effects of spices and their derivatives have been tested against a wide range of microorganisms over the years, their mode of action is still not completely understood. In fact, spices and their essential oils can contain many different bioactive compounds present in variable amounts.

Bioactive compounds of spices such as terpenes, terpenoids (thymol and carvacrol), and phenylpropenes (eugenol and cinnamaldehyde) are responsible for their antimicrobial activity. Terpenes possess lesser antimicrobial activity than the other compounds. Terpenoids exert their antimicrobial activity by their functional groups (hydroxyl groups and delocalized electrons) affecting the permeability or disrupting important energy-generating processes leading to cell death. The antimicrobial activity of eugenol is performed at membrane and protein level and reacts and cross-links with DNA and proteins. Overall, antimicrobial activity of spices is a synergistic effect of the combination of all the bioactive compounds present in them [36]. The main limitation of spices as antimicrobial agents is the need of high amounts of natural compounds that comprise the organoleptic profile of foods. Therefore, combinations of spices or their pure natural compounds and additional technologies represent a promising alternative to reduce the amount of spices used and solve this problem.

Therapeutic Properties

Numerous studies have shown that nutraceuticals derived from spices such as clove, coriander, garlic, ginger, onion, pepper, and turmeric prevent various chronic diseases by targeting inflammatory pathways [57]. Nutraceuticals are natural, bioactive chemical compounds that have health-promoting, disease-preventing, or general medicinal properties [16].

A recent cross-sectional study carried out in adults living in Midwestern USA concluded that the majority of participants currently used one or more spices on a daily basis but were unaware of their potential health benefits [45]. This study also concluded that most participants shared interest in learning about the health benefits of spices. Therefore, since limited clinical studies have examined the therapeutic effects of spice-derived nutraceuticals in humans, the aim of this section is to gather and review all the beneficial effects of spices on human health supported by clinical studies. Table 6.2 shows the most commonly used spices according to the FDA, their proved health-promoting properties (published clinical trials and currently on going), and the number of registered clinical trials [95].

Metabolic Disorders

Many spices have antioxidant and anti-inflammatory properties and could also have potential therapeutic properties in diabetes [2]. Only few spices have demonstrated to reduce the glycemic response in animals and human clinical trials. Cumin, cinnamon, garlic, ginger, onion, and turmeric have shown antidiabetic properties in human studies [6]. The antidiabetic properties of these spices involve improving insulin sensitivity, stimulating insulin secretion, decreasing carbohydrate absorption, increasing peripheral glucose uptake, inhibiting hepatic glycogenolysis, exerting antioxidant effects, inhibiting hepatic glycogenolysis, and potentiating endogenous incretins [6].

Cinnamon has the potential to lower blood glucose in animal models and humans. To date, several randomized controlled studies have studied the effect of cinnamon on T2DM in adults. These studies have evaluated the effect of cinnamon on glycosylated hemoglobin, fasting plasma glucose, total cholesterol, LDL cholesterol, and triglycerides [67]. However, the short duration of studies is flawed; design has made the available evidence difficult to interpret.

The first randomized double-blind placebo-controlled clinical trial to evaluate the effects of cinnamon on individuals with T2DM was conducted in 2003. Sixty diabetic patients (30 men and 30 women) received either placebo or 3 different doses of cinnamon powder (1, 3, 6 g/day, respectively) for 40 days. Cinnamon was found to reduce fasting blood glucose, triglycerides, LDL cholesterol, and total cholesterol levels [52]. Other clinical study has reported that cinnamon decreased glycosylated hemoglobin (HbA1c) in 109 patients with T2DM [24].

Fenugreek seeds have been found to diminish hyperglycemia in normal individuals and those with diabetes in several different clinical trials carried out in the past few years [91]. Fasting blood glucose, 24-h urinary sugar excretion, serum cholesterol, and triglyceride levels were significantly reduced in diabetic patients. Clinical symptoms like polyuria, polyphagia, and polydipsia were also improved. These effects of fenugreek seeds seem to be due to the gum fiber present in them. Inclusion of fenugreek in amounts of 25–50 g in the daily diet can be an effective supportive therapy in the management of diabetes. Fenugreek is reported to be absolutely safe for consumption based on a long-term animal study [91].

Ginger supplementation might be considered as a beneficial natural remedy for regulating triglycerides and LDL cholesterol. The lowering effect of ≤2 g/day ginger was greater on triglycerides and total cholesterol [77]. Ginger is a safe, non-expensive, and available traditional remedy with negligible side effects at usual dosages. However, further long-term studies are needed to confirm these results.

Turmeric is another important spice claimed to possess beneficial hypoglycemic effects and to improve glucose tolerance in a limited number of clinical studies. Moreover, it has been demonstrated that turmeric had a synergistic effect with metformin in T2DM in lowering fasting blood glucose. When T2DM patients received turmeric supplementation with metformin, both fasting blood glucose and HbA1c levels were significantly reduced as compared to controls treated metformin alone [62].

Cumin supplementation has been found to be more effective than glibenclamide in the treatment of T2DM. The antihyperglycemic effect of cumin may be due to the protection of surviving pancreatic β-cells, the increase in insulin secretion, and glycogen storage [9].

The antidiabetic, hypolipidemic, and antioxidant properties of coriander and anise have been assessed in vivo by the administration of coriander seed powder (5 g/day) to diabetic patients for 60 days. It was found that coriander and anise decreased blood sugar, decreased serum lipids and lipoproteins, improved HDL, and controlled lipid peroxidation [80].

Clove extracts also improved the function of insulin and lower glucose, total cholesterol, LDL, and triglycerides in people with diabetes. Thirty-six people with T2DM were given capsules containing 0, 1, 2, or 3 g of cloves per day for 30 days followed by a 10-day washout period. At the end of the 30 days, the diabetic patients who had been taking some level of clove supplementation showed a decrease in serum glucose, triglycerides, serum total cholesterol, and LDL [51].

Cardiovascular Diseases

Although very few clinical studies regarding the use of spices and cardiovascular diseases have been performed, Harvard Medical School recommends the use of spices instead of salt and butter in order to prevent high blood pressure and heart disease. A salty diet may raise blood pressure, increasing the risk of heart attack and stroke. It has been found that people who enjoy spicy foods (especially chili peppers) eat less salt and have lower blood pressure than people who prefer less spicy foods. These findings suggest that gradually adding small amounts of spice to your food may help reduce use of salt and, therefore, lower blood pressure [37].

A randomized crossover study has shown that the post meal triglyceride response can be reduced by the inclusion of a culinary spice blend (black pepper, cinnamon, cloves, garlic, ginger, oregano, paprika, rosemary, and turmeric) in a high-fat meal by the inhibition of enzymes responsible for lipid digestion in the small intestine [65]. Post-meal triglycerides are an important indicator of cardiovascular risk and a potential target for therapeutic intervention. These data suggest that the regular inclusion of spices in the diet may help attenuate the effect of large fat loads on cardiovascular risk.

Cancer

There are several spices such as turmeric, garlic, ginger, and black cumin with proven anticarcinogenic effects in animal models of cancer. These spices have shown chemopreventive effects against different types of cancers – skin, stomach, pancreas, liver, colon, and oral – in experimental models. Zheng et al. [104] have reviewed recent studies on some spices for the prevention and treatment of cancers paying special attention to bioactive components and mechanisms of action. These authors suggest the potential therapeutic strategy of using spices to prevent or treat cancers [104]. However, cancer-preventive effects have not been conclusively proven in humans. Bioactive compounds composing these spices reduce oxidative stress inhibit cell division, promote apoptosis in cancerous cells, and regulate inflammation contributing to cancer prevention [92].

One of the most studied spices for the application in cancer treatment is turmeric. Curcumin obtained from turmeric shows antioxidant, anti-inflammatory, and antitumor properties demonstrated in preclinical and clinical trials. Antitumor activity is proposed to be due to the activation of apoptosis and inhibition of inflammation, angiogenesis, and metastasis in the tumor microenvironment [25]. There are numerous clinical trials being carried out to allow corroborating the in vitro antitumor activity of curcumin and its effectiveness as a therapeutic agent in different types of tumors such as: colon, gastric, cervical, endometrial, breast, pancreatic, prostate, lung, and lymphoma [25]. Consequently, numerous patents have been developed in connection with the administration and use of curcumin against different types of cancer.

Garlic has also been studied in a few clinical trials to examine its potential anticancer effects. Different randomized clinical trials have evaluated the effect of garlic intake on gastric cancer risk. In one study, patients who received garlic extract had a reduction of risk for all tumors combined by 33% and the risk for stomach cancer by 52% in comparison with the placebo group [59]. In contrast, findings from another randomized trial involving individuals with precancerous stomach lesions found that garlic supplementation (800 mg garlic extract plus 4 mg steam-distilled garlic oil daily) did not improve the prevalence of precancerous gastric lesions or reduced the incidence of gastric cancer [102]. A randomized study in Japan compared the effects of daily high-dose and low-dose intakes of garlic extract on individuals with colorectal adenomas, and after 12 months, 67% of the low-intake group developed new adenomas compared with 47% in the high-intake group [93]. Diallyl disulfide and diallyl trisulfide may be the main contributors of the anticancer action of garlic. Garlic compounds may work by multiple mechanisms, including mutagenesis inhibition, induction of phase II detoxification enzymes, inhibition of DNA adduct formation, affecting the intrinsic pathway for apoptotic cell death, and cell cycle machinery that may cumulatively contribute to their anticancer activities [92]. Future research is needed in the clinical assessment of these compounds for the prevention or treatment of cancers in humans.

Neurodegenerative Disorders

Recently, numerous spices, medicinal plants, fruits, and vegetables possessing high antioxidant activity have received much attention as food supplements to slow the loss of cognitive function with aging and to protect against Alzheimer's disease. A 6-month trial examined curcumin's safety and its effects on biochemical and cognitive measures on Alzheimer's disease. Thirty-three patients were randomly assigned to receive 1–4 g of curcumin as capsule or powder. A rise of amyloid β_{40} levels in serum and a slower disease progression was observed in patients treated with curcumin. This finding indicated that curcumin disaggregates amyloid β_{40} deposits in the brain, releasing amyloid β_{40} for circulation and disposal. In addition, this study found no side effects from curcumin [88]. Not all studies have demonstrated benefits, although a 12-month randomized, placebo-controlled, double-blind study of 1500 mg/d BiocurcumaxTM showed that most of the benefit was attributed to a significant decline in the placebo arm at 6 months as assessed by the Montreal Cognitive Assessment [79].

Most of the literature about nutraceuticals derived from spices discusses only curcumin, given that this spice may have potential against neurodegenerative diseases, owing to its strong anti-inflammatory and antioxidant properties. However, the potential of many other spices needs also to be explored. Therefore, more preclinical and clinical studies are urgently needed to fully explore the potential of spice-derived nutraceuticals as neuroprotective agents.

Conclusion

Herbs and spices have been traditionally used in culinary practices and in traditional medicine for centuries. Among all the herbs reviewed in this chapter, green tea is the one with the most compelling evidence for health benefits in humans. Turmeric is the spice with more scientific evidence from human studies with potential health-promoting properties in cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic disorders. Despite the numerous studies regarding the health properties of green tea and turmeric, they still have not received neither the FDA nor the EFSA approval to prevent or treat disease. Daily intake of herbs and spices has the potential to contribute to a better health. However, there is a need for an increase in research in the mechanism of action ("phytochemomics") and clinical trials, to improve the evidence-based regarding the efficacy of most herbs and spices.

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References

1. Akhondzadeh S, et al. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry. 2003;74(7):863–6. https://doi.org/10.1136/JNNP.74.7.863.
2. Al-Waili N, et al. Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials. Redox Rep. 2017;22(3):99–118. https://doi.org/10.1080/13510002.2017.1297885.
3. Aljamal A. Effects of bay leaves on blood glucose and lipid profiles on the patients with type 1 diabetes. World Acad Sci Eng Technol. 2010;4(9):409–12.
4. Alonso-Castro AJ, et al. Mexican medicinal plants used for cancer treatment: pharmacological, phytochemical and ethnobotanical studies. J Ethnopharmacol. 2011;133(3):945–72. https://doi.org/10.1016/J.JEP.2010.11.055.
5. Aqil F, Ahmad I, Mehmood Z. Antioxidant and free radical scavenging properties of twelve traditionally used Indian medicinal plants. Turk J Biol. 2006;30(3):177–83. https://doi.org/10.1207/S15326950DP3102_03.
6. Beidokhti MN, Jäger AK. Review of antidiabetic fruits, vegetables, beverages, oils and spices commonly consumed in the diet. J Ethnopharmacol. 2017;201:26–41. https://doi.org/10.1016/j.jep.2017.02.031.
7. Berrington D, Lall N. Anticancer activity of certain herbs and spices on the cervical epithelial carcinoma (HeLa) cell line. Evid Based Complement Alternat Med. 2012;2012:11. https://doi.org/10.1155/2012/564927.
8. Bettuzzi S, et al. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res. 2006;66(2):1234–40. https://doi.org/10.1158/0008-5472.CAN-05-1145.

9. Bi X, Lim J, Henry CJ. Spices in the management of diabetes mellitus. Food Chem. 2017;217:281–93. https://doi.org/10.1016/j.foodchem.2016.08.111.
10. Birtić S, et al. Carnosic acid. Phytochemistry. 2015;115:9–19. https://doi.org/10.1016/J.PHYTOCHEM.2014.12.026.
11. Bogdanski P, et al. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. Nutr Res. 2012;32(6):421–7. https://doi.org/10.1016/j.nutres.2012.05.007.
12. Bower A, Marquez S, de Mejia EG. The health benefits of selected culinary herbs and spices found in the traditional mediterranean diet. Crit Rev Food Sci Nutr. 2016;56(16):2728–46. https://doi.org/10.1080/10408398.2013.805713.
13. Bown D. New encyclopedia of herbs and their uses: the definitive guide to the identification, cultivation and uses of herbs. New York: Dorling Ki; 2001.
14. Bozkurt H. Utilization of natural antioxidants: green tea extract and Thymbra spicata oil in Turkish dry-fermented sausage. Meat Sci. 2006;73(3):442–50. https://doi.org/10.1016/J.MEATSCI.2006.01.005.
15. del Castillo MD, et al. Phytochemomics and other omics for permitting health claims made on foods. Food Res Int. 2013;54(1):1237–49. https://doi.org/10.1016/j.foodres.2013.05.014.
16. del Castillo MD, Iriondo-DeHond A, Martirosyan DM. Are functional foods essential for sustainable health? Ann Nutr Food Sci. 2018;2(1):1015.
17. CBI. Through what channels can you get spices and herbs onto the European market? Centre for the promotion of imports from developing countries. 2018.
18. Chen IJ, et al. Therapeutic effect of high-dose green tea extract on weight reduction: a randomized, double-blind, placebo-controlled clinical trial. Clin Nutr. 2016;35(3):592–9. https://doi.org/10.1016/j.clnu.2015.05.003.
19. Choan E, et al. A prospective clinical trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. Urol Oncol. 2005;23(2):108–13. https://doi.org/10.1016/j.urolonc.2004.10.008.
20. Ciriano MG, et al. Use of natural antioxidants from lyophilized water extracts of *Borago officinalis* in dry fermented sausages enriched in ω-3 PUFA. Meat Sci. 2009;83(2):271–7. https://doi.org/10.1016/J.MEATSCI.2009.05.009.
21. de Ciriano MG-I, et al. Effect of lyophilized water extracts of *Melissa officinalis* on the stability of algae and linseed oil-in-water emulsion to be used as a functional ingredient in meat products. Meat Sci. 2010;85(2):373–7. https://doi.org/10.1016/j.meatsci.2010.01.007.
22. Food and Agriculture Organization of the United Nations (FAO) Revision of The Classification of Food and Feed: Class A: Primary Food Commodities of Plant Origin Type 05: Herbs and Spices (Codex (Cx/Pr 18/50/7)); China. 2017;1–23.
23. Costa A, et al. Antibacterial activity of the essential oil of *Origanum vulgare* L.(Lamiaceae) against bacterial multiresistant strains isolated from nosocomial patients. Rev Bras. 2009;19(1B):236–41.
24. Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. J Am Board Fam Med. 2009;22(5):507–12. https://doi.org/10.3122/jabfm.2009.05.080093.
25. Doello K, et al. Latest in vitro and in vivo assay, clinical trials and patents in cancer treatment using curcumin: a literature review. Nutr Cancer. 2018;70(4):569–78. https://doi.org/10.1080/01635581.2018.1464347.
26. Dwivedi S, Vasavada MN, Cornforth D. Evaluation of antioxidant effects and sensory attributes of Chinese 5-spice ingredients in cooked ground beef. J Food Sci. 2006;71(1):C12–7. https://doi.org/10.1111/j.1365-2621.2006.tb12381.x.
27. Dwyer JT. The potential of spices and herbs to improve the health of the public through the combination of food science and nutrition. Nutr Today. 2014;49:S3–4. https://doi.org/10.1097/01.NT.0000453843.06840.2d.
28. El-Agbar ZA, et al. Comparative antioxidant activity of some edible plants. Turk J Biol. 2007;32:193–6.
29. Elson CE, et al. Impact of lemongrass oil, an essential oil, on serum cholesterol. Lipids. 1989;24(8):677–9. https://doi.org/10.1007/BF02535203.
30. Embuscado ME. Spices and herbs: natural sources of antioxidants – a mini review. J Funct Foods. 2015;18:811–9. https://doi.org/10.1016/j.jff.2015.03.005.
31. European Commission. Regulation (Ec) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. Off J Eur Communities. 2008:1–342. https://doi.org/2004R0726-v.7. of 05.06.2013.
32. European Commission. Annex II Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. Off J Eur Union. 2012:1–295. https://doi.org/10.1201/9781315152752.
33. European Parliament. DIRECTIVE 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. 2003; 8784(211011). https://doi.org/2004R0726-v.7. of 05.06.2013.
34. Farzaneh V, Carvalho IS. A review of the health benefit potentials of herbal plant infusions and their mechanism of actions. Ind Crop Prod. 2015;65:247–58. https://doi.org/10.1016/j.indcrop.2014.10.057.

35. Food and Agriculture Organization of the United Nations. Codex Alimentarius General Standard for Food Additives CODEX STAN 192-1995. 2018.
36. Gottardi D, et al. Beneficial effects of spices in food preservation and safety. Front Microbiol. 2016;7:1–20. https://doi.org/10.3389/fmicb.2016.01394.
37. Harvard Heart Letter. To eat less salt, enjoy the spice of life; 2018. https://www.health.harvard.edu/heart-health/to-eat-less-salt-enjoy-the-spice-of-life.
38. Hernández-Hernández E, et al. Antioxidant effect rosemary (*Rosmarinus officinalis* L.) and oregano (*Origanum vulgare* L.) extracts on TBARS and colour of model raw pork batters. Meat Sci. 2009;81(2):410–7. https://doi.org/10.1016/J.MEATSCI.2008.09.004.
39. Hernández-Ochoa L, et al. Use of essential oils and extracts from spices in meat protection. J Food Sci Technol. 2014;51(5):957–63. https://doi.org/10.1007/s13197-011-0598-3.
40. Herrera T, et al. Teas and herbal infusions as sources of melatonin and other bioactive non-nutrient components. LWT Food Sci Technol. 2018;89:65–73. https://doi.org/10.1016/j.lwt.2017.10.031.
41. Herrera-Arellano A, et al. Effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* in patients with mild to moderate hypertension: a controlled and randomized clinical trial. Phytomedicine. 2004;11(5):375–82. https://doi.org/10.1016/j.phymed.2004.04.001.
42. Horžić D, et al. The composition of polyphenols and methylxanthines in teas and herbal infusions. Food Chem. 2009;115(2):441–8. https://doi.org/10.1016/J.FOODCHEM.2008.12.022.
43. Hosseini A, Ghorbani A. Cancer therapy with phytochemicals: evidence from clinical studies. Avicenna J Phytomed. 2015;5(2):84–97.
44. Huang W-Y, Cai Y-Z, Zhang Y. Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. Nutr Cancer. 2009;62(1):1–20. https://doi.org/10.1080/01635580903191585.
45. Isbill J, Kandiah J, Khubchandani J. Use of ethnic spices by adults in the United States: an exploratory study. Health Promot Perspect. 2018;8(1):33–40. https://doi.org/10.15171/hpp.2018.04.
46. Jandaghi P, et al. Lemon balm: a promising herbal therapy for patients with borderline hyperlipidemia—a randomized double-blind placebo-controlled clinical trial. Complement Ther Med. 2016;26:136–40. https://doi.org/10.1016/j.ctim.2016.03.012.
47. Jassim SAA, Naji MA. Novel antiviral agents: a medicinal plant perspective. J Appl Microbiol. 2003;95(3):412–27. https://doi.org/10.1046/j.1365-2672.2003.02026.x.
48. Jatoi A, et al. A Phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. Cancer. 2003;97(6):1442–6. https://doi.org/10.1002/cncr.11200.
49. Kaefer CM, Milner JA. The role of herbs and spices in cancer prevention. J Nutr Biochem. 2008;19(6):347–61. https://doi.org/10.1016/J.JNUTBIO.2007.11.003.
50. Kaefer CM, Milner JA. Herbs and spices in cancer prevention and treatment, herbal medicine: biomolecular and clinical aspects. Boca Raton, Florida, USA: CRC Press/Taylor & Francis; 2011.
51. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444:840–6.
52. Khan A, et al. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003;26(12):3215–8.
53. Khan A, Zaman G, Anderson RA. Bay leaves improve glucose and lipid profile of people with type 2 diabetes. J Clin Biochem Nutr. 2009;44(1):52–6. https://doi.org/10.3164/jcbn.08-188.
54. Kianbakht S, et al. Antihyperlipidemic effects of *Salvia officinalis* L. Leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clinical trial. Phytother Res. 2011;25(12):1849–53. https://doi.org/10.1002/ptr.3506.
55. Kulisic-Bilusic T, et al. Antioxidant and acetylcholinesterase inhibiting activity of several aqueous tea infusions *in vitro*. Food Technol Biotechnol. 2008;46(4):368–75.
56. Kumar Y, et al. Recent trends in the use of natural antioxidants for meat and meat products. Compr Rev Food Sci Food Saf. 2015;14(6):796–812. https://doi.org/10.1111/1541-4337.12156.
57. Kunnumakkara AB, et al. Chronic diseases, inflammation, and spices: how are they linked? J Transl Med. 2018;16(1):1–25. https://doi.org/10.1186/s12967-018-1381-2.
58. Lehto S, et al. Comparison of food colour regulations in the EU and the US: a review of current provisions. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2017;34(3):335–55. https://doi.org/10.1080/19440049.2016.1274431.
59. Li H, et al. An intervention study to prevent gastric cancer by micro-selenium and large dose of allitridum. Chin Med J. 2004;117(8):1155–60. https://doi.org/10.1046/j.1528-1157.2003.32702.x.
60. Llamas NE, et al. Second order advantage in the determination of amaranth, sunset yellow FCF and tartrazine by UV–vis and multivariate curve resolution-alternating least squares. Anal Chim Acta. 2009;655(1–2):38–42. https://doi.org/10.1016/J.ACA.2009.10.001.
61. Longo L, Vasapollo G. Anthocyanins from Bay (*Laurus nobilis* L.) Berries. J Agric Food Chem. 2005;53(20):8063–7. https://doi.org/10.1021/jf051400e.

62. Maithili Karpaga Selvi N, et al. Efficacy of turmeric as adjuvant therapy in type 2 diabetic patients. Indian J Clin Biochem. 2015;30(2):180–6. https://doi.org/10.1007/s12291-014-0436-2.
63. Mariutti LRB, Nogueira GC, Bragagnolo N. Lipid and cholesterol oxidation in chicken meat are inhibited by sage but not by garlic. J Food Sci. 2011;76(6):C909–15. https://doi.org/10.1111/j.1750-3841.2011.02274.x.
64. Maron DJ, et al. Cholesterol-lowering effect of a theaflavin-enriched green tea extract. Arch Intern Med. 2003;163(12):1448. https://doi.org/10.1001/archinte.163.12.1448.
65. McCrea CE, et al. Effects of culinary spices and psychological stress on postprandial lipemia and lipase activity: results of a randomized crossover study and in vitro experiments. J Transl Med. 2015;13(1):1–12. https://doi.org/10.1186/s12967-014-0360-5.
66. McKay DL, et al. *Hibiscus Sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J Nutr. 2009;140(2):298–303. https://doi.org/10.3945/jn.109.115097.
67. Medagama AB. The glycaemic outcomes of cinnamon, a review of the experimental evidence and clinical trials. Nutr J. 2015;14(1):1–12. https://doi.org/10.1186/s12937-015-0098-9.
68. Momose Y, Maeda-Yamamoto M, Nabetani H. Systematic review of green tea epigallocatechin gallate in reducing low-density lipoprotein cholesterol levels of humans. Int J Food Sci Nutr. 2016;67(6):606–13. https://doi.org/10.1080/09637486.2016.1196655.
69. Mozaffari-Khosravi H, et al. The effects of sour tea (*Hibiscus sabdariffa*) on hypertension in patients with type II diabetes. J Hum Hypertens. 2009;23(1):48–54. https://doi.org/10.1038/jhh.2008.100.
70. National Institute of Aging. What are clinical trials and studies? 2017. Available at: https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies.
71. Nations, F. and A. O. of the U. Codex Alimentarius: general standard for food additives. In: Codex Alimentarius: general standard for food additives. Rome: Food and Agriculture Organization of the United Nations (FAO); 2017.
72. Nurmi A, et al. Consumption of juice fortified with oregano extract markedly increases excretion of phenolic acids but lacks short- and long-term effects on lipid peroxidation in healthy nonsmoking men. J Agric Food Chem. 2006;54(16):5790–6. https://doi.org/10.1021/jf0608928.
73. Opara EI, Chohan M. Culinary herbs and spices: their bioactive properties, the contribution of polyphenols and the challenges in deducing their true health benefits. Int J Mol Sci. 2014;15(10):19183–202. https://doi.org/10.3390/ijms151019183.
74. Peter KV, Shylaja MR. Introduction to herbs and spices: definitions, trade and applications. In: Peter KV, editor. Handbook of Herbs and Spices. Cambridge: Woodhead Publishing; 2012. p. 1–24.
75. Pezeshk S, Rezaei M, Hosseini H. Effects of turmeric, shallot extracts, and their combination on quality characteristics of vacuum-packaged rainbow trout stored at 4 ± 1°C. J Food Sci. 2011;76(6):387–91. https://doi.org/10.1111/j.1750-3841.2011.02242.x.
76. Pistollato F, Battino M. Role of plant-based diets in the prevention and regression of metabolic syndrome and neurodegenerative diseases. Trends Food Sci Technol. 2014;40:62–81. https://doi.org/10.1016/j.tifs.2014.07.012.
77. Pourmasoumi M, et al. The effect of ginger supplementation on lipid profile: a systematic review and meta-analysis of clinical trials. Phytomedicine. 2018;43:28–36. https://doi.org/10.1016/j.phymed.2018.03.043.
78. Radha Krishnan K, et al. Antimicrobial and antioxidant effects of spice extracts on the shelf life extension of raw chicken meat. Int J Food Microbiol. 2014;171:32–40. https://doi.org/10.1016/j.ijfoodmicro.2013.11.011.
79. Rainey-Smith S, Brown B, Sohrabi H, Shah T, Goozee K, Gupta V, Martins R. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br J Nutr. 2016;115(12):2106–13. https://doi.org/10.1017/S0007114516001203.
80. Rajeshwari U, Shobba I, Andallu B. Comparison of aniseeds and coriander seeds for antidiabetic, hypolipidemic and antioxidant activities. Spatulla DD. 2011;1:9–16.
81. Rastogi S, Pandey MM, Rawat AKS. Traditional herbs: a remedy for cardiovascular disorders. Phytomedicine. 2016;23(11):1082–9. https://doi.org/10.1016/J.PHYMED.2015.10.012.
82. Rjzk EM, El-Gharably AM, Tolba KH. Carotenoid pigments composition of Calendula flower and its potential uses as antioxidant and natural colorant in manufacturing of hard candy. Arab Univ J Agric Sci. 2008;16(2):407–17.
83. Sá C, et al. Sage tea drinking improves lipid profile and antioxidant defences in humans. Int J Mol Sci. 2009;10(9):3937–50. https://doi.org/10.3390/ijms10093937.
84. Sancho RAS, et al. Effect of annatto seed and coriander leaves as natural antioxidants in fish meatballs during frozen storage. J Food Sci. 2011;76(6):C838–45. https://doi.org/10.1111/j.1750-3841.2011.02224.x.
85. Santos-Buelga C, Mateus N, De Freitas V. Anthocyanins. Plant pigments and beyond. J Agric Food Chem. 2014;62(29):6879–84. https://doi.org/10.1021/jf501950s.
86. Schmidt U, et al. Efficacy of the Hawthorn (*Crataegus*) preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II. Phytomedicine. 1994;1(1):17–24. https://doi.org/10.1016/S0944-7113(11)80018-8.
87. Shan B, et al. The *in vitro* antibacterial activity of dietary spice and medicinal herb extracts. Int J Food Microbiol. 2007;117(1):112–9. https://doi.org/10.1016/J.IJFOODMICRO.2007.03.003.

88. Shim GS, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with alzheimer disease. J Clin Psychopharmacol. 2008;28(1):110–3.
89. Silva IF, et al. Antimicrobial screening of some medicinal plants from Mato Grosso Cerrado. Braz J Pharmacogn. 2009;19(1 B):242–8. https://doi.org/10.1590/S0102-695X2009000200011.
90. Silva N, Fernandes Júnior A. Biological properties of medicinal plants: a review of their antimicrobial activity. J Venom Anim Toxins Incl Trop Dis. 2010;16(3):402–13. https://doi.org/10.1590/S1678-91992010000300006.
91. Srinivasan K. Plant foods in the management of diabetes mellitus: spices as beneficial antidiabetic food adjuncts. Int J Food Sci Nutr. 2005;56(6):399–414. https://doi.org/10.1080/09637480500512872.
92. Srinivasan K. Antimutagenic and cancer preventive potential of culinary spices and their bioactive compounds. PharmaNutrition. 2017;5(3):89–102. https://doi.org/10.1016/j.phanu.2017.06.001.
93. Tanaka S, et al. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. Hiroshima J Med Sci. 2004;53(3–4):39–45. https://doi.org/10.1093/jn/136.3.810S. [pii].
94. Tapsell LC, Scientific TC, Sullivan DR. Health benefits of herbs and spices: the past, the present, the future. Med J Aust. 2006;185(4 Suppl):S4–24.
95. U.S. Food and Drug Administration (FDA). CPG Sec. 525.750 spices – definitions. 2015. Available at: https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074468.htm.
96. U.S. Department of Agriculture. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. 2015. Available at: https://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf. Accessed 11 Oct 2016.
97. Vasavada MN, Dwivedi S, Cornforth D. Evaluation of garam masala spices and phosphates as antioxidants in cooked ground beef. J Food Sci. 2006;71(5):292–7. https://doi.org/10.1007/s00191-013-0315-7.
98. WHO. Diet, nutrition and the prevention of chronic diseases. World Health Organization Technical Report Series, 916. 2003, p. i–viii-1-149-backcover. ISBN 92 4 120916 X ISSN 0512-3054 (NLM classification: QU 145).
99. Wojdyło A, Oszmiański J, Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chem. 2007;105(3):940–9. https://doi.org/10.1016/j.foodchem.2007.04.038.
100. Yashin A, et al. Antioxidant activity of spices and their impact on human health: a review. Antioxidants. 2017;6(3):70. https://doi.org/10.3390/antiox6030070.
101. Yi W, Wetzstein HY. Anti-tumorigenic activity of five culinary and medicinal herbs grown under greenhouse conditions and their combination effects. J Sci Food Agric. 2011;91(10):1849–54. https://doi.org/10.1002/jsfa.4394.
102. You WC, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst. 2006;98(14):974–83. https://doi.org/10.1093/jnci/djj264.
103. Zeraatpishe A, et al. Effects of *Melissa officinalis* L. on oxidative status and DNA damage in subjects exposed to long-term low-dose ionizing radiation. Toxicol Ind Health. 2011;27(3):205–12. https://doi.org/10.1177/0748233710383889.
104. Zheng J, et al. Spices for prevention and treatment of cancers. Nutrients. 2016;8(8):495. https://doi.org/10.5194/acpd-11-10449-2011.