Chapter 19
Antioxidants in the Prevention and Treatment of Cancer

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Abstract Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are constantly produced in all aerobic organisms, mostly as a consequence of normal cellular aerobic respiration. Many factors outside the body, such as unhealthy diets and behaviours, exposure to environmental pollutants and radiation pollution, also trigger the production of abnormally high concentrations of highly reactive and toxic ROS and NOS in tissues and organs of biological systems. The excessive production of ROS/RNS causes damage to DNA, proteins and lipids and can increase the risk of cancer. Antioxidants maintain redox homeostasis and prevent ROS-/RNS-induced damages that have been associated with cancer development. In the body, antioxidant defence systems include endogenous (enzymatic and non-enzymatic antioxidants) and exogenous antioxidants supplied by plant foods. Plants or parts of plants with medicinal properties are traditionally used in health care and disease prevention and treatment. Plants are considered relatively safe, efficient and inexpensive ways of producing several valuable molecules, including many anticancer drugs. Rational food selection based on therapeutic properties and antioxidant constituents might be a useful strategy for cancer prevention. This chapter summarises recent progress on the production and health benefits of antioxidants derived from food and medicinal plants and their use in cancer prevention and treatment.

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This chapter also outlines most recent anticancer drugs originally derived from medicinal plants and discusses lead structures isolated from natural product with anticancer potential use as adjuvants in conventional anticancer drugs.

Keywords Antioxidants • Healthy diet • Food • Medicinal plants • Cancer prevention and treatment

19.1 Introduction

Noncommunicable diseases (NCDs), mainly cancers, are responsible for about two-thirds of deaths worldwide, mostly in low- and middle-income countries (Ezzati and Riboli 2012). Each year, almost 7 million people die from cancer and close to 11 million new cases are diagnosed, with more than half occurring in the developing world (WHO 2012). The incidence of cancer rises globally because of increased human exposure to environmental pollutants and unhealthy lifestyle factors (Anand et al. 2008, Sankpal et al. 2012, Pacheco et al. 2016). Modern cancer therapies have significantly prolonged the life in many cancer patients but have not succeeded in reducing cancer mortality. Chemotherapy and radiation are toxic to healthy tissues and organs and cause serious side effects. Therefore, patients worldwide use alternative and/or complementary plant therapeutic strategies during cancer treatment (Lee et al. 2014, Wang et al. 2014, Abdallah et al. 2015, Poonthananiwatkul et al. 2015).

The consumption of medicinal plants and herbal remedies is higher than modern medicines largely because of their easy availability, low cost and minimal side effects. In the field of cancer therapy, 49% of the 85 molecules approved between 1940 and the end of 2014 are natural or natural-derived products (Newman and Cragg 2016). Bioactive compounds in plants can be defined as secondary plant metabolites eliciting pharmacological or toxicological effects in human and animals. Plant secondary metabolites have been identified as cancer chemopreventive agents (Kinghorn et al. 2004). Examples of plant-derived anticancer compounds are reserpine (Lupulescu 1983, Abdelfatah and Efferth 2015), quinine (Solary et al. 1992), Taxol (Expósito et al. 2009), curcumin (Park et al. 2013) and aspirin (Alfonso et al. 2014). Many plant-derived anticancer agents including vinblastine; vincristine (isolated from the *Catharanthus roseus* G. Don.); etoposide and teniposide (*Podophyllum peltatum* Linn.); paclitaxel, also named as Taxol (isolated from the bark of *Taxus brevifolia* Nutt.); camptothecin (isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne); and homoharringtonine (isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea*) are in clinical use against a range of cancers (Prakash et al. 2013).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), including the oxygen free radicals, superoxide radical ($^{\bullet}O_2^-$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), nitric oxide ($NO^{\bullet}$) and the highly reactive and toxic, hydroxyl radical ($^{\bullet}OH$) and peroxynitrite ($ONOO^-$), are constantly produced in all aerobic organisms, mainly as a consequence of normal cellular aerobic respiration. Factors

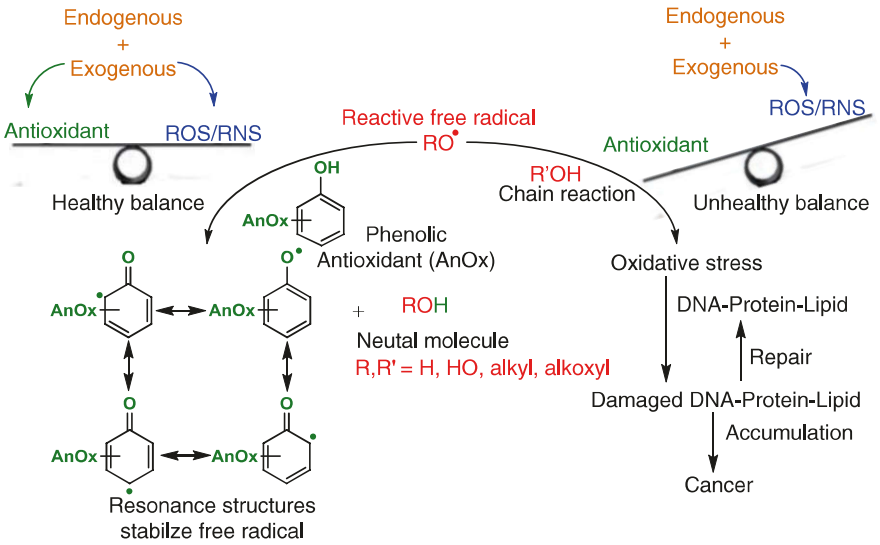


Fig. 19.1 Role of antioxidant-reactive oxygen species (ROS) balance in preventing/promoting cancer

outside the body, such as unhealthy diets (high content in fats, free sugars, salt and low fruit and vegetable intake) and unhealthy behaviours (tobacco smoking, alcohol consumption, physical inactivity), exposure to environmental pollutants (cigarette smoke, nitrogen oxides, sulphur dioxide, particulate matter, polycyclic aromatic hydrocarbons, heavy metals and pesticides) and radiation pollution (ionising and nonionising radiation, ultraviolet radiation and many other radioactive substances) also contribute to the generation of abnormally high concentrations of ROS and NOS (Fig. 19.1) in tissues and organs of biological systems (Sankpal et al. 2012, Poljšak and Fink 2014). The excessive production of ROS/RNS and the resulting oxidative/nitrosative stress may induce damage of cellular macromolecules, including DNA proteins and lipids, and can increase the risk of cancer development (Storz 2005, Ying and Hofseth 2007, Ortega et al. 2010, Reuter et al. 2010). Therefore, modulation of intracellular ROS/RNS levels by antioxidants can be used to target oxidative stress-mediated cancer initiation, promotion and progression.

Antioxidants mainly act as chemical electron quencher and stop or reduce the free-radical chain reaction. The effectiveness of an antioxidant is related to many factors, including activation energy, rate constants, oxidation-reduction potential and solubility properties. The efficiency of an antioxidant increases with decreasing phenolic oxygen-hydrogen bond strength (Shahidi and Naczk 2006). Thus, an antioxidant with a phenolic moiety can readily transfer electron or easily donate hydrogen atom from two phenolic sites to scavenge free radicals; and its radical intermediates are relatively stable due to delocalisation of electrons on the aromatic ring. The stable radical intermediate decreases the formation of new radicals, thus slowing chain free-radical reactions and improves defence efficiency. Rational food selection based on therapeutic properties and antioxidant constituents might be a useful strategy for cancer prevention. Fruit and vegetable antioxidants are crucial for protection against

ROS/RNS molecules that are produced in the human body by the breakdown of nutrients from food and/or after exposure to multiple environmental factors (Balsano and Alisi 2009, Jacob et al. 2012, Aboul-Enein et al. 2013, Poljšak and Fink 2014). Evidence suggests that regular and sustained consumption of fruits and vegetables may reduce the risk of NCDs, including cancer (Potter and Steinmetz 1996, La Vecchia et al. 2001, Riboli and Norat 2003, Benetou et al. 2008, Boffetta et al. 2010, Choi et al. 2015). In this chapter, plant sources of antioxidants and methods to enhance their production will be addressed. The rational use of plant antioxidants designed for cancer prevention will be discussed. This is followed by a brief description of recent anticancer drugs derived from medicinal plants and lead structures with anticancer potential. Finally, the potential interaction of plant medicinal extracts with known anticancer drugs is discussed.

19.2 Plant Antioxidants

Plant primary metabolites are sugars, fatty acids, amino acids and nucleic acids, which are required for plant growth, development and reproduction (Kasote et al. 2015). Plants also produce secondary metabolites with antioxidant properties as an adaptive defence mechanism that provides protection against environmental biotic and abiotic stresses. They are also essential to the normal reproduction, growth and development of plants (Kasote et al. 2015). The plant phenolic compounds include a variety of structures ranging from small molecules (phenolic acids) to complex structures (polyphenols). Plant antioxidant defence systems have also diverse structural features, which include the enzymatic compounds, superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), ascorbate peroxidase (APX) and glutathione reductase (GR), as well as non-enzymatic water-soluble compounds, such as ascorbic acid, glutathione and flavonoids, and lipid-soluble molecules, such as alpha-tocopherol, beta-carotene and lycopene (Arora et al. 2002, Gill and Tuteja 2010).

19.3 Processing of Plant-Derived Antioxidants

Many reports have investigated the effects of processing, cultivation, packing, temperature and storage conditions on the antioxidant activity in food, fruits and vegetables. Antioxidant phytochemicals present widely in fruits, vegetables, spices, herbs and medicinal plants and belong to various classes of compounds with a wide variety of physical and chemical properties (Carlsen et al. 2010, Fu et al. 2011a, Nahak et al. 2014). A recent study by Castro-Lopez and co-authors evaluated the changes in the overall antioxidant properties of fruit beverages under different storage conditions by measuring the stability of phenolic compounds, ascorbic acid, total carotenoids and total antioxidant activity (Castro-Lopez et al. 2016). These compounds were

stable and in some cases increased during the first 12 days at temperatures between 4 and 8 °C. Carotenoids and ascorbic acid were slightly degraded through the storage period, possibly by oxidation or interaction with other components (Castro-Lopez et al. 2016). The bioactive compounds of the plants have been successfully isolated and identified as our chemical techniques have improved. Extraction of crude drugs depends on the physical nature of the drug and chemical properties of other constituents present in plants (Xu et al. 2017).

Plants cultivated in an organic environment are perceived to be more nutritious, better tasting, and environmentally friendlier compared to food cultivated under conventional conditions. Ren and co-workers studied the relationship between cultivation practices on the production of secondary metabolites in onions (a major source of polyphenols in human diet) grown under conventional, organic and mixed systems (Ren et al. 2017). Phenolics, total flavonoids and antioxidant activities were measured over a 4-year period. Total phenolic and flavonoid contents were generally higher in red onion and were significantly higher in those grown under organic cultivation compared to mixed and conventional treatments (Ren et al. 2017). The antioxidant contents of fruits are strongly influenced by factors such as rootstock (Remorini et al. 2008), climatic conditions and ripening stages (Scordino et al. 2012). Monitoring the nutritional value of fruits during the ripening process is helpful to determine the optimal date for harvesting and to achieve the best quality for both fresh consumption and processing.

Fruit peels are richer in nutritional value than the edible fleshy parts. Fruit peels are usually discarded because they may be indigestible or contaminated by pesticides. However, high concentrations of phenolic compounds are present in fruit peels, making them attractive as source of functional foods and nutraceuticals for health (Varzakas et al. 2016). Peels of peach and nectarine contain at least twice as much phenolics (Tomas-Barberan et al. 2001) and carotenoids and ascorbic acid (Gil et al. 2002) compared to their fleshy parts. Pomegranate peel extracts have more potential as a health supplement rich in polyphenolic antioxidants than the pulp extract (Li et al. 2006). Importantly, the antioxidant activity of fruit flesh tends to increase during ripening, while in the peel this trend is not always the case and can vary in different fruits (Dabbou et al. 2017).

The chemicals used in postharvest technology of horticultural crops must comply with food safety rules and regulations. Fresh fruit and vegetables lose weight due to water loss and respiration after harvest. Ethylene is the ripening promoting agent, leading to crop flesh softening together with increases in the rates of various other ripening processes such as discoloration, weight loss, general senescence and respiration. The antioxidant content is good indicator of the internal cell situation, and fruits with high antioxidant content are considered healthy. Strawberries and their fresh juice show high antioxidant activities that are susceptible to postharvest loss. Methyl jasmonate plays a key role in cell communication including ethylene production, defence responses and increasing the antioxidant capacity of different harvested fruits and horticultural crops. Methyl jasmonate enhances antioxidant activity hence increases the fruit storage period by enhancing the defence systems (Asghari and Hasanlooe 2016).

Plant polyphenols primarily occur in conjugated forms, with one or more sugar residues linked to hydroxyl groups. The cooking process either increases (Dewanto et al. 2002) or decreases (Mazzeoa et al. 2011) polyphenol levels, depending on the type of plants and the cooking procedure (time, pressure, etc.). The polyphenol content in cooked vegetables depends on whether the phenolic moiety exists in a linked or free form. A study of antioxidant activity in cooked carrots (peeled and unpeeled) reported that the antioxidant activity was usually higher in cooked and unpeeled carrots but that it was either unchanged or decreased in peeled carrots (Biezanowska-Kopec et al. 2016).

Mushrooms are frequently used for their unique taste, aroma, nutritional value and medicinal potential, and many species are available worldwide (Pesti 2014). Mushrooms have a high proportion of indigestible fibre and antioxidant constituents. The effects of $NO^{\bullet}$ on the contents of phenolics, flavonoids and antioxidant activity in mushroom have been examined. Postharvest nitric oxide fumigation of mushrooms significantly enhanced antioxidant activity, most likely by inducing the production of secondary metabolites (Dong et al. 2012).

19.4 Antioxidant Activity of Selected Fruits and Vegetables

Grains are important sources of many nutrients including antioxidants, minerals and fibres, and the antioxidant activities of various fractions of grain obtained during milling process have been studied (Miller et al. 2000). The antioxidant activity is highest in bran, whereas refined flour had the lowest activity. The antioxidant activity of dry beans increases with increased redness of the beans; red kidney beans have higher antioxidant activities than grapes, cabbage, blueberries and strawberries (Miller et al. 2000).

A systematic evaluation of antioxidant activity and total phenolic contents of 62 fruits was evaluated using a ferric reducing antioxidant power (FRAP) assay (Fu et al. 2011b), which is based on the ability of antioxidants to reduce ferric (III) ions to ferrous (II) ions (Benzie and Strain 1996). The Trolox equivalent antioxidant capacity (TEAC) assay, based on the ability of antioxidants to scavenge 2,2′-azinobis(3-ethylbenzothiazoline-6-sulphonic acid radicals (ABTS), was also used to evaluate the free radical scavenging capacities of 62 fruits. Chinese dates, pomegranates, guavas, sweetsop, persimmons, Chinese wampee (*Clausena lansium*) and plum had the strongest antioxidant activities among the 62 fruits tested, while olives had the strongest free radical scavenging ability.

The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide has been determined (Carlsen et al. 2010), and the antioxidant content of common fruits, vegetables, spices and nuts is summarised in Table 19.1. The data could be used as database to identify and rank diets in terms of antioxidant intake and designing healthy meal plans. The results also suggest that the antioxidant content of plant-based foods is higher than in animal-based foods. Depending on the mean values, one can conclude that plant products such as fruits, nuts, chocolate and berries have from 5 to 33 times higher antioxidant content than

Table 19.1 Antioxidant activities of selected food ingredients (adapted from Carlsen et al. 2010)

Food ingredients	Antioxidant content, mmol/100 g	Food ingredients	Antioxidant content, mmol/100 g
African baobab tree, leaves (dry, crashed)	48.1	Green tea (prepared)	1.5
Allspice (dried ground)	100.4	Maize (white flour)	0.6
Amla (Indian gooseberry, dried)	261.5	Mango (dried)	1.7
Apples	0.4	Millet	1.3
Apples (dried)	3.8	Mint leaves (dried)	116.4
Apple juice	0.27	*Moringa stenopetala* (dried leaves, stem)	11.9
Apricots dried	3.1	*Moringa stenopetala* (fresh leaves, stem)	3.7
Artichoke	3.5	Nutmeg (dried ground)	26.4
Basil dried	19.9	Okra (gumbo) from Mali (dry, flour)	4.2
Bay leaves dried	27.8	Oranges	0.9
Bilberries dried	48.3	Orange juice	0.64
Beans	0.8	Oregano (dried ground)	63.2
Black tea prepared	1.0	Papaya	0.6
Black olives	1.7	Peanuts roasted with pellicle	2.0
Blueberry jam	3.5	Pecans with pellicle	8.5
Broccoli (cooked)	0.5	Pistachios	1.7
Buckwheat white flour	1.4	Plums, dried	3.2
Buckwheat whole meal flour	2.0	Pomegranate	1.8
Chestnuts with pellicle	4.7	Pomegranate juice	2.1
Chilli red and green	2.4	Prunes	2.4
Cinnamon sticks and whole bark	26.5	Prune juice	1.0
Cinnamon dried ground	77.0	Red wine	2.5
Clove dried, whole and ground	277.3	Rosemary (dried ground)	44.8
Cocoa with milk	0.37	Saffron (dried ground)	44.5
Coffee prepared	2.5	Saffron (dried stigma)	17.4
Cranberry juice	0.92	Sage (dried ground)	44.3
Crisp bread (brown)	1.1	Strawberries	2.1
Curly kale	2.8	Sunflower seeds	6.4
Dates (dried)	1.7	Thyme (dried ground)	56.3
Dill (dried ground)	20.2	Tomato juice	0.48
Dog rose (wild, dried)	78.1	Walnuts with pellicle	21.9
Espresso (prepared)	14.2	Wheat bread (toasted)	0.6
Estragon (dried)	43.8	Whole wheat bread (toasted)	1.0
Fruit from the African baobab tree	10.8	Walnuts with pellicle	21.9
Ginger (dried)	20.3	Zereshk (red sour berries)	27.3
Grape juice	1.2		

the means of meat products. Spices and herbs, although contributing little in terms of weight to a meal, make a large contribution to antioxidant intake. Breakfast cereals, chocolate-containing foods, coffee and tea are important sources of dietary antioxidants. Of note is that the antioxidant content in human breast milk is comparable to pomegranate juice, strawberries and coffee and higher than commercially available infant formula milk. Remarkably, dried fruits are higher in antioxidants than their corresponding fresh fruits and fruit juice. Red cabbage, red beans and red grapes are relatively high in antioxidants compared to their green counterparts. There is a striking difference between red and green cabbage, with the purple cabbage pigment contributing a high level of antioxidant activity. Many popular drinks tend to have relatively moderate levels of antioxidants. In general, spices have the highest antioxidant levels followed by nuts, fruits and vegetables. The antioxidant activity of melons is much lower than other fruits.

In summary, fruit and vegetable antioxidants exhibit health beneficial effects at least in part through prevention of ROS-induced DNA, protein and lipid oxidative damages. Fruit and vegetable antioxidant contents are highly dependent on cultivation, processing, packing, storage conditions and temperature. To enhance or maintain antioxidant content, storage temperature is kept between 4 and 8 °C for 2 weeks, as higher temperatures and or longer times lowering antioxidant content. The entire tissue of fruits and vegetables is rich in phenolic compounds, and in most cases the waste by-products, such as peels, can present higher content of antioxidants. Cultivating fruits and vegetable in organic media improves their antioxidant activity, and postharvest use of chemicals such as methyl jasmonate and nitric oxide significantly enhances antioxidant activities particularly in strawberries and mushrooms, respectively.

19.5 Nutrition and Cancer Prevention

Philosophers, scholars and scientists have for some time tried to develop a relationship between food and therapy, as food and medicinal plants were the only sources for treating different diseases at that time. As chemical techniques became more advanced, treatment of diseases became more reliant on specific molecules prepared under controlled conditions. Although single molecule treatment strategies were successful in treating many diseases, they were expensive and unaffordable in many societies. However, many therapeutic agents were unable to treat NCDs like cancer, leading scientists to re-examine the use of food and medicinal plants as a source of disease prevention and therapy (Back et al. 1995).

19.5.1 Antioxidants for Cancer Prevention

Cancer is a chronic disease with many causes, but unhealthy diets and lifestyle behaviours, as well as exposure to a wide variety of environmental pollutants, may increase the risk at least in part through ROS and RNS generation which induced oxidative stress and lead to cancer initiation and development (Waris and Ahsan

2006, Preedy 2014). Therefore, a fine balance between the levels of ROS/RNS and antioxidants within the cell is crucial for normal physiological function (Fig. 19.1). Any impairments of the redox systems can result in a redox imbalance, consequently promoting damage to key cellular structures including DNA, proteins and lipids, which play a pivotal role in the development of cancer (Fig. 19.1). Since DNA damage from micronutrient deficiencies is likely to be a major cause of cancer (Ames 2001) and ROS appear to play an active role in the development of cancer (Waris and Ahsan 2006), there has been much investigation of the role of nutritional antioxidant intake in the prevention of cancer (Mut-Salud et al. 2016). Some studies have focused on the effects of increasing the dietary intake of vitamins, carotenoids and/or minerals on prostate (Santillo and Lowe 2006), rectal (Hu et al. 2007), gastric (Lazarević et al. 2011), pancreatic (Bravi et al. 2011) and breast (Saquib et al. 2011) cancer.

The use of antioxidants during cancer treatment could interfere with the actions of prescribed anticancer drugs to decrease drug efficacy and prevent cancer cells from undergoing apoptosis. Data from randomised clinical trials show benefit of supplementation with beta-carotene, vitamin C and vitamin E, selenium and zinc alone or in combination on cancer prevention, selenium and zinc alone or in combination with other antioxidant supplements (Hajhashemi et al. 2010, Greenlee et al. 2012, Huang et al. 2016). Antioxidant supplementation, particularly with beta-carotene and vitamin E, does not reduce primary cancer incidence or cancer mortality (Jiang et al. 2010, Chen and Alpert 2016). Selenium supplementation may reduce cancer incidence and cancer mortality in men, but not in women, but clearly more studies are needed to confirm the cancer preventive effects of selenium (Bardia et al. 2008). The standard guideline for patients being treated for cancer is that supplements should not be taken before, during and after the treatment, whereas antioxidants from dietary sources are not restricted. The general conclusion is that while antioxidant supplementation may not prevent cancer formation, healthy diets likely do with organically grown food having high antioxidant contents (Chhabra et al. 2013). Plants grown free of pesticides will maintain high levels of antioxidants. Organic plants are rich sources of in vitamins, minerals and fibres, which facilitate digestion, absorption, distribution and elimination of antioxidants (Volpe et al. 2015, Dietz et al. 2016).

19.5.2 Healthy Nutrition for Cancer Prevention

Many would agree that humans evolved as omnivores, and healthy nutrition usually includes foods derived from plant and animal sources. Now, a healthy diet is seen as one designed to reduce excess body fat and limit the intake of drinks with high sugar, but there are as many healthy dietary patterns as there are concepts of what constitutes a healthy nutrition (Kushi et al. 2012). The consumption of plant foods with a variety of nutrients is more beneficial over single constituent, because interactions between food phytochemicals are important for cancer prevention (Liu 2004).

Colorectal cancer is the second most diagnosed cancer in females and the third most commonly diagnosed cancer in males worldwide (Torre et al. 2015). It is thought that 50–80% of colorectal cancers may be due to environmental factors, mainly unhealthy dietary habits (Karagianni and Triantafillidis 2009). Red meat, processed meat, cheese, alcoholic drinks as well as foods containing iron, animal fats and sugars can lead to colorectal cancer (Zaharek-Girgasky et al. 2015). Recommendations on specific antioxidant supplements, while important, reveal no benefit of antioxidant use among stage-II colorectal cancer survivors (Tsinovoi et al. 2017). Foods containing dietary fibre, as well as garlic, milk and calcium, may protect against colorectal cancer. Similarly, there is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, fish, and foods containing vitamin D and selenium may protect against colorectal cancer. Fibre derived from fruits, vegetables and grains is an important component of nutrients. Despite limited data, many experts recommend diets with high fibre content, although any unfavourable effects are not known (Chiba et al. 2015). Dietary fibre is thought to protect against colorectal cancer at least in part by increasing production of short-chain fatty acids, stool mass, and by decreasing colonic transit time, change in colonic pH and modulation of bile acid metabolism (Sehdev and O'Neil 2015).

Chemotherapy significantly improves clinical outcomes in cancer patients but can also result in toxic effects. In oesophageal cancer, treatment with 5-fluorouracil (5-FU)/cisplatin plus docetaxel increases response rates but is also associated with an increased toxicity (Tanaka et al. 2016b). Gastrointestinal toxicity caused by chemotherapy adversely affects nutritional status by decreasing food intake, which can lead to delay or discontinuation of chemotherapy. Oral mucositis, one of the most common gastrointestinal toxicities, results in increased pain, difficulty in swallowing, nutritional compromise and increased risk of infection. A diet containing glutamine induces oral mucositis in oesophageal cancer patients receiving chemotherapy; whereas a diet containing glutamine was administered before starting chemotherapy, glutamine and other minerals helped to maintain nutritional status and reduce the incidence of oral mucositis in oesophageal cancer (Tanaka et al. 2016a).

Dietary polyphenols function as chemopreventive agents and can inhibit conversion of normal cells into cancer cells. The methanol extract of dried pomegranate peels contains 44% phenolic compounds, with the presence of gallic acid and catechin as major components (Murthy et al. 2004). Pomegranate peel extract tends to inhibit the development of colonic premalignant lesions in an azoxymethane-induced colorectal carcinogenesis in rat (Waly et al. 2012). Pomegranate-derived components inhibit DNA damage, which is a key event involved in the initiation phase of cancer development (Turrini et al. 2015). Pomegranate peel extract inhibits cell proliferation of the human immortalised myelogenous leukaemia cells, K562 cells, mainly by cell cycle arrest and apoptosis induction (Asmaa et al. 2015). Powder of dried pomegranate peel contains 30% polyphenols (Folin-Ciocalteu method, equivalent gallic acid), and the concentrations of punicalagin and ellagic acid are 8% and 5%, respectively (Al-Gubory et al. 2016). The antioxidant activity of pomegranate fruit resides in its ability to reduce the production of ROS and RNS and to increase the enzymatic activity of SOD, GPX and CAT (Turrini et al. 2015).

Healthy mice fed with pomegranate peel in diet exhibit lower plasma MDA concentrations, reduced content of MDA in the small intestine and liver and higher levels of Cu/Zn-SOD (SOD1) and GPX activities in the small intestine compared to mice fed the control diet (Al-Gubory et al. 2016). There is substantial evidence that pomegranate-derived products are promising chemopreventive/chemotherapeutic agents, as they exert anti-inflammatory, anti-proliferative and anti-tumorigenic effects by modulating multiple signalling pathways (Sharma et al. 2017).

Curcumin (a naturally occurring compound found in the turmeric spice), quercetin (the most abundant dietary flavonoids found in many fruits and vegetables) and green tea (epigallocatechin-3-gallate) display anti-carcinogenic properties alone or in combination. There is substantial data indicating that curcumin has high antioxidant and ROS-/RNS-scavenging properties (Sreejayan and Rao 1997, Das and Das 2002, Kim et al. 2003, Sumanont et al. 2004, Ak and Gülçin 2008, Barzegar and Moosavi-Movahedi 2011). Importantly, curcumin inhibits carcinogenesis in multiple organs in various animal models (Das and Vinayak 2015). Irrespective of the route of administration, curcumin has low bioavailability, though metabolites of curcumin remain for longer periods in different tissues. Activation of the antioxidant defence systems contributes to cancer prevention (Das and Vinayak 2012). The effects of curcumin in cancer prevention may occur via modulation of stress-activated genes by inducing phase-II antioxidant enzymes, activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signalling and restoration of the tumour suppressor p53 gene (Das and Vinayak 2014).

Green tea is the most widely consumed beverage after water (Yang et al. 2009). Studies in animal models of carcinogenesis show that green tea inhibits tumorigenesis during the initiation, promotion and progression stages. Green tea polyphenols have dual effects and act as antioxidants and/or pro-oxidants to exert preventive effects against cancer (Forester and Lambert 2011). The dual effects of green tea can either induce oxidative stress (leading to ROS-mediated cancer cell death) or scavenge ROS under conditions of high oxidative stress (preventing cellular damage).

Curcumin and green tea catechin alone or in combination can inhibit the proliferation of the human colon adenocarcinoma HCT 15 and HCT 116 cells and the human larynx carcinoma Hep G-2 cells through induction of apoptosis (Manikandan et al. 2012). Combined treatment with curcumin and quercetin induces apoptosis through the mitochondrial pathway and inhibits proliferation of human gastric cancer MGC-803 cell (Zhang et al. 2015b). Therefore, combining chemically similar or different polyphenols can be used as an efficient anticancer treatment (Niedzwiecki et al. 2016).

Soybeans are rich in polyphenols, proteins and fibres. Isoflavones are a subclass of flavonoids found mainly in soybeans and act as antioxidants to inhibit oxidative stress and regulate cellular signalling in cancer. Soy isoflavones have an important role in reducing the incidence of hormone-sensitive cancers, or hormone-dependent cancers, such as breast and prostate cancers (Amaral et al. 2017, Rienks et al. 2017). Isoflavone-based antioxidants from soybeans target multiple signalling pathways, particularly those that are related to the homeostatic control of cell cycle and

apoptosis (Sarkar and Li 2002, 2003), leading to inhibition of cancer development and progression. Isoflavones belong to the phytoestrogen group and have some structural similarity with oestradiol, causing isoflavones to also exert weak oestrogenic activity. Since oestrogen plays an important role in breast cancer development and survival, many questions remain open about the risks and benefits of diets high in soy (Fox et al. 2008). Clearly more clinical trials are needed to evaluate the effects of isoflavone, either alone or in combination with conventional drugs, for the prevention and treatment of cancer.

19.5.3 Rational Diet Design for Cancer Prevention

Many diets are based on regional and cultural influences, and the relation of the nutrient contents and benefits of various diets on health and prevention of disease has been studied by many groups. A Mediterranean diet is considered to be one of the healthiest diets and is based on large amount of fresh fruits, vegetables, whole grains, olive oil and herbs (Potentas et al. 2015), making it rich in vitamins, polyphenols, minerals, carotenoids, lycopenes, resveratrol and other antioxidants that may have anticancer properties (John and Anderson 2014). The Mediterranean diet can be a preventative measure in breast cancer, especially in postmenopausal women (Fung et al. 2005). There is an inverse association between consumption of a Mediterranean diet supplemented with extra virgin olive oil and breast cancer incidence (Mourouti and Panagiotakos 2016, Toledo et al. 2015). More specifically, a Mediterranean diet supplemented with extra virgin oil is associated with a 62% lower risk of malignant breast cancer (John and Anderson 2014).

Diet and body weight are related and may contribute to cancer risk (Nomura et al. 2016, Kohler et al. 2016). A healthy weight is usually determined by using weight and height to calculate body mass index (Ferrer et al. 2016). Consuming a healthy diet helps in maintaining a healthy weight and provides nutrients that may assist in preventing cancer (Bail et al. 2016). A diet high in sugar and fat promotes obesity, which may indirectly increase cancer risk. Fat intake raises the levels of prolactin and oestrogen, which can facilitate the development of breast cancer (Potentas et al. 2015, Toledo et al. 2015). Managing cancer prevention doesn't mean that sugar- and fat-containing foods must be completely removed from the diet. In fact, many foods contain nutrients that are essential to good health; however, their intake must be carefully controlled and physical activity should be included as part of a healthy lifestyle behaviour (Rennie et al. 2015).

Data on the health benefits of antioxidant supplements are ambiguous and difficult to generalise (Hong et al. 2015); hence institutional recommendations on antioxidant supplements tend to be more conservative (Tsinovoi et al. 2017). Health-care experts are careful to recommend antioxidant therapies unless they are able to show benefits and understanding of their toxicity, side effects and treatment responses.

Healthy diets that maintain a healthy weight are primarily plant based; low in red and processed meats; low in simple sugars, refined carbohydrates and saturated fatty acids; and limited alcohol consumption. Common features for healthy diet include:

1. High consumption of fruits and vegetables, spices, nuts and whole grain
2. Moderate consumption of seafood, milk and dairy products
3. Low consumption of meat, soft drinks, alcohol and processed food
4. Olive oil as the main source of fat

Fruit and vegetables fall into five different colour categories: red, purple/blue, orange, green and white/brown. Each colour carries its own set of unique disease-fighting chemicals. A diverse combination of leaf shape and fruit and vegetable colours with the above options (fresh and organic quality) will provide the greatest synergic effect in cancer prevention.

19.6 Anticancer Agents Derived from Medicinal Plants

The World Health Organization (WHO) estimated that the plant-derived drug trade was worth US$100 billion in 2007 and is expected to reach US$5 trillion by 2050 (Greenwell and Rahman 2015). Advances in synthesis of pharmaceuticals can generate new drugs from medicinal plants that are more effective in cancer treatment. However, many pharmaceutical companies stopped investing in natural product research and focus primarily on rational drug design using high-throughput screening and combinatorial and computational chemistry (Wermuth and Aldous 2015). Drug design is based on single small molecule with low molecular weight, chiral centres and hydrogen as donor and acceptor atoms.

The drug design concept supports Lipinski's five rules (RO5) and produced many useful drugs. This is based on analysis of the physicochemical properties of more than 2000 drugs and candidate drugs in clinical trials. RO5 predicts that poor absorption or permeation is more likely when there are more than five hydrogen-bond donors and ten hydrogen-bond acceptors, the molecular weight is greater than 500 Da and the octanol-water partition coefficient log P is not greater than 5 (Lipinski et al. 2001). The origin of the rule's name is based on the fact that all numbers are multiples of five. Unfortunately such approaches are not equally successful in the design of more effective and less toxic anticancer drug. Cancer is a complex disease requiring treatments with either complex molecules with many chiral centres that can act specifically on cancer cells or combinational therapy where two or more drugs are likely more effective treatment (Price et al. 2008). Several cancer chemotherapeutics originate from medicinal plants, largely because they provide structurally complicated molecules that are difficult to synthesise chemically and/or be synthesised in significant quantities (Seyfried et al. 2016).

Many drug-derived plants have been approved, with many more leads being generated (Wermuth and Aldous 2015).

19.6.1 Approved Anticancer Drugs Derived from Medicinal Plants

Plants are considered relatively safe, efficient and inexpensive sources for producing several drugs, as evidenced by the fact that 70–95% of the population in developing countries using traditional medicines (Fridlender et al. 2015). Herbal medicine is used as a complementary treatment with conventional drugs (Robinson and Zhang 2011). Studies of medicinal plants as potential sources of anticancer agents were started in the 1940s and about 175 molecules approved for cancer treatment since then; 75% of approved molecules are derived from a non-synthetic approach of which about 49% is produced directly or derived from natural products (Newman and Cragg 2012, Cragg and Newmann 2013). Moreover, between 2012 and 2014, 18 natural product-based anticancer drugs were approved: 3 as natural products, 3 as natural product derivatives and 12 as a natural product pharmacophore or mimic of natural product (Newman and Cragg 2016) (Table 19.2). An important issue related to plant-derived drugs is around copyright claims, and one solution to resolve this is the use of semi-synthetic or synthetic analogues. Another issue is that some anticancer drugs derived from medicinal plants do not comply with Lipinski's RO5 (Ganesan 2008) as they are highly complex molecules characterised by high molecular weights and rich of stereogenic centres; thus some physicochemical properties of active natural products such as lipophilicity and solubility are not always well represented in synthetic analogues. Therefore, some plant-derived drugs require manipulation of the chemical structure by generating simple derivatives to improve bioavailability while maintaining or enhancing anticancer activity.

19.6.2 Potential Anticancer Drugs Derived from Medicinal Plants

Medicinal plants are rich sources of lead compounds, which often require further fine-tuning of their physicochemical properties (Cragg and Newmann 2013). Identification of lead compounds is the starting point for further development in drug design; reducing their poor solubility, bioavailability, toxicity and moderate activity are key features for further manipulation and optimisation. Medicinal chemists at pharmaceutical companies usually initiate intensive programme of structure-property relationship to improve lead compounds with anticancer activity, as well as their bioavailability and toxicity. Lead compound is a new pharmacophore with the potential to generate molecules with unique properties and reduced cross-resistance

Table 19.2 List of selected approved drugs derived from natural sources (Newman and Cragg 2016)

Generic name	Trade name	Mechanism	Approval year	Cancer type
Blinatumomab	Blincyto	Binds to CD19, CD3 expressed on the surface of B-and T cells	2014	Blood cancer Leukaemia
Nivolumab	Opdivo	Blocks a negative regulator of T-cell activation and response	2014	Metastatic melanoma
Obinutuzumab	Gazyva	Targets the CD20 antigen expressed on the surface of pre B- and mature B-lymphocytes	2013	Chronic lymphocytic leukaemia
Ramucirumab	Cyramza	Binds VEGF receptor 2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C and VEGF-D	2014	Gastric cancer
Paclitaxel nanoparticles	Taxol	Microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation	2014	Lung cancer
Trastuzumab emtansine	Kadcyla	Upon binding to subdomain IV of the HER2 receptor	2013	Breast cancer
Apatinib mesylate	Aitan	Tyrosine kinase inhibitor that selectively inhibits the VEGF receptor 2 (VEGFR2, also known as KDR)	2014	Gastric carcinoma, metastatic breast cancer, advanced hepatocellular carcinoma
Ceritinib	Zykadia	Inhibitor of anaplastic lymphoma kinase	2014	Non-small-cell lung cancer
Afatinib	Gilotrif	Covalently binds to the kinase domains of EGFR, HER2 and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation	2013	Non-small-cell lung cancer
Belinostat	Beleodaq	Histone deacetylase inhibitor	2014	Non-Hodgkin's T-cell lymphoma
Dabrafenib mesylate	Tafinlar	Inhibitor of some mutated forms of BRAF kinases, as well as wild-type BRAF and CRAF kinases	2013	Melanoma Metastatic melanoma
Ibrutinib	Imbruvica	Inhibitor of Bruton's tyrosine kinase (Btk)	2014	Leukaemia Chronic lymphocytic leukaemia

(continued)

Table 19.2 (continued)

Generic name	Trade name	Mechanism	Approval year	Cancer type
Idelalisib	Zydelig	Inhibitor of phosphoinositide-3 kinase (PI3K) delta	2014	Chronic lymphocytic leukaemia, follicular lymphoma
Regorafenib	Stivarga	Targeting angiogenic, stromal and oncogenic receptor tyrosine kinases (TK)	2013	Gastric cancer
Trametinib	Mekinist	Reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2	2013	Melanoma Metastatic melanoma

potential (Cragg and Newmann 2013, Sarker and Nahar 2012, Sharma and Gupta 2015). Selected lead structures with anticancer property isolated in 2016 are presented in Table 19.3.

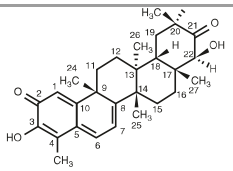
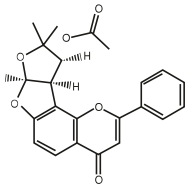
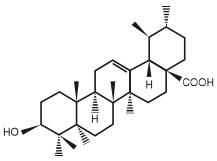
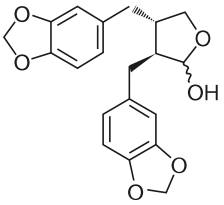
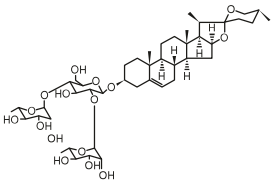
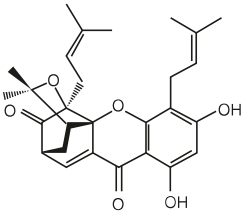
Tingenin b (22β-hydroxytingenone) was obtained from *Maytenus spinosa* (an endemic shrub native to South America) and has promising anticancer property against breast cancer as it induces apoptosis in the breast stem cells, MCF-7 (Cevatemre et al. 2016). (−)-Pseudosemiglabrin was isolated from the aerial parts of *Tephrosia apollinea* (dwarf shrub widely distributed in Africa) and its structural and stereochemical features described by X-ray (Ahmed Hassan et al. 2014). The cytotoxicity of (−)-pseudosemiglabrin was evaluated in nine cancer cell lines where it had dose-dependent anti-proliferative effects on most of the cancer cell lines, with significant inhibitory effect on the proliferation of leukaemia, prostate and breast cancer cell lines but with no toxicity in normal human fibroblasts (Ahmed Hassan et al. 2014).

Ursolic acid, a triterpenoid, was isolated from the ethyl acetate extract of *Betula utilis* (a birch tree native to the Himalayas) bark along with other triterpenoids that were characterised by spectroscopic methods (Mishra et al. 2016). Ursolic acid was tested for in vitro cytotoxic activity against six different cancer cell lines and was selective for breast cancer cells over normal breast epithelial cells (MCF 10A). Cancer cell selectivity is mainly due to the activation of the extrinsic apoptosis pathway via up-regulation of death receptors 4 and 5 (DR4, DR5).

(−)-Cubebin isolated from the defatted acetone extract of *Piper cubeba* seeds can be converted to four different derivatives to get insight on its structure-activity relationship. All compounds were characterised by nuclear magnetic resonance and mass spectrometry and tested for anticancer property against six human cancer cell lines (A549, K562, SiHa, KB, HCT116 and HT29), with the natural lignan (−)-cubebin having high effect against A549, K562 and KB cell lines but being less effective against other cell lines (Rajalekshmi et al. 2016).

Dioscin, a natural steroid saponin, isolated from the root extract of *Dioscorea villosa* (wild yams, a tuberous vine that is native to China and North America), was identified and tested for purity with chromatographic (TLC, LC-ELSD) and spectral

Table 19.3 List of recent leads isolated from natural product with potential anticancer activity

Plant	Name	Structure	Anticancer activities IC50 (48 h)	Target tissues in vitro
Maytenus sp.	Tingenin B		2.38 μM	MCF-7
Tephrosia apollinea	(−)-Pseudosemiglabrin		18.2 μM	MCF-7
Betula utilis	Ursolic acid		2.5–5 μM	MCF-7
Piper cubeba	(−)-Cubebin		8.16–8.66 μM	A549, K562KB
Dioscorea villosa	Dioscin		4.4 μM	HeLa
Garcinia hanburyi	Forbesione		8.0 μM	Ham-1

(IR, 1D- and 2D-NMR, ESI-HRMS) analysis (Aumsuwan et al. 2016). Using human breast cancer cell line MCF-7 (oestrogen receptor positive) and MDA-MB-231 (oestrogen receptor negative) under a hormone-free environment, dioscin reduced cell viability of both cell lines in a concentration- and time-dependent manner and did alter the expression of several genes (especially in MDA-MB-231 cell line) that

encode for proteins involved in the regulation of cellular function such as cell growth, proliferation and migration. The findings support the potential therapeutic ability of dioscin as an anticancer agent in invasive breast cancer. Forbesione, a caged xanthone isolated from *Garcinia hanburyi* (small- to medium-sized Asian tree), has antitumour effect on cholangiocarcinoma in in vitro and in vivo settings. Forbesione activates multiple mechanisms, including induction of S-phase cell cycle arrest and stimulation of the death receptor pathway (Bouery et al. 2016). Forbesione alters the expression of genes and proteins related to cell cycle and apoptosis regulation, and hamsters treated with forbesione for 4 weeks showed no toxic side effect, suggesting that forbesione represents a promising anticancer drug candidate (Bouery et al. 2016) that deserves further investigation.

19.6.3 Combination of Medicinal Plant Extracts with Anticancer Drugs

Medicinal plants are often used together with traditional cancer therapy to improve survival rate and quality of life. Some medicinal plant extracts used by cancer patients either improve anticancer drug efficiency or reduce the toxicity induced by the chemotherapy (Guerriero et al. 2017, Zhang et al. 2016). Earlier studies reported that a plant extract derived from *Caesalpinia spinosa* (Molina, a small leguminous tree or thorny shrub native to south America) reduced spleen metastasis in mice that were transplanted with the murine mammary tumour cell line, 4T1 (Urueña et al. 2013). More recently, Molina was further evaluated in highly resistant human cancer cell lines with or without multidrug resistance phenotypes, such as MES-SA/Dx5, K562, 4T1 and TS/A cell lines (Sandoval et al. 2016). The synergistic effect of Molina extracts and doxorubicin was evaluated in vitro and in vivo using mice transplanted with TS/A cells. The ethanol extract of Molina was cytotoxic to cells regardless of their resistance phenotype but had a synergistic effect with doxorubicin in MES-SA Dx5 Pgp + cells while also increasing survival in TS/A (mouse mammary carcinoma) cell lines. These data suggest that treatment with Molina could be used as an adjuvant with conventional chemotherapy to treat multidrug-resistant tumours.

The bark of *Cinnamomum cassia* (cinnamon, a tree widely cultivated in southern and eastern Asia) is frequently used as spice. It has high antioxidant content (Lin et al. 2003) and potential anticancer (Lee et al. 2004) activities. Cis-diamminedichloroplatinum (CDDP) is one of the most important chemotherapeutic agents for cancer treatment (Strumberg et al. 2002). The aqueous extract of cinnamon exerts protective effects against the toxicity induced by CDDP in the cancer cells, MCF-7 and HepG2, by preventing the activation of various cellular mechanisms mediating apoptotic cell death, without compromising the anticancer efficiency of CDDP (Elkady and Ramadan 2016). *Piper nigrum* (black pepper) is a medicinal plant that possesses a potent cytotoxic effect on breast cancer cell lines as investigated in studies of N-nitrosomethylurea (NMU)-induced mammary tumori-

genesis in rats (Sriwiriyajan et al. 2016). The dichloromethane extract of *Piper nigrum* had potent cytotoxic effects against MCF-7 breast cancer cells compared to colorectal, lung and neuroblastoma cells. Moreover, the extract inhibited mammary tumorigenesis in rats without significant effect on the liver and bone marrow. The bioactive ingredients *in Piper nigrum* need to be isolated and identified for further studies. The combinational effects of natural products and known anticancer drugs have recently been reviewed (Cai et al. 2016, Clark and Lee 2016, Farzaei et al. 2016).

19.6.4 Potential Anticancer Extracts from Medicinal Plants

Phytochemical compounds extracted from *Maytenus spinosa* were active against six solid tumour cell lines at micromolar concentrations (de Almeida et al. 2010). Compounds from *Betula utilis* have antioxidant, anti-inflammatory and anticancer properties (Singh et al. 2012). In an attempt to investigate the influence of extraction solvents on the anticancer properties of medicinal plants, 35 extracts were screened for cytotoxic activities against three different cancer cell lines (B16F10, MCF-7 and HeLa) (Alzeer et al. 2014). Acetone consistently gave lower extraction yields but was more cytotoxic, whereas other solvent systems had much higher extraction yields with lower cytotoxicity. The acetone extract of *Salvia officinalis* L. (sage) has potent anticancer property (IC_{50} = 14–36 μg/ml) in the three cell lines. Interestingly, coconut water is a potential alternative to classical organic solvents as it consistently provides the highest extraction yields and increased the sensitivity of *S. officinalis* L in the human breast cancer cell line MCF-7.

Breast cancer is the most common and prevalent cancer and one of the leading causes of death among women worldwide. The aqueous extract of *Urtica dioica* (a widespread and perennial herbaceous plant in Europe and North America) showed antioxidant effects, induced apoptosis as demonstrated by DNA fragmentation and inhibited proliferation of the human breast cancer cell line, MCF-7 (Fattahi et al. 2013). Methanolic crude extract of *Piper cubeba* seeds has a cytotoxic activity against the breast cancer cell lines, MCF-7 and MDA-MB-468, with low cytotoxicity against normal fibroblast L929 cells (Graidist et al. 2015). *Piper nigrum* extract upregulated p53 and downregulated oestrogen receptor, E-cadherin, matrix metalloproteinases 9 and 2 and vascular endothelial growth factor levels in breast cancer rats (NMU)-induced mammary tumorigenesis in rats, suggesting that *Piper nigrum* can enhance breast cancer cell response to phytochemicals, then induce cell cycle arrest and inhibit cancer cell proliferation (Deng et al. 2016).

Colorectal cancer is the third most common cancer in the world (Haggar and Boushey 2009). Hydroalcoholic extract of *Urtica dioica* inhibited proliferation of gastric and colorectal cancer cells at least in part by inducing apoptosis, while it had no toxic effect on normal cells (Ghasemi et al. 2016). Ethanol extract of *Sorbus rufopilosa* (small ornamental trees used to produce jams and wine and have high

antioxidant content) induced G2/M arrest and apoptosis and inhibited proliferation of human colon adenocarcinoma HT29 cells (Oh et al. 2016). Apoptosis in HT29 cells was associated with p53 up-regulation through both extrinsic and intrinsic pathways. The extract showed higher sensitivity in HT29 cells over HepG2 and A549 cells (Oh et al. 2016).

Actinidia arguta (hardy kiwi fruit or baby kiwi fruit) is known for its good taste and as a healthy food. To enrich its antioxidant and health potential, 1-methylcyclopropene was used during postharvest processing to delay kiwi fruit ripening and softening (Lim et al. 2016). The methanol/water extract of hardy kiwi fruit exhibits inhibitory effect against cancer cell proliferation, high sensitivity and dose-dependent inhibition of Hep3B but with low effect on HepG2 and LoVo cell lines. The plant species *Taraxacum coreanum*, *Youngia sonchifolia* and *Ixeris dentata* belong to the family *Compositae* (commonly referred to as the sunflower family), and they are sources of natural antioxidants, mainly polyphenolic bioactive compounds (Cho et al. 2013, Chon and Kang 2013, Kang 2014). The anticancer effects of extracts prepared from these plants were investigated where they had anticancer property in the human melanoma cell lines, A375P and A375SM (Lee et al. 2016). Of the three extracts, *Ixeris dentata* had the most potent anticancer effect and inhibited tumour growth in mice without any toxicity following 4 weeks of treatment (Lee et al. 2016). More recently, it has been reported that *Ixeris dentata* extract induces apoptosis in vitro and in vivo through the phospho-Akt and phospho-nuclear factor-κB (NF-κB) signalling pathway in MDA-MB-231 breast cancer cells and tumours (Shin et al. 2017). The anticancer effects of extracts prepared from some plants of the family *Compositae*, together with their strong antioxidant activity and wide distribution throughout the world, may indicate that this family of medicinal plants can be used as potential natural source for the development of therapeutic compounds for prevention and treatment of cancer.

19.7 Conclusions

Plants or parts of plants with medicinal properties have been used for thousands of years as folk medicines in developing countries and are also a source of health benefits in developed countries. Herbal medicines offer inexpensive option and provide synergic effects with other therapies. With rapid population growth, deforestation and increasing urbanisation, protection of medicinal plants is of great concern. Utilising all plant parts, including stem, leaf, root and bark, can increase sustainability. Worthy of note that methods of conservation have been developed to overcome sustainability issues include tissue culture (Graebe and Novelli 1966), germplasm conservation (Lu et al. 1993), propagation of plants in sterile conditions (Sharma 2005) and cryopreservation (Zhang et al. 2015a).

To prevent ROS-induced oxidative damage, plants produce a very large and diverse group of antioxidants that are produced as a defence system against abiotic (light, drought, salt, heat, cold, wounding, pollutants) and biotic (pathogens, herbi-

vore) stressors (Kasote et al. 2015, Sewelam et al. 2016). Plant foods and medicinal plants are therefore important sources of antioxidants that help human to maintain a balance between pro-oxidant and antioxidant levels under physiological and pathological conditions. Decreases of endogenous antioxidants lead to oxidative stress, with long-term effects that include DNA oxidation, protein cross linking and lipid oxidation, ultimately leading to onset and progression of noncommunicable diseases. Plants are considered relatively safe, efficient and inexpensive ways of producing several valuable molecules, including many anticancer drugs. Rational food selection based on therapeutic properties and antioxidant constituents might be a useful strategy for cancer prevention (Mut-Salud et al. 2016). Although the design of drugs against cancer is one of the most difficult pharmaceutical problems, much can be achieved by intelligent application of natural and chemical principles. Natural products offer diverse molecules with high structural complexity which are essential for achieving high selectivity for cancer cells as reviewed recently (Asadi-Samani et al. 2016, Boss et al. 2016, George et al. 2017).

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