



Review

Anti-proliferative, genotoxic and cytotoxic effects of phytochemicals isolated from Anatolian medicinal plants

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Received April 23, 2020; Accepted May 8, 2020; Published June 25, 2020

Doi: <http://dx.doi.org/10.14715/cmb/2020.66.4.19>

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Abstract: The potential of natural products in cancer prevention and treatment has received worldwide interest in recent years from the nutraceutical and pharmaceutical industry point of view. Medicinal plants have been traditionally used as they exhibit a wide range of therapeutic effects due to their phytoconstituents which play an active role against oxidative stress-associated diseases such as cancer. They may block or suppress multistage carcinogenesis mainly through mechanistic regulation of the myriad of deregulated cellular pathways. Bioactive constituents isolated from different plants have been shown to induce reversal of drug resistance, restoration of apoptosis, inhibition of cell proliferation and stimulation of the immune system, etc. These phytochemicals such as terpenoids, flavonoids, phenolic acids, carotenoids, alkaloids, tannins, anthraquinones, and saponins can be present in any of the plant parts like root, stem, leaves, bark, seed, flower, and fruit which produce a definite physiological response in the organism. Turkish flora is a rich reservoir of wide-ranging bioactive chemicals having premium pharmacological importance. This review provides an overview of the anticancer properties of various Turkish medicinal plant species against different type of cancers via anti-proliferative, genotoxic and cytotoxic effects.

Key words: Medicinal plants; Phytochemicals; Cancer prevention and therapy; Antioxidant activity.

Introduction

Cancer is the second leading cause of death worldwide. According to the report of the International Agency for Research on Cancer of the World Health Organization in 2014, the most prevalent cancer was lung cancer in 2012 followed by breast cancer, colon cancer, and prostate cancer (1). Because of rapidly developing resistance against modern clinical drugs and significant off-target effects, botanicals offer a precious reservoir of pharmacologically effective products to inhibit and/or prevent cancer. Eliminating toxicity issues of current drugs, edible phytochemicals are considered to be an inexpensive and accessible approach in chemoprevention. Nearly, 80% of all drugs approved by the FDA during the last three decades for cancer therapy are either natural products per se or are based thereon, or mimicked natural products in one form or another (2).

Many clinical trials on the use of nutritional supplements and modified diets to prevent cancer are on-

going. Medicinal plants are utilized both internally like herbal teas and externally such as poultice, decoction, ointment and other herbal formulations in order to cure a broad spectrum of ailments (3,4). The relevant biological activities are attributed to a vast array of phytochemicals ('phyto' is from the Greek word meaning plant)—the bioactive non-nutrient plant compounds. More than 10,000 phytochemicals have been identified to date (5). The most consistent chemoprotective effects were reported for higher levels (dietary intake, serum, plasma, or urinary metabolites) of β -carotene and renal cell cancer, flavonoids and lung cancer, isothiocyanates and gastrointestinal cancer, lignans and postmenopausal breast cancer (6).

Carcinogenesis is generally recognized as a multistep process in which distinct molecular and cellular alterations occur (7). There are many difficulties associated with its treatment, the most common of which include drug resistance, toxicity and the low specificity of currently available cytotoxic drugs (8). Phytochemicals exert anticancer effects through modulation of cellu-

lar and molecular events relying on antioxidant and anti-inflammatory properties (5,9). Furthermore, phytochemicals have been shown to restore apoptosis in drug-resistant cancer cells, downregulate oncogenes, upregulate tumor-suppressor genes, as well as inhibit angiogenesis and metastatic spread (7).

The anticancer effects of medicinal plants have been recognized for centuries. The United States National Cancer Institute reported that about 3,000 plant species have demonstrated reproducible anticancer activity among screened approximately 35,000 species (10). With a rich diversity of plants where more than 12,000 taxa are growing, Turkey is the richest among the Mediterranean, European and neighboring countries (11). Endemic plants are represented as one third of the native taxa (12). The most frequently employed plant families in traditional Turkish ethnic medicine are the Lamiaceae, Rosaceae and Asteraceae families (3). Identification of new sources of phytochemicals is an essential step in improving the translation of these laboratory findings to clinically efficient drugs. As can be seen in Table 1, the dominant families that were subjected in cancer studies are Lamiaceae, Liliaceae, Rosaceae, Asteraceae, Scrophulariaceae, Rubiaceae, Moraceae, Hypericaceae, and Ericaceae. Both endemic and non-endemic Turkish medicinal plants belonging to a variety of plant families and their phytochemicals responsible for anticancer effects on various cell lines and animal models were highlighted in this review.

Apiaceae

The family Apiaceae comprises about 170 aromatic plant species occurring from central Asia westward to northern Africa that is well-known in folk medicine for the treatment of various organ disorders (13). The plant family Apiaceae is known to produce a set of unusual fatty acids in the seed oils in which petroselinic acid as the predominant constituent (14). Essential oils from Italian *Eryngium* rich in sesquiterpene hydrocarbons, with germacrene D as the major compound, were found to be highly cytotoxic against tumor cells (15). Subgenus *Eryngium* L. is centered in the Mediterranean type climate and Turkey is an eminent region for the genus (16). Anti-inflammatory and antinociceptive activity of Turkish *Eryngium* species have been reported (17). Among extracts derived from 11 different plant species grown in Turkey, methanolic *Eryngium campestre* extract and aqueous *Asarum europaeum* (Aristolochiaceae) extract obtained from Bolu province indicated by far strongest tumor inhibition rates, 86% and 100%, respectively (18). Triterpene saponins, coumarin derivatives, monoterpene glycosides and flavonoids comprise the phytochemical composition of *E. campestre* (19).

A famous traditional Chinese Medicine, Radix Bupleuri, originating from herbs belong to *Bupleurum* L. is a widely used herbal drug in Asia to treat of a number of diseases including common cold with fever, influenza, hepatitis, malaria and menoxenia for more than 2000 years (20). The anti-proliferative activity of *Bupleurum* species has been linked to the presence of different lignans whereas anti-inflammatory, hepatoprotective and immunomodulatory activities has been attributed to saikosaponins (21). Kars, Akin, & Saraccedil (2012)

investigated Turkish endemic *Bupleurum* root extracts against human breast carcinoma cells. *B. turcicum* and *B. pauciradiatum* root extracts were more toxic to the MCF-7/Pac cell line than the root extracts of other three species. *B. turcicum* root extract had the highest free radical scavenging activity although *B. lycaonicum* root extract has about 1.5-fold more total phenolic content with respect to others. Moreover, higher saikosaponin A, saikosaponin D and isoquercitrin contents of the root extracts were found in comparison to podophyllotoxin, catechin and quercetin contents (22).

Asteraceae

The genus *Centaurea* belonging to the Asteraceae family comprises nearly about 600 species through the World and mostly distributed in the Mediterranean region and Western Asia (23). Turkish flora is one of the gene centers of *Centaurea* having nearly two hundred species many of which (> 60%) are endemic (24). In Anatolian folk medicine, some *Centaurea* species have been employed as herbal remedies in the treatment of fever, hemorrhoids, diabetes, and peptic ulcer (25,26). Secondary metabolites present in this genus, revealed in previous pharmacological studies, including sesquiterpene lactones (27,28), acetylenic compounds (29), and flavonoids (30).

Different Turkish authors achieved bioactivity-guided isolation of antiproliferative flavonoids from *Centaurea carduiiformis* DC (31) and sesquiterpene lactones from *Centaurea solstitialis* L. ssp. *solstitialis* (32). The anticancerogenic properties of Solstitialin A and 15-dechloro-15-hydroxychlorojanerin against cervical and kidney has been reported by Erenler *et al.* (2016), that were exhibited the highest antiproliferative activity in methanolic extract isolated from stem of plant *C. solstitialis* L. ssp. *Solstitialis* (32).

An endemic *Centaurea* species, *C. drabifolia* Sibth. & Sm. subsp. *detonsa* collected from the Central Anatolia region of Turkey, has been reported to contain acylated guaiane sesquiterpenes (33). Antiproliferative activity of an apolar organic extract from aerial parts was shown on two cancer cell lines, namely acute lymphoblastic leukemia and its multidrug-resistant subline likely attributed to aguerin B and cynaropicrin contents (33). Similarly, aerial parts of endemic *Centaurea fenzlii* Reichardt collected from East Anatolian region indicated significant cytotoxic effects on the MCF-7 breast cancer cell line (34). Hispidulin was reported as the main component (34). In the study of Sen and coworkers (2015), chloroform and methanol extracts of another endemic *Centaurea* species, *C. kilaea* Boiss. showed the highest antitumor activity with IC₅₀ of 73.92 and 70.11 µg/mL, respectively against prostate carcinoma *in vitro* (35).

Ericaceae

Rhododendron luteum and *Rhododendron ponticum*, which are non-evergreen short trees with green leaves and have flowers of different colors and usually used as a decoration plants, grow naturally in Turkey, especially in eastern Black Sea Region (18,36). Extracts of the *Rhododendron* species are composed of several bioac-

tive compounds (Table 1), but they also contain “grayanotoxins”, a class of terpenoids that exhibit phytotoxic effects, and for this reason the usage of this genus in traditional medicine is limited (37). On the other hand, grayanotoxins exhibit cytotoxic effects on cancer cells. Recently, Bilir and co-workers demonstrated the dose-dependent cytotoxic effect of *Rhododendron ponticum* L. floral extract with grayanotoxin-I and grayanotoxin-III on brain tumors. Removal of grayanotoxins during extraction process is a convenient option for eliminating the side effects of *Rhododendron* species (38). Antiproliferative activity of *Rhododendron luteum* on colon and liver cancer cells was reported (39). More importantly, it was pointed out that the *Rhododendron luteum* floral extract exhibited selective cytotoxicity against colon and liver cancer cells.

Fabaceae

Astragalus L. is a member of the Fabaceae family which containing up to 3000 species (40). The aqueous extract of *Astragalus* roots are traditionally used for treatment of nephritis, diabetes, leukemia and wound-healing in both Anatolia and Chinese medicine (41,42). *Astragalus* is the largest genus in Turkey where it is represented by 439 species and 204 of them are endemic (43). One of the endemic species is *Astragalus chrysochlorus* that growing in 32°-36° meridian of southern Anatolia (44). The cytotoxic effects of the ethyl acetate extract of *Astragalus chrysochlorus* roots on cervix cancer cells was reported (45). It was also indicated that there was a significant change especially on antiapoptotic genes due to the presence of the root extract. Rebalancing pro- and anti-apoptotic proteins through upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins is necessary to induce apoptosis in drug-resistant cancer cells. Özbek *et al.* (2008) studied on the antimutagenic effects of methanol extract of *Astragalus* L. species growing in the eastern Anatolia region of Turkey. They indicated that *Astragalus* extracts can be considered to be protective agents against cancer, as they showed antimutagenic effects (46).

Hypericaceae

Members of the *Hypericum* genus have been used as traditional medicinal plant for hundreds of years. The genus contains approximately 400 species that grow widely at temperate region of the world, where 89 *Hypericum* species in present the flora of Turkey which 43 are endemic (47). Ari and co-workers (2017) investigated the anti-proliferation and cytotoxic activities of the crude methanol extracts of *Hypericum olympicum* L. and *H. adenotrichum* on brain and liver cancer cells. Their findings showed that, these extracts have potential anti-growth activity against brain and liver cancer cells in a dose dependent manner, moreover, induce cell death via necrosis (48).

Lamiaceae

The Lamiaceae family, also known as Labiatae, are herbs or shrubs often with an aromatic smell (49). They are common in the Mediterranean countries for the fact

that some of them produce a high amount of essential oil that enables them to survive the hot summer season. It consists of approximately 236 genera and 6,900 to 7,200 species (50). Many prevalent culinary herbs, such as basil, lavender, marjoram, mint, basil, oregano, perilla, rosemary, sage, skullcap, and thyme are members of this family (51). Besides its great economic importance, this family contributes significantly to the endemic flora of Greece and Turkey (52). In Lamiaceae species, essential oils, hydroxycinnamic acids and flavonoids were found as the major bioactive constituents (53).

Essential oils are the subtle, highly concentrated, aromatic, and volatile liquids. These are extracted from the flowers, seeds, leaves, stems, bark, and roots of plants, usually through steam or hydro-distillation. These natural oils are mixtures of complex and volatile compounds that are synthesized by aromatic plants as secondary metabolites (13). The composition of *Origanum vulgare* essential oil from distinct geographical origins is predominantly described by carvacrol and thymol as the major constituents. Phenolic acids and flavonoids are also present substantially (54). Anticancer effects of various *Oreganum* species from different origins have been well documented in the literature (55–59). Essential oil of *Origanum vulgare* L. ssp. *viride* (Boiss.) Hayek that was collected from Black Sea region of Turkey and carrying anti-proliferative activity was dominated by caryophyllene oxide, while sabinene and eucalyptol were the main monoterpene volatiles (60). It has been shown that luteolin 7-*O*-glucuronide and luteolin 7-*O*-xyloside present in *O. vulgare* L. ssp. *vulgare* have antimutagenic properties (61). On the other hand, the essential oils from Turkish *O. onites* containing linalool as the most abundant component have been reported to possess higher membrane-protective effects than thymol and carvacrol (62).

Another Lamiaceae genus containing thymol and carvacrol is *Thymus* L. is represented by 38 species and 64 taxa, 24 of which are endemic in Turkey and the East Aegean Islands (63). There are several chemotypes of *Thymus vulgaris*. Rosmarinic acid, luteolin, apigenin, eriodictyol, and some methylated flavones were also reported in thyme (64,65). Essential oil of Turkish *Thymus revolutus* Celak, an endemic species, has γ -terpinene and *p*-cymene as major constituents (66). In the study of Özkan and Erdoğan (2017), the cytotoxic effects of *Thymus revolutus* Celak have been evaluated against lung cancer and epidermoid carcinoma cells. Occurrence of membrane lipid peroxidation and oxidation of DNA, due to elevated levels of malondialdehyde and 8-hydroxy-2'-deoxyguanosine have been indicated (67). In addition, a potent proliferative activity has been reported for hexane and water extracts of *Thymus spathulifolius*, an endemic ethnomedicinal plant from Sivas Province (68).

Liliaceae

Species belonging to the Liliaceae have been a focus for phytochemists since they contain structurally complex and biologically fascinating steroidal alkaloids. The Liliaceae family consists of more than 3500 species worldwide (69). *Colchicum* L. (Liliaceae) is represented by 35 species, of which 14 are endemic and known as

Table 1. Anticancer effects of various phytochemicals isolated from Anatolian medicinal plants.

Family	Plant species	Part(s) used	Important compounds	Mode of action	Type of cancer	References
Apiaceae	<i>Bupleurum heldreichii</i> *	Root	Saikosaponin A Saikosaponin D isoquercitrin	Antiproliferative activities	Breast Carcinoma	(22)
	<i>Eryngium campestre</i> *	Aerial parts	Various Antioxidative Compounds	Antitumour activity	<i>in vitro</i>	(135)
Aristolochiaceae	<i>Asarum europaeum</i> *	Aerial parts	Tannin	Antitumour activity	<i>in vitro</i>	(135)
Asteraceae	<i>Centaurea drabifolia</i> subsp. <i>detonsa</i> (Bornm.)*	Aerial parts	seven sesquiterpene lactones belonging to the guaiane class (1–7)	Antiproliferative activity	Acute lymphoblastic leukemia	(33)
	<i>Centaurea fenzlii</i> Reichardt*	Aerial parts	Hispidulin	Strong growth-inhibitory effect on breast cancer cells	Breast Carcinoma	(34)
	<i>Echinacea pallida</i> (Nutt.) Nutt.	Root	Pentadeca-(8E, 13Z)-dien- 11-yn-2-one	Antiproliferative activity	Uterus carcinoma Rat Brain tumor	(31)
	<i>Chrysophthalmum montanum</i>	Root	Phenolic Acids, mainly: Vanilic Acid Flavonoids Fatty Acids mainly: Linoleic Acid	Antiproliferative activities	Cervix Carcinoma	(136)
Betulaceae	<i>Alnus glutinosa</i> (L.) Gaertn.	Aerial Parts	Phenolic Acids Flavonoids	Antiproliferative activities	Brain Tumor Cervix Carcinoma	(32)
Cucurbitaceae	<i>Momordica charantia</i>	Fruit	Vitamin C, E, Carotenoids Lycopenes Flavonoids	Antioxidant and chemoprotective actiy: reduce ethoxyresorufin O-deethylase (EROD) and methoxyresorufin O-deethylase (MROD) activities in liver microsomes	Liver Carcinoma	(137)
Ericaceae	<i>Rhododendron luteum</i>	Flower	Flavonoids Chromones Terpenoids Steroids.	Selective cytotoxicity against colon and liver cancer cells	Colon and Liver Carcinoma	(39)
	<i>Rhododendron ponticum</i>	Flower	Grayanotoxin I and III	Selective cytotoxic and anti- proliferative effects on glioma cells	Brain Tumor	(38)
Fabaceae (Leguminosae)	<i>Astragalus spp.</i>	Aerial Parts	Antioxidative Compounds	Antimutagenic activity	Protective Effect Againts Cancer	(46)

	<i>Astragalus chrysochlorus</i>	Root	Saponines Flavonoids	Antiproliferative activities: change on especially antiapoptotic genes	Cervix Carcinoma	(45)
	<i>Glycyrrhiza glabra</i> ,	Aerial Parts	Phenolic Acids Flavonoids	Antiproliferative activities	Brain Tumor Cervix Carcinoma	(119)
Hypericaceae	<i>Hypericum adenotrichum</i>	Flowers	Phenolic Compounds	Induced non-apoptotic cell death	Brain and Liver Carcinoma	(48)
	<i>Hypericum Retusum</i>	Flower, Fruit and Seed	Protocatechuic Acid Catechin Caffeic Acid Syringic Acid	Acetyl and butyryl-cholinesterase inhibitory activity antioxidant and antigenotoxic effect	Cervix Carcinoma	(138)
	<i>Hypericum olympicum</i>	Flowers	Phenolic Compounds	Induced non-apoptotic cell death	Brain and Liver Carcinoma	(48)
Lamiaceae	<i>Melissa officinalis</i>	Aerial Parts	Polyphenols mainly: Rosmarinic Acid Trimeric Compounds Luteolin-7-O-Glucoside	Induces apoptosis: decrease the Ki-67 activity in tumoral tissues and induced the activation of caspase-7	Mammary tumors <i>in vivo</i>	(139)
	<i>Origanum rotundifolium</i>	Aerial Parts	Vitexin Globoidnan A Caprolactam Rosmarinic acid Apigenin Ferulic acid	Antiproliferative activity	Cervix Carcinoma Colorectal Adenocarcinoma Brain Tumor Cells	(140)
	<i>Origanum acutidens</i>	Aerial Parts	Carvacrol <i>p</i> -cymene γ -terpinene Borneol	Antiproliferative activity Radical scavenging activity	Colorectal adenocarcinoma Cervical adenocarcinoma	(141)
	<i>Origanum acutidens</i>	Herbal Parts	Carvacrol, <i>p</i> -Cymene Linalyl Acetate Borneol (<i>E</i>)-Caryophyllene	Cytotoxic effects Induce activation of caspase-7	Breast Carcinoma	(142)
	<i>Rosmarinus officinalis</i>	Leaves	Carnosol Rosmarinic Acid Hesperetin Caffeic Acid Ferulic Acid Vanillic Acid	Selectively inhibits adenosine deaminase activity in cancerous gastric tissue	Gastric Carcinoma	(133)

	<i>Satureja boissieri</i>	Aerial Parts	<i>p</i> -Cymene γ -Terpinene Thymol Carvacrol	Cytotoxic effects	Cervical Carcinoma	(143)
	<i>Scutellaria orientalis ssp. carica*</i>	Aerial parts	apigenin, baicalein, chrysin luteolin wogonin	Anti-leukemic activity	Promyeloic leukaemia	(144)
	<i>Thymus revolutus</i> Célak*	Aerial parts	γ -terpinene <i>p</i> -cymene	Antitumor and Prooxidative activity	Lung Carcinoma	(67)
	<i>Ziziphora clinopodioides</i>	Aerial Parts	<i>n</i> -Alkanes mainly; Pulegone Menthol Menthone	Cytotoxic effects	Colon Carcinoma Breast Carcinoma	(145)

Liliaceae	<i>Allium sivasicum</i>	Herbal Parts	Several Anticancer Compounds	Antiproliferative activity	Breast Carcinoma	(89)
	<i>Allium sativum</i>	All Parts	Several Antioxidative Compounds	Selectively inhibits adenosine deaminase activity in cancer cells	Urinary Bladder Carcinoma	(146)
	<i>Asphodeline lutea</i>	Root	Anthraquinones Bianthraquinones Naphthalenes Flavonoids Hydroxycinnamic Acid	Antiproliferative activity	Breast Carcinoma	(78)
	<i>Colchicum sanguicolle</i>	Tubers	Various Antioxidative Compounds	Antitumor activity	Cervical Carcinoma	(73)
	<i>Colchicum sanguicolle</i> K.M. Perss*	Aerial parts	Various Antioxidative Compounds	Antiproliferative activity	Cervical Carcinoma	(74)
	<i>Urginea maritima</i> (L.) Baker	bulb and leaves	Various Antioxidative Compounds	Induces more cytotoxicity than standard chemotherapeutics	Lung Carcinoma	(86)

Lythraceae	<i>Punica granatum</i>	Fruit Peel	Phenolic Compounds mainly Ellagic Acid	Antioxidant and apoptotic activity: reduces cell proliferation and induces apoptosis	Breast Carcinoma	(147)
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Moraceae	<i>Morus nigra</i>	Fruit	Phenolic Compounds Ascorbic Acid Chlorogenic Acid	Induce apoptosis via increase caspase activity and reduce mitochondrial membrane potential	Prostate Carcinoma	(107)
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	<i>Morus rubra</i>	Fruit	Phenolics Flavonoids Anthocyanins Carotenoids	Induce cell cycle arrest at the G1 phase and apoptosis via reduce mitochondrial membrane potential	Colon Carcinoma	(108)
Pinaceae	<i>Pinus nigra</i> ssp. <i>pallasiana</i> . var. <i>şeneriana</i> *	Pine needles	α -pinene, β -pinene, myrcene, linalyl acetate germacrene-D (<i>E</i>)-caryophyllene α -humulene and δ -cadinene	Induced apoptosis via reduced mitochondrial membrane potential	Breast Carcinoma	(148)
Plantaginaceae	<i>Plantago major</i>	Leaves	Tannins Glycosides Phenolic Compounds	Cytotoxic effects	Ehrlich Ascites Tumor	(149)
Polygonaceae	<i>Rheum palmatum</i>	All Parts	Anthraquinones mainly Emodin	Inhibits adenosine deaminase activity	Protective Effect Against Gastric and Colon Carcinoma	(150)
Rosaceae	<i>Crataegus monogyna</i>	Aerial Parts	Phenolic Acids Flavonoids	Antiproliferative activities	Brain Tumor Cervix Carcinoma	(119)
	<i>Rosa canina</i>	Fruits	Phenolic Acids Proanthocyanidins Tannins Flavonoids Pentacyclic Triterpenes	Induced cell cycle arrest at the S phase and apoptosis via reduced mitochondrial membrane potential	Colon Carcinoma	(116)
	<i>Prunus laurocerasus</i>	Fruits	Phenolic Acids Flavonoids Cyanogenic Glycosides	Antiproliferative activities: destroy the cellular membrane in tumor cell lines	Cervix, Colorectal Carcinoma Brain Tumor	(118)
	<i>Prunus cerasus</i>	Fruit	Anthocyanins Melatonin	Antiproliferative activity: induce apoptosis	Breast Carcinoma	(120)

	<i>Verbascum</i> spp.	All Parts	Iridoid and neolignan type glycosides Oleanane triterpenes Flavonoids Saponins Steroids Alkaloids	Selective cytotoxic effects on cervical and ovarian cancer cells	Cervical and Ovarian Carcinoma	(130)
Theaceae	<i>Camellia sinensis</i>	Aerial Parts	Flavonoids	Protection against cancer cells: carcinogenic chemical induced oxidative injury	Protective Effect Against Cancer	(134)
Urticaceae	<i>Urtica dioica</i>	Aerial Parts	Flavonoids	Carcinogenic chemical induced oxidative injury	Protective effect <i>in vivo</i>	(134)
	<i>Urtica dioica</i>	Leaves	Carnosol Rosmarinic Acid Hesperetin Caffeic Acid Ferulic Acid Vanillic Acid	Selectively inhibits adenosine deaminase activity in cancerous gastric tissue	Gastric Carcinoma	(133)
Vitaceae	<i>Vitis vinifera</i>	Aerial Parts	Phenolic Acids Flavonoids	Antiproliferative activities	Brain Tumor Cervix Carcinoma	(119)

‘Acicigdem’ in Turkey (70). Troponone alkaloid components of the distinct species belonging to the genus *Colchicum* were dissimilar according to the different regions and growth stages (71). Colchicine, the main alkaloid of genus *Colchicum*, is an antitumor agent that is classified as a mitotic inhibitor (72). An effective *in-vitro* antitumor activity on cervical carcinoma cells has been indicated for Turkish *Colchicum sanguicolle* methanolic extract with IC_{50} values of 0.01 mg/mL and 0.001 mg/mL at 48 hrs for HeLa and C4-I cell lines, respectively (73). In addition, an endemic species, *Colchicum sanguicolle* K.M. Perss, revealed significant selective toxicity against the HeLa cell line whereas indicated low cytotoxicity on the Vero cell line (74). The degree of selectivity is defined by its selectivity index ($SI = IC_{50}$ normal cell/ IC_{50} cancer cell) (75).

Plants of the genus *Asphodeline* have been traditionally used as medicinal plants in various parts of the world. The genus contains 20 taxa, 12 of which are endemic in Turkey (76). A number of *Asphodeline* species are used to alleviate warts and heal wounds and to treat earaches and hemorrhoids in Turkish folk medicine. Moreover, species of *A. cilicica*, *A. damascena*, *A. globifera*, *A. lutea* and *A. taurica* are consumed as salad vegetables in different regions (77). In the study of Lazarova and coworkers (2015), methanolic extracts of *A. lutea* roots from Turkish and Bulgarian origins were assessed for their ability to regulate the growth of the breast cancer cell line MCF-7 and the noncancerous breast epithelial cell line MCF-10A and their anti-proliferative effect were reported. A naphthalene derivative (2-acetyl-1,8-dimethoxy-3-methylnaphthalene) was the major compound in Bulgarian accession while Turkish accession had caffeic acid as the most abundant (78).

Eremurus spectabilis (serish -common name and ciris -local name) belongs to the family Liliaceae and is geographically distributed in the region of South Asia and Central Asia, including Iran, West Pakistan, Afghanistan, Iraq, Palestine, Lebanon, Syria, Caucasus and Turkey (79). Growing in spring and localized in the east of Turkey, *Eremurus* species used in folk medicine to cure ailments such as hemorrhoids and diabetes, and also used as antihypertensive and antidysuria agents (80). Recently, anticancer activity of Turkish *E. spectabilis* leaves and roots originating from Bingol Province has been reported against prostate cancer cells. Acetone, ethanol and water extracts activated mitochondrially-triggered apoptosis in PC-3 cells by up-regulation of Bax and caspase-3 and down-regulation of Bcl-2 mRNA (81).

Urginea maritima (L.) Baker (Liliaceae) is a cardiac glycoside-producing native Mediterranean medicinal plant, commonly known as squill (82). In traditional medicine, it has been used for many centuries due to its for powerful digitalis-like cardiac effect (83), and is also used as a diuretic and heart stimulant (84). Bulbs of *Urginea indica* have been reported with potent *in-vivo* antitumor activity against growth of an ascites tumor (85). A bioactive bufadienolide that was subsequently shown to be proscillaridin A has been isolated from alcoholic Egyptian *U. maritima* extracts (82). Turkish *Urginea maritima* (L.) Baker has been reported to be a strong candidate for drug development against solid tumors. The bulb extract (1 µg/mL) was found more cytotoxic

than cisplatin (1 µg/mL), gemcitabine (1 nm/mL), or the leaf extract (1 µg/mL). Hence, the authors claimed that *U. maritima* extracts induced more cytotoxicity than standard chemotherapeutics in the A549 non-small cell lung cancer cell line (86).

The genus *Allium* belonging to the family Liliaceae includes approximately 500 species all over the world (87). *Allium* L. is one of the largest genera in the Turkish flora. The total number known from Turkey is 190 of which 75 taxa are endemic (88). The members of this genus have been reported to possess antitumoral (89), antimicrobial (90), antioxidant (91), antiviral (92), antidiabetic (93) properties. The potential use of *Allium* species as anti-cancer agents has been reviewed previously (94,95). A well-known plant is garlic (*Allium sativum*) having a place among oldest cultivated plants in Middle and West Asia (96). A lower prevalence of cancer has been indicated countries where garlic is traditionally consumed in higher amounts (97). It has sulfur-containing phytochemicals such as diallyl disulfide which has been found as highly effective in affording protection against cancer in animal and clinical studies (98,99). The antiproliferative properties *Allium sivasicum* collected from Sivas region was investigated on breast cancer cell lines, namely MCF-7 ($IC_{50} = 21 \pm 1,4$ µg/mL), MDA-MB-468 ($IC_{50} = 22 \pm 1,4$ µg/mL) and MDA-MB-231 ($IC_{50} = 24 \pm 1,3$ µg/mL). In addition, the aqueous extract of *A. sivasicum* exhibited mean tumor volume inhibition ratio of 38% in the treated group in comparison with the untreated in female albino Wistar rats (89).

Moraceae

Morus rubra L. and *Morus nigra* L. are the most extensive *Morus* species that belongs to the family Moraceae. These species have been cultivated in Europe and Asia since pre-Roman times (100,101). The deep-colored *Morus* fruits, commonly known as mulberries, are a rich source of phenolic compounds such as flavonoids, anthocyanins and carotenoids (102). Since the *Morus* species contain various phenolic content in high amounts, the fruits exhibit antimicrobial, antioxidant, antidiabetic, anti-HIV, anti-inflammatory, hypolipidemic, hepatoprotective, antiobesity, neuroprotective and anticancer activities (102–106). Proapoptotic and antiproliferative properties of *Morus nigra* dimethyl sulfoxide extract on prostate cancer cells was evaluated. Researchers reported that *Morus nigra* extract arrested the cell cycle of prostate cancer cells at the G1 phase, therefore inducing apoptosis by increased caspase activity and reduced mitochondrial membrane potential of prostate cancer cells (107). A similar proapoptotic and antiproliferative mechanism was also observed in the effect of *Morus rubra* extract on colon cancer cells, which is summarized in Table 1 (108). On the other hand, to understand in more detail the exact anticancer mechanism, phytochemical analyses should be carried out in addition to *in vivo* biological activity experiments (107,108).

Rosaceae

The family Rosaceae is a remarkable taxon with res-

pect to systematic biology (109). It is diversified particularly in the northern hemisphere and comprises more than 100 genera and 3000 species (110). Numerous well-known and beloved species of economic importance. Temperate zone members of the family are well known for edible fruits (111) in addition to some timber crops and medicinals (112). For example, cherry, apricot, almond, peach, apple, pear, plum, hawthorn, strawberry, blackberry, and rosehip belong to Rosaceae (112). When antioxidant activities of infusions prepared from 70 medicinal plants belonging to different taxa were compared, leaves of raspberry, blackberry, and strawberry were among eleven of the most effective plants (113).

Rosa canina L. from in Rosaceae has long been used for medicinal purposes. Turkey has one of the most substantial native populations of rose species with about 25% of rose species growing in Turkey (114). Phytochemicals such as phenolic acids, proanthocyanidins, tannins, flavonoids, pentacyclic triterpenes have been reported (115). *R. canina* is traditionally used to treat of colds, asthma, hemorrhoids, infections, chronic pains, arthritis, and inflammatory diseases in both Western and Asian countries (114–116). Being also a good source of vitamin C, it has been reported that only polyphenols contribute to its antiproliferative activity (117). The fruits have recently been suggested as a source of potent novel phytochemical anticancer agents. It was reported that *R. canina* extract reduced mitochondrial membrane potential and the expression of telomerase in human colon cancer cells; it induced apoptosis and cell cycle arrest at the S phase. Moreover, selective cytotoxic effect of the extracts on colon cancer cells was highlighted (116).

Besides the anticancer properties of natural extracts, recent studies showed that, natural extracts can be more effective therapeutic agents against tumors than standard chemotherapeutic candidates (118). It was demonstrated that the methanol extract of *Crataegus monogyna* (Rosaceae) exhibited better antiproliferative activity than standard chemotherapeutics 5-fluorouracil and cisplatin on brain tumors and cervical cancer cells (119). Furthermore, the natural extracts can be added to the standard anticancer drugs for increasing their treatment effectiveness and reducing their side effects. Aydın *et al.* (2016) showed that high concentration of *Prunus laurocerasus* aqueous fruit extract destroyed the cellular membrane of tumor cells. Furthermore, they indicated that when the *P. laurocerasus* aqueous fruit extract did not show effective anticancer properties, it can still be a potential adjuvant therapy to current chemotherapeutic agents. For this reason, adding the *P. laurocerasus* extract to the chemotherapeutic formulation has been suggested. The fatty acid-rich bioactive components of Turkish cherry laurel fruit extracts have been reported to be responsible for the chemoprotective effect against HT29, HeLa, C6 and Vero cell lines (118). Furthermore, aqueous ethanolic extracts prepared from cherry pulp have been evaluated for their anti-cancer activity. The antiproliferative activity of *Prunus cerasus* was shown on breast cancer cells. The extract induced apoptosis and reduced the asymmetric dimethylarginine concentration. Therefore, *P. cerasus* extract may be considered as a novel prophylactic therapeutic agent for breast can-

cer (120).

Rubiaceae

Galium aparine L. and *Morinda citrifolia* L. belong to the Rubiaceae family, which are commonly used in folk medicine for the treatment of wounds, fever and hypertension (121,122). The previous studies showed that these plants contain several anticarcinogenic compounds, as they can be a part of cancer treatment strategies (Table 1). *Galium aparine* grows throughout Anatolia and is a typical climbing plant (123). Atmaca and co-workers (2016) identified 14 major phytochemicals and 34 volatile compounds in the ethanol extract of the aerial parts of *G. aparine*. They reported that the extract induced apoptosis of breast cancer cells, while it did not show any negative effects on normal breast epithelial cells. More importantly, they assumed that the *G. aparine* extract may enable the killing of apoptosis resistant breast cancer cells (124). In another study, the anticarcinogenic effect of *Morinda citrifolia* was investigated via *in vivo* experiments. It was found that the fruit of *M. citrifolia* induces apoptosis of breast cancer cells. Therefore, it can be used the treatment of breast cancer either on its own or in combination with doxorubicin, which is a most commonly used chemotherapeutic for breast cancer (121).

Scrophulariaceae

The Scrophulariaceae contains more than 220 genera, where *Scrophularia* spp. and *Verbascum* L. spp. commonly grow in Turkey. In the traditional practices, these plants are used for the treatment of scabies, eczema, psoriasis, hemorrhoids, rheumatic pain, superficial fungal infections, wounds and diarrhea. (125,126). The major bioactive compounds in the Scrophulariaceae plants are of sugar esters, iridoid glycosides, oleanane type triterpenoids, flavonoids, polysaccharides, saponins, steroids and alkaloids (127,128). Anti-inflammatory and anti-neoplastic effects of *Scrophularia* spp., have been reported. Moreover, it has been shown that the methanol extract of *Scrophularia* spp. induced apoptosis in breast cancer cells as well as exhibited strong antiproliferative properties (129). *Verbascum* L. is another genus that belongs to Scrophulariaceae family, where the methanol extract of *V. pycnostachyum* has selective cytotoxic effects on cervical and ovarian cancer cells (130).

Urticaceae

In traditional medicine, both roots and leaves of *Urtica dioica* are used as an adjuvant remedy in the treatment of several diseases especially for cancer therapy (131). The bioactive compounds of *U. dioica* leaves have been shown to inhibit the genetic transcription factor which activates the tumor necrosis factor- α (TNF- α) (132). The anticancer properties of *U. dioica* have also been demonstrated by the inhibitory activity on adenosine deaminase. The inhibition of adenosine deaminase in cancerous gastric tissues was reported for the aqueous extract (133). In an *in-vivo* study, rats that had been exposed to the chemical carcinogen trichloroacetic

acid (TCA) were fed a beverage of *U. dioica* for 50 days and investigated the protective effects of the beverage. They observed that since the *U. dioica* contains strong antioxidant compounds (Table 1), the oxidative stress, which is induced by TCA, was remarkably reduced in the *U. dioica* fed rats. Thus, they reported that *U. dioica* beverage can be thought as a potential cancer preventive supplement since has a protective effect against oxidative injury (134).

Concluding Remarks

It is exciting to note that Anatolian plants provide a rich source of whole extracts and isolated bioactive phytochemicals of pharmacological importance. However, much of the available data have been derived through preliminary findings. Future studies are needed with in-depth and detailed research with special focus on regulation of deregulated pathways by natural products obtained from Turkish flora in different cancers to realistically evaluate potential of bioactive components.

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