Chapter 20
Efficacy of Nano-phytochemicals Over Pure Phytochemicals Against Various Cancers: Current Trends and Future Prospects

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20.1 Phytochemicals and Nano-phytochemicals as Potent Anticancer Agents

Cancer remains a universal destructive disease and the second most common cause of death in humans. Approximately 7.6 million mortalities per year are attributed to cancer. Developing nations are facing more cancer incidence and now represent about 60% of the deaths (Siegel et al. 2017). The World Health Organization has predicted that about 15 million new incidences of cancer will emerge globally in 2020. Anticancer activity is the consequence of natural or synthetic compounds to reverse, repress, or check the development of cancer. As the present radiotherapy and chemotherapy treatments do not distinguish normal cells from cancer cells and thus can cause severe side effects, researchers and the pharmaceutical industry are concerned to develop a smart drug that can cure this destructive disease without affecting normal healthy cells (Jafri et al. 2018). Fortunately, India is a vast resource of medicinal plants and natural products. Epidemiological observation suggests that Indian herbs, spices, and their isolated phytochemicals possess significant anticancer potential and that their consumption is associated with reduction of the progression of some cancers. The anticancer properties of several phytochemicals isolated from different medicinal plants have been reported. Table 20.1 depicts the anticancer properties of some potent phytochemicals and their anticancer mechanisms.

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Table 20.1 Potent phytochemicals and their anticancer mode of action against some cancers

Sample no.	Name of phytochemicals	Nature of phytochemical and the plant source	Mode of action in the induction of apoptosis	References
1.	Apigenin	A flavonoid present in the flowers of chamomile plants but also found in plenty in parsley, celery, celeriac, and chamomile tea	Encourages apoptosis, inhibits oxidative stress by scavenging free radicals, promotes anti-angiogenesis	Shukla and Gupta (2010)
2.	Berberin	An alkaloid present in *Hydrastis canadensis* Common name: Goldenseal or orangeroot	Apoptosis induction, blocks cell-cycle progression, inhibits signal transduction pathway, impairs cell adhesion and invasion	Tan et al. (2011)
3.	Combretastatin A4	Phenolic compound found in *Combretum caffrum* Common name: Cape bushwillow	Inhibits angiogenesis, encourages cell-cycle arrest via inhibition of tubulin polymerization	Tozer et al. (2002)
4.	Cucurbitacin B	A terpenoid present in *Trichosanthes cucumerina* Common name: Chichinda, snake gourd or Padwal	Apoptosis induction, inhibits cell-cycle progression, impairs signal transduction pathways, prevents angiogenesis	Kaushik et al. (2015)
5.	Curcumin	*Curcuma longa* Common name: Turmeric or Haldi	Enhances the expression of tumor suppressor genes and downregulation of oncogenes, promotes anti-angiogenesis, inhibits signal transduction pathway, damages cell adhesion and invasion properties	Ahmad et al. (2016)
6.	Epigallocatechin-3-gallate (EGCG)	*Camellia sinensis* Common name: Green tea	Initiates apoptosis, reduces oxidative stress by scavenging free radicals, inhibits angiogenesis, enhances the expression of the tumor suppressor gene, inhibits signal transduction pathways	Singh et al. (2011)
7.	Ellagic acid	A predominant phenol abundant in numerous fruits and vegetables	Triggers apoptosis, reduces oxidative stress and scavenges free radicals, inhibits angiogenesis, damages cell adhesion and invasion properties	Zhang et al. (2014)

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Table 20.1 (continued)

Sample no.	Name of phytochemicals	Nature of phytochemical and the plant source	Mode of action in the induction of apoptosis	References
8.	Emodin	A glycoside present in *Rhamnus frangula* Common name: Alder buckthorn	Encourages apoptosis, hinders tyrosine kinase enzyme action, reduces oxidative stress by scavenging free radicals, augments anti-angiogenesis, inhibits signal transduction pathway, upregulates the expression of tumor suppressor genes	Wei et al. (2013)
9.	Ferulic acid or hydroxycinnamic acid	A phenolic phyto-compound present in the cell walls of plants	Induces apoptosis, reduces oxidative stress by scavenging free radicals	Srinivasan et al. (2007)
10.	Gambogic acid	A glycoside present in *Garcinia hanburyi* (resins) Common name: Gamboge	Induces apoptosis, promotes anti-angiogenesis, inhibits telomerase enzyme action, inhibits signal transduction pathway	Kashyap et al. (2016)
11.	Genistein	Found in *Genista tinctoria* Common name: Dyer's greenweed or Dyer's broom	Encourages apoptosis, inhibits angiogenesis, inhibits cell-cycle progression, induces the expression of tumor suppressor gene	Li et al. (2012)
12.	Hesperitin	Found abundantly in citrus fruits	Induces apoptosis, promotes anti-angiogenesis, encourages the expression of tumor suppressor gene	Roohbakhsh et al. (2015)
13.	Honokiol	A lignin present in *Magnolia grandiflora* Common name: Southern magnolia, lily tree, laurel magnolia	Induces apoptosis, promotes anti-angiogenesis, and inhibits tumor growth; impairs signal transduction pathways	Fried and Arbiser (2009)
14.	Isoliquiritigenin	A terpenoid present in *Glycyrrhiza uralensis* Common name: Liquorice root, liquorice, sweetroot, Gan Cao	Enhances apoptosis, impairs signal transduction pathways, inhibits cell-cycle progression, obstructs angiogenesis, damages cell adhesion and invasion properties	Orlikova et al. (2011)
15.	Kaempferol	A flavonoid present in various plants and plant-derived foods	Encourages apoptosis, inhibits angiogenesis	Kim and Choi (2013)

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Table 20.1 (continued)

Sample no.	Name of phytochemicals	Nature of phytochemical and the plant source	Mode of action in the induction of apoptosis	References
16.	Luteolin	Found in *Salvia tomentosa* and also found in some dietary sources including carrots, green pepper, chamomile tea, broccoli, parsley, olive oil	Induces apoptosis, inhibits oxidative stress by scavenging free radicals, prevents the expression of the oncogene, impairs signal transduction pathway, encourages the expression of a tumor-suppressing gene, promotes cell-cycle arrest, prevent angiogenesis	Lin et al. (2008)
17.	Morin	*Morus alba* Common name: White mulberry	Promotes apoptosis, encourages anti-angiogenesis	Park et al. (2015)
18.	Naringenin	A predominant flavanone, abundant in grapefruit and also found in a variety of fruits and herbs	Promotes apoptosis, inhibits angiogenesis, encourages tumor suppressor gene expression, impairs signal transduction pathway	Ahamad et al. (2014)
19.	Nobiletin	A flavonoid isolated from citrus peels	Encourages apoptosis, inhibits angiogenesis, induces the expression of tumor suppressor gene, scavenging free radicals, and reduces oxidative stress	Rawson et al. (2014)
20.	Piperine	A predominant alkaloid of *Piper nigrum* Common name: Black pepper	Induction of apoptosis, upregulates tumor suppressor genes, activation of caspase-3, damages signal transduction pathways	Jafri et al. (2019)
21.	Quercetin	A major flavonoid present in several fruits and vegetables: apples, berries, red onions, green tea, etc.	Encourages apoptosis, reduce oxidative stress by scavenging free radicals, inhibits angiogenesis, impairs signal transduction pathway	Khan et al. (2016)
22.	Resveratrol	A phenol found in cranberry (*Vaccinium macrocarpon*), grapes (*Vitis vinifera*), and peanut (*Arachis hypogaea*)	Encourages apoptosis, reduces oxidative stress by scavenging free radicals, promotes cell-cycle arrest, inhibits expression of oncogene	Varoni et al. (2016)

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Table 20.1 (continued)

Sample no.	Name of phytochemicals	Nature of phytochemical and the plant source	Mode of action in the induction of apoptosis	References
23.	Silibinin	*Silybum marianum* Common names: *Carduus marianus*, milk thistle, blessed milk thistle, Scotch thistle	Induces apoptosis, promotes anti-angiogenesis, reduces oxidative stress by scavenging free radicals, hinders cell-cycle progression, enhances tumor suppressor gene expression, impairs cell adhesion and invasion properties	Ting et al. (2013)
24.	Tetrandrine	An alkaloid present in *Stephania tetrandra* Common name: Fang Ji	Apoptosis induction, anti-inflammatory and anti-carcinogenic effectiveness, anti-angiogenic agent	Chen (2002)
25.	Thymoquinone	A predominant quinone found abundantly in *Nigella sativa* Common name: Caraway, black cumin, or Kalonji	Promotes apoptosis, reduces oxidative stress by scavenging free radicals, arrests cell cycle, impairs cell adhesion and invasion, encourages enzyme induction and thus enhances detoxification, hinders angiogenesis	Woo et al. (2012)
26.	Vincristine	A potent alkaloid existing in *Catharanthus roseus* Common name: Sadabahar or periwinkle	Encourages apoptosis in cancerous cells, inhibition of cell-cycle progression via inhibiting polymerization of tubulin	Moudi et al. (2013)
27.	Vinblastine	An alkaloid existing in *Catharanthus roseus* Common name: Sadabahar or periwinkle	Encourages apoptosis in cancerous cells, inhibition of cell-cycle progression via inhibiting polymerization of tubulin	Moudi et al. (2013)
28.	Zerumbone	A predominant terpenoid found abundantly in *Zingiber zerumbet* Common name: Awapuhi, bitter ginger, pinecone ginger	Encourages cell-cycle arrest, inhibits expression of the oncogene, reduces oxidative stress by scavenging free radicals	Rahman et al. (2014)

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Table 20.1 (continued)

Sample no.	Name of phytochemicals	Nature of phytochemical and the plant source	Mode of action in the induction of apoptosis	References
29.	α-Mangostin	A xanthonoid obtained from *Garcinia mangostana* Common name: Mangosteen	Triggers apoptosis, reduces oxidative stress by scavenging free radicals, encourages cell-cycle arrest, enhances caspase-3 activity	Jafri et al. (2018)
30.	β-Lapachone	A quinone found in *Tabebuia avellanedae* Common name: Pink tabebuia	Induces apoptosis, impairs signal transduction pathway, reduces oxidative stress by scavenging free radicals	Kung et al. (2014)

20.2 The Advantage of Nano-phytochemicals Over Pure Phytochemicals

Phytochemicals have potential ability to protect against many chronic diseases such as heart disease, diabetes, neuronal degeneration, and cancer (Subramanian et al. 2016). Phytochemicals possess significant antiproliferative and apoptotic effects against various cancer cells and are widely used in anticancer research (Fig. 20.1). These phytochemicals induce apoptotic effects on various cancerous cells through different apoptotic signaling pathways and check cell-cycle progression, regulating the antioxidant system and detoxification.

Although the phytochemicals possess marvelous antiproliferative and apoptotic potential, they also have some limitations to be target-effective drugs because of their lower solubility in water, poor penetration power for entering targeted cells, restricted therapeutic potential, hepatic disposition, and prompt absorption by normal cells (Bhadoriya et al. 2011). Hence, to overcome these issues, scientists have shifted their interests toward a nano-based targeted drug delivery system of some promising phytochemicals to enhance their aqueous solubility, target specific to cancerous cells, improving cellular uptake, bioavailability and reducing the quantities of phytochemicals to achieve a secure therapeutic level of these potent phytochemicals for future targeted drug delivery systems (Fig. 20.2). The nano-phytochemicals also have various advantages over the pure phytochemicals in having excellent stability in the blood, a multi-efficient design, and hence improved anticancer effectiveness compared to the pure phytochemicals.

20.2.1 Role of Nanoform Phytochemicals in Cancer Research

Nanotechnology has improved the bioavailability, solubility, and targeted delivery of active phytochemicals by using nanoparticles as a carrier and enhancing the bioactivity of potent phytochemicals (Nishiyama 2007). There are some previous

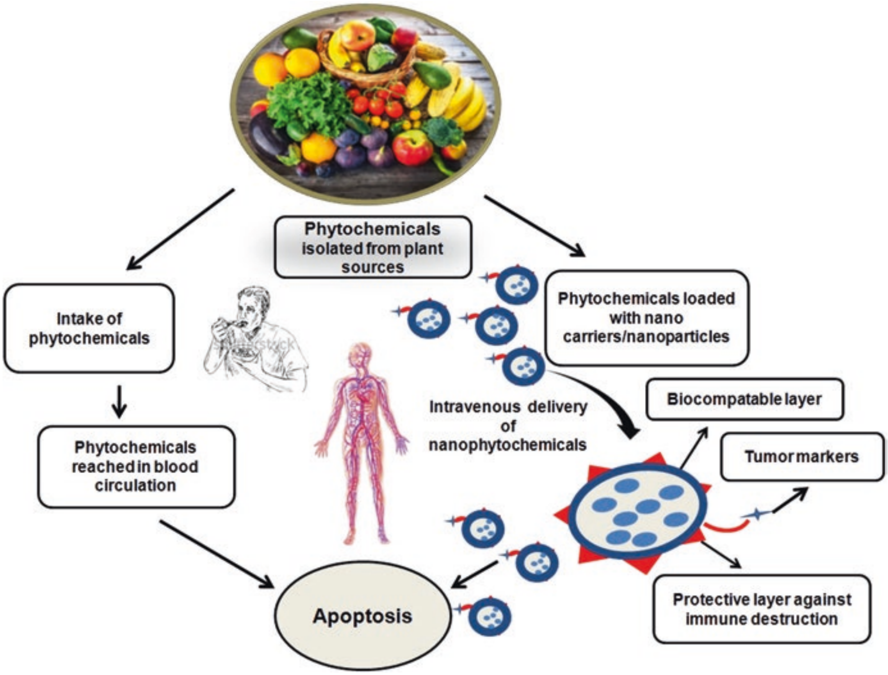

Fig. 20.1 Apoptotic induction by phytochemicals and nano-phytochemicals in cancer cells

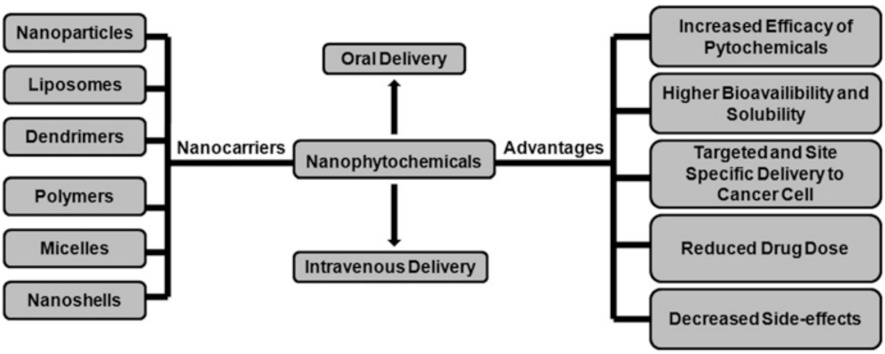

Fig. 20.2 Schematic presentation of nanocarrier nano-phytochemicals and their advantages in cancer research

reports of the active phytochemical-loaded nanoparticles targeting against cancer cells with reduced side effects. Table 20.2 shows some promising nano-phytochemicals and their anticancer potential against some cancers.

20.2.1.1 Broccoli Gold Nanoparticles

Broccoli (*Brassica oleracea*) is a cruciferous vegetable that is potentially protective against some cancers (Steinmetz and Potter 1991a, b). Broccoli phytochemicals are loaded with polyphenols, glucosinolates (GLs), vitamin C, carotene, folic acid, and fibers (Conaway et al. 2001; Mahn and Reyes 2011). These constituents enhance antioxidant activities and stimulate phase-2 detoxification enzymes (Tang et al. 2006; Qazi et al. 2010). Broccoli-loaded gold nanoparticles (B-Au NPs) were synthesized and were analyzed against some cancerous cells, such as MDA-MB-231, SkBr3, and T47D cells of breast carcinoma, PC-3 cells of prostate carcinoma, and U266 cells of myeloma to evaluate the anti-cancerous activity (Khoobchandani et al. 2013). The findings revealed that the conjugated B-Au NPs possessed excellent anti-cancerous effects against breast carcinoma, prostate carcinoma and myeloma cells.

20.2.1.2 Gold Quercetin Nanoparticles

Quercetin is a predominant flavone that possesses antioxidant and antiinflammatory properties and provides valuable health benefits to humans (Aguirre et al. 2011). It is isolated from many food items such as leafy vegetables, citrus fruits, red wine, green tea, apples, berries, onions, and *Ginkgo biloba* (Davis et al. 2009). A previous study reported the synthesis of gold-quercetin nanoparticles (GQ NPs) and its anticancer activity against liver carcinoma (Ren et al. 2017). The GQ NPs regulated abnormal proliferation, colony formation, and cell migration in liver cancer cells, and subsequently inhibited cancer progression. GQ NPs encouraged apoptosis in liver carcinoma cells by activation of caspases (3, 9) and expression of cytochrome *c* (Cyto-c). The study showed that GQ NPs impair the caspase/Cyto-c pathway, obstruct NF-κB/COX-2 and Akt/ERK1/2, and suppress AP-2β/hTERT signaling pathways.

20.2.1.3 Curcumin Nanoparticles

Curcumin has both anticancer and cancer prevention properties. Curcumin is a natural bioactive polyphenolic constituent, found in turmeric, with properties to inhibit proliferation and metastasis in a wide range of cancers (Joe et al. 2004). However, poor solubility in water has limited the systemic bioavailability of curcumin when administered orally. To overcome the solubility and bioavailability restrictions of curcumin, it was loaded on various types of nanoparticles. Methoxy polyethylene glycol (mPEG) and polycaprolactone (PCL) co-polymers enhanced the anticancerous activity of curcumin with efficient loading capability and sustainable release in A549 cells of lung epithelial carcinoma. This curcumin-loaded nanoparticle effectively enters into lung carcinoma A549 cells and interacts with the nucleus to encourage apoptosis (Yin et al. 2013). Poly lactic-co-glycolic acid curcumin

Table 20.2 Promising nano-phytochemicals and their anticancer potential against some cancers

Sample no.	Nano-phytoconstituents	Source of phytochemical	Mode of action	References
1.	Broccoli nanoparticle	Broccoli	Anticancer action against MDA-MB-231, SkBr3, and T47D cells of breast carcinoma, PC-3 cells of prostate carcinoma, and U266 cells of myeloma	Khoobchandani et al. (2013)
2.	Quercetin nanoparticle	Leafy vegetables, citrus fruits, red wine, green tea, apples, berries, onions, *Ginkgo biloba*	Inhibits growth in hepatic carcinoma cells, modulates caspase activities, upregulates cytochrome *c*, obstructs NFκB/COX-2 and Akt/ERK1/2 expression	Davis et al. (2009), Ren et al. (2017)
3.	Curcumin nanoparticle	Turmeric (*Curcuma longa*)	Inhibits phosphoinositide 3-kinase pathway, suppresses tumor burden, induced apoptosis,, enhanced therapeutic ability	Yin et al. (2013), Yallapu et al. (2014), Esfandiarpour-Boroujeni et al. (2017)
4.	*Selaginella doederleinii* nanoparticle	*Selaginella doederleinii* Hieron	Inhibits growth in A549 cells of human lung carcinoma	Syaefudin et al. (2016)
5.	*Nigella sativa* nanoparticles	*Nigella*	Upregulates miR-34 a,d, represses Rac1 mRNA protein expression, enhances antiproliferative and apoptotic properties	Bhattacharya et al. (2015), Ganea et al. (2010), Dehghani et al. (2015)
6.	Honokiol nanoparticle	*Magnolia officinalis*	Antiproliferative effect against osteosarcoma cells, induces apoptosis, inhibits proliferation of tumors and prevents angiogenesis, micro-vessel generation. and cell-cycle arrest	Cheng et al. (2016), Li et al. (2008)
7.	Silibinin nanoparticle	*Silybum marianum*	Suppresses cell proliferation, inhibits hTERT expression, prevents metastasis and angiogenesis in breast cancer cells	Ebrahimnezhad et al. (2013), Amirsaadat et al. (2017), Xu et al. (2013)
8.	Ursolic acid nanoparticles	Epicuticular waxes of apples, peels of fruits, herbs and spices such as rosemary and thyme	Encourages anticancer activity, promotes lysosomal destruction, enhances ROS augmentation, promotes apoptosis in MCF-7 cells of breast carcinoma	Baishya et al. (2016), Jiang et al. (2017)

(continued)

Table 20.2 (continued)

Sample no.	Nano-phytoconstituents	Source of phytochemical	Mode of action	References
9.	β-Lapachone nanoparticle	Bark of the Lapacho tree	Activates anti-cancerous and radiotherapeutic efficacy	Jeong et al. (2009)
10.	Ferulic acid nanoparticles	Vegetable sources, oat flours, wheat, rice	Reduces cancer cell proliferation, promotes intracellular ROS production, enhances DNA damage, lipid peroxidation, and encourages apoptosis	Zhao and Moghadasian (2008), Kumar and Pruthi (2014)

nanoparticles (PLGA-CUR NPs) showed tumor regression properties against prostate carcinoma cells by inhibiting colony formation and cell growth in prostate cancer cell xenografted mice (Yallapu et al. 2014). PLGA-CUR NPs conjugated with epidermoid growth factor receptor were targeted to GE11 peptides in breast carcinoma cells in vitro and in a tumorous mice model. It extended the epidermal growth factor receptor (EGFR) expression in MCF-7 cells of breast carcinoma and reduced the phosphoinositide-3 kinase pathway, suppressed tumor growth, suppressed cancer cell proliferation, and improved drug clearance from the circulation (Jin et al. 2017). Curcumin-loaded magnetic nanoparticles were also significantly taken up in MDA-MB-231 cells of human epithelial breast carcinoma. These nanoparticles showed strong anticancer activity via strong penetration power into the cell by endocytosis (Yallapu et al. 2012). The uploaded curcumin magnetic nanoparticles exhibited strong magnetic resonance properties and potentially enhanced the anticancer targeting capacity of curcumin.

Nano-curcumin effectively decreased the level of miRNA-21, β-catenin, and the expression of E6/E7 HPV oncoproteins in a mouse cervical cancer model (Zaman et al. 2016). Also, curcumin-loaded silica nanoparticles (Dinda et al. 2012) and curcumin-loaded folate-modified chitosan nanoparticles (Esfandiarpour-Boroujeni et al. 2017) have significant anticancer effect against HepG2 cells of hepatocellular carcinoma and MCF-7 cells of breast carcinoma, respectively.

20.2.1.4 *Selaginella doederleinii* Leaf Nanoparticles

Selaginella doederleinii Hieron possesses several bioactive phytochemicals and has been extensively used in traditional herbal medicine for curing rheumatoid arthritis and various cancers, specifically lung cancer, cervical cancer, choriocarcinoma, and nasopharyngeal carcinoma (Abdille et al. 2005; Ishii et al. 2005; Wang et al. 2015). *Selaginella* leaf extract nanoparticles (SDNPs) reduced the viability of lung carcinoma A549 cells and were least toxic to normal Chang liver cells (Syaefudin et al. 2016). The findings revealed the apoptotic potential of SDNPs and the targeted drug delivery system without affecting the normal Chang cells.

20.2.1.5 *Nigella sativa* Nanoformulation

Nigella sativa, commonly known as nigella, kalonji, black caraway, and black cumin, is broadly used as a traditional medicine universally (Heiss and Oeggl 2005). Thymoquinone is one of the major active phyto-constituents present in *Nigella sativa* and possesses various pharmacological properties: antimicrobial, antiinflammatory, antipyretic, hypoglycemic, analgesic, and antioxidant (Ali and Blunden 2003). Previous studies reported the anticancer and antimutagenic activity of thymoquinone in Caco-2, HT-29, HCT-116, DLD-1, and LoVo cancerous cells (Gali-Muhtasib et al. 2006). The encapsulated thymoquinone (TQ) nanoparticles (TQ NPs) were synthesized with the help of biodegradable polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG) (less than 50 nm in size) and significantly enhanced anticancer efficacy by increasing bioavailability and solubility (Bhattacharya et al. 2015) of TQ. In vitro study in MCF-7 cells of breast carcinoma and in vivo tumor-bearing mice demonstrated that PEG-TQ NPs enhance miR-34a, repress Rac1 mRNA protein expression, prevent cell migration, and hinder angiogenesis. TQ loaded with modified molecular micelles, PLGA nanoparticles, and chitosan myristic acid nanogel exhibited more antioxidant and antiproliferative effectiveness at low doses with controlled release as compared with pure TQ against MCF-7 cells and MDA-MB-231 of breast carcinoma (Ganea et al. 2010; Dehghani et al. 2015). These findings showed that TQ NP have a more potent apoptotic effect than pure TQ.

20.2.1.6 Honokiol Nanoparticle

Honokiol is a polyphenol, a lignan obtained from the medicinal plant *Magnolia officinalis* (Li et al. 2008). It possesses multifactorial pharmacological properties and is widely used to treat stomach upset, inflammation, nervous disturbance, and anxiety (Chiang et al. 2006; Kim and Cho 2008; Deng et al. 2008; Fried and Arbiser 2009). It also showed antineoplastic and apoptotic effectiveness against various cancerous cells (Yuan et al. 2009; Steinmann et al. 2012; Avtanski et al. 2013; Cheng et al. 2014; Subramaniam et al. 2015). Honokiol-loaded synthesized nanoformulation co-polymer micelles with monomethoxy polyethylene glycol and polycaprolactone (HK-MPEG/PCL) increased bioavailability and solubility. The anticancer activity of HK-MPEG/PCL showed reduced tumor growth and apoptotic induction in a cancer nude mouse model and prevented angiogenesis (Cheng et al. 2016). Another study on honokiol-loaded co-polymer synthesized with folate and polyethyleneimine nanoparticles (HK NPs) significantly prevented metastasis, proliferation, tumor growth, angiogenesis, and cell-cycle progression (Gou et al. 2010). The developed HK NPs potentially encouraged apoptosis of HNE-1 cells of nasopharyngeal carcinoma as compared to pure honokiol.

20.2.1.7 Silibinin-Loaded Nanoparticle

Silibinin is a natural antioxidant and a polyphenolic flavonoid found in *Silybum marianum*, also known as silybin or milk thistle (Davis-Searles et al. 2005). It possesses multifactorial pharmacological effects such as hepato-protective, antioxidant, and anticarcinogenic activities. Silibinin encourages apoptosis via inhibiting cell-cycle progression, preventing proliferation, impairs angiogenesis, and enhancing immune stimulation in several cancers (Mateen et al. 2010; Nejati-Koshki et al. 2012; Surai 2015). Some previous studies demonstrated that silibinin arrested the cancer cycle and inhibited the growth, progression, and angiogenesis of tumorous cells (Singh et al. 2006; Liang et al. 2014). Silibinin-loaded nanoparticles with PLGA-PEG co-polymer were synthesized to evaluate the anticancer potential and expression of the hTERT gene in T47D cells of breast carcinoma and A549 cells of lung carcinoma. The findings showed that hTERT expression more efficiently reduced the cell viability of both cancerous cells with the increasing concentrations of nano-silibinin as compared to the pure silibinin (Ebrahimnezhad et al. 2013; Amirsaadat et al. 2017). The silibinin-loaded phosphatidylcholine lipid nanoparticles significantly reduced the growth and angiogenesis of breast carcinoma (Xu et al. 2013). These findings suggested that nano-form silibinin was a more efficient anticancer agent than pure silibinin.

20.2.1.8 Ursolic Acid Nanoparticle

Ursolic acid is a plant-derived triterpenoid that is present in epicuticular waxes of apples, fruit peels, herbs, and spices such as rosemary and thyme (Shanmugam et al. 2013). Ursolic acid has multifactorial pharmacological properties, such as antiinflammatory (Chattopadhyay et al. 2002), antidiabetic (Jang et al. 2010), anti-epileptic, anticancer (Tannock 2011), and liver protective (Shanmugam et al. 2011; Prasad et al. 2011) elements. Ursolic acid-based mesoporous silica nanospheres (UAMSN) were synthesized with the help of pH-sensitive chitosan and folic acid for the targeted drug delivery of tumor cells (Jiang et al. 2017). Enhanced apoptotic effects of ursolic acid-encapsulated PLGA nanoparticles (UA-NPs) were found in B16F10 mouse melanoma cells as compared with pure ursolic acid (Baishya et al. 2016). Folate and chitosan-based nanocarriers for the delivery of ursolic acid (FA-CS-UA-NPs) were studied for in vitro MCF-7 cells of breast carcinoma and in an in vivo tumor xenograft mouse model (Jin et al. 2016). The findings revealed FA-CS-UA-NPs penetrated into the cells via endocytosis and encouraged apoptosis. The FA-CS-UA-NPs had the potential to localize into the mitochondria, induce excessive reactive oxygen species (ROS), and enhance apoptosis in cancerous cells.

20.2.1.9 β-Lapachone Nanoparticle

Beta-lapachone is a quinone that is abundant in the bark of *Tabebuia avellanedae* (Lapacho tree) and has potent anti-cancerous properties (Pardee et al. 2002). It generates apoptosis via modulating NADPH quinone oxidoreductase-1 (NQO1) in cancerous cells (Blanco et al. 2007). Lapachone-loaded silver nanoparticles (Lap Au NPs) were synthesized and targeted on anti-EGFR antibody through intravenous injection of Lap Au NPs to tumor-bearing xenografted mice, showing an enhanced tumor suppression effect as well as enhanced radiotherapeutic efficacy (Jeong et al. 2009).

20.2.1.10 Ferulic Acid Nanoparticles

Ferulic acid is a phenolic phytochemical found in vegetable sources, oat flours, whole grain wheat, and rice (Zhao and Moghadasian 2008; Kumar and Pruthi 2014). A ferulic acid-loaded synthesized PLGA nanoparticle (FA-PLGA-NP) enhances apoptosis in NCI-H460 cells of lung carcinoma as compared to its pure form (Merlin et al. 2012). The FA-PLGA-NPs encourage apoptosis via decreasing cell proliferation, generating excessive intracellular ROS, enhanced DNA damage, and lipid peroxidation.

20.3 Conclusion

Numerous studies on phytochemicals have shown significant anticancer potential but some limitations. Studies on nano-phytochemicals, both in vitro and in animal models, showed enhanced bioavailability, improved cellular uptake, reduced doses, and enhanced solubility, overcoming the limitations of pure phytochemicals. Further, the potent anticancer nano-phytochemicals without side effects that are not destructive to normal cells are still to be investigated. The ongoing research on nano-phytochemicals opens a new avenue for cancer cure by following promising phytochemicals with the advanced approaches of nanotechnology.

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References

Abdille MH, Singh RP, Jayaprakasha GK (2005) Antioxidant activity of the extracts from *Dillenia indica* fruits. Food Chem 90:891–896

Aguirre L, Arias N, Macarulla MT et al (2011) Beneficial effects of quercetin on obesity and diabetes. Open Nutraceuticals J 4:189–198

Ahamad MS, Siddiqui S, Jafri A et al (2014) Induction of apoptosis and antiproliferative activity of naringenin in human epidermoid carcinoma cell through ROS generation and cell cycle arrest. PLoS One 9:e110003

Ahmad MZ, Alkahtani SA, Akhter S et al (2016) Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: current state-of-the-art. J Drug Target 24:273–293

Ali BH, Blunden G (2003) Pharmacological and toxicological properties of *Nigella sativa*. Phytother Res 17:299–305

Amirsaadat S, Pilehvar-Soltanahmadi Y, Zarghami F et al (2017) Silibinin-loaded magnetic nanoparticles inhibit hTERT gene expression and proliferation of lung cancer cells. Artif Cells Nanomed Biotechnol 45:1649–1656

Avtanski DB, Nagalingam A, Kupusamy P et al (2013) Targeting epithelial-mesenchymal transition in breast cancer cells using Honokiol, a natural phenolic compound. Cancer Res 73:299

Baishya R, Nayak DK, Kumar D et al (2016) Ursolic acid loaded PLGA nanoparticles: in vitro and in vivo evaluation to explore tumor targeting ability on B16F10 melanoma cell lines. Pharm Res 33:2691–2703

Bhadoriya SS, Mangal A, Madoriya N et al (2011) Bioavailability and bioactivity enhancement of herbal drugs by "Nanotechnology": a review. J Curr Pharm Res 8:1–7

Bhattacharya S, Ahir M, Patra P et al (2015) PEGylated-thymoquinone-nanoparticle mediated retardation of breast cancer cell migration by deregulation of cytoskeletal actin polymerization through miR-34a. Biomaterials 51:91–107

Blanco E, Bey EA, Dong Y et al (2007) β-Lapachone-containing PEG–PLA polymer micelles as novel nanotherapeutics against NQO1-overexpressing tumor cells. J Control Release 122:365–374

Chattopadhyay D, Arunachalam G, Mandal AB et al (2002) Antimicrobial and anti-inflammatory activity of folklore: *Mallotus peltatus* leaf extract. J Ethnopharmacol 82:229–237

Chen YJ (2002) Potential role of tetrandrine in cancer therapy. Acta Pharmacol Sin 23:1102–1106

Cheng S, Welty M, Eliaz I et al (2014) Honokiol inhibits growth and migration of renal cell carcinoma. Cancer Res 74:3203

Cheng Y, Zheng S, Teng Y et al (2016) Preparation of honokiol with biodegradable nanoparticles for treatment of osteosarcoma. RSC Adv 6:94278–94286

Chiang CK, Sheu ML, Hung KY et al (2006) Honokiol, a small molecular weight natural product, alleviates experimental mesangial proliferative glomerulonephritis. Kidney Int 70:682–689

Conaway CC, Getachun SM, Liebes LL et al (2001) Disposition of glucosinolates and sulphoraphanes in human after ingestion of steam and fresh broccoli. Nutr Cancer 38:168–178

Davis JM, Murphy EA, Carmichael MD (2009) Effects of the dietary flavonoid quercetin upon performance and health. Curr Sports Med Rep 8:206–213

Davis-Searles PR, Nakanishi Y, Kim NC et al (2005) Milk thistle and prostate cancer: differential effects of pure flavonolignans from *Silybum marianum* on antiproliferative end points in human prostate carcinoma cells. Cancer Res 65:4448–4457

Dehghani H, Hashemi M, Entezari M et al (2015) The comparison of anticancer activity of thymoquinone and nanothymoquinone on human breast adenocarcinoma. Iran J Pharm Res 14:539

Deng J, Qian Y, Geng L et al (2008) Involvement of p38 mitogen-activated protein kinase pathway in honokiol-induced apoptosis in a human hepatoma cell line (hepG2). Liver Int 28:1458–1464

Dinda AK, Prashant CK, Naqvi S et al (2012) Curcumin loaded organically modified silica (ORMOSIL) nanoparticle; a novel agent for cancer therapy. Int J Nanotechnol 9:862–871

Ebrahimnezhad Z, Zarghami N, Keyhani M et al (2013) Inhibition of hTERT gene expression by silibinin-loaded PLGA-PEG-Fe3O4 in T47D breast cancer cell line. Bioimpacts 3:67

Esfandiarpour-Boroujeni S, Bagheri-Khoulenjani S, Mirzadeh H et al (2017) Fabrication and study of curcumin loaded nanoparticles based on folate-chitosan for breast cancer therapy application. Carbohydr Polym 168:14–21

Fried LE, Arbiser JL (2009) Honokiol, a multifunctional antiangiogenic and antitumor agent. Antioxid Redox Signal 11:1139–1148

Gali-Muhtasib H, Roessner A, Schneider-Stock R (2006) Thymoquinone: a promising anti-cancer drug from natural sources. Int J Biochem Cell Biol 38:1249–1253

Ganea GM, Fakayode SO, Losso JN et al (2010) Delivery of phytochemical thymoquinone using molecular micelle modified poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles. Nanotechnology 21:285104

Gou M, Gong C, Zhang J et al (2010) Polymeric matrix for drug delivery: Honokiol-loaded PCL-PEG-PCL nanoparticles in PEG-PCL-PEG thermosensitive hydrogel. J Biomed Mater Res Part A 93:219–226

Heiss AG, Oeggl K (2005) The oldest evidence of *Nigella damascena* L. (Ranunculaceae) and its possible introduction to central Europe. Veg Hist Archaeobot 14:562–570

Ishii T, Yasuda K, Akatsuka A (2005) A mutation in the SDHC gene of complex increases oxidative stress resulting in apoptosis and tumorigenesis. Cancer Res 65:203–209

Jafri A, Siddiqui S, Deep A et al (2018) Induction of apoptosis by alpha-mangostin in human hepatocellular carcinoma cells via nuclear fragmentation and ROS dependent mitochondrial pathway. J Clin Exp Hepatol 8:S116

Jafri A, Siddiqui S, Rais J et al (2019) Induction of apoptosis by piperine in human cervical adenocarcinoma via ROS mediated mitochondrial pathway and caspase-3 activation. EXCLI J 18:154–164

Jang SM, Kim MJ, Choi MS et al (2010) Inhibitory effects of ursolic acid on hepatic polyol pathway and glucose production in streptozotocin-induced diabetic mice. Metabolism 59:512–519

Jeong SY, Park SJ, Yoon SM et al (2009) Systemic delivery and preclinical evaluation of Au nanoparticle containing β-lapachone for radiosensitization. J Control Release 139:239–245

Jiang K, Chi T, Li T et al (2017) A smart pH-responsive nano-carrier as a drug delivery system for the targeted delivery of ursolic acid: suppresses cancer growth and metastasis by modulating P53/MMP-9/PTEN/CD44 mediated multiple signaling pathways. Nanoscale 9:9428–9439

Jin H, Pi J, Yang F et al (2016) Folate-chitosan nanoparticles loaded with ursolic acid confer anti-breast cancer activities in vitro and in vivo. Sci Rep 6:30782

Jin H, Pi J, Zhao Y et al (2017) EGFR-targeting PLGA-PEG nanoparticles as a curcumin delivery system for breast cancer therapy. Nanoscale 9:16365–16374

Joe B, Vijaykumar M, Lokesh BR (2004) Biological properties of curcumin cellular and molecular mechanisms of action. Crit Rev Food Sci Nutr 44:97–111

Kashyap D, Mondal R, Tuli HS et al (2016) Molecular targets of gambogic acid in cancer: recent trends and advancements. Tumor Biol 37:12915–12925

Kaushik U, Aeri V, Mir SR (2015) Cucurbitacins – an insight into medicinal leads from nature. Pharmacogn Rev 9:12–18

Khan F, Niaz K, Maqbool F et al (2016) Molecular targets underlying the anticancer effects of quercetin: an update. Nutrients 8:529

Khoobchandani M, Zambre A, Katti K et al (2013) Green nanotechnology from Brassicaceae: development of broccoli phytochemicals-encapsulated gold nanoparticles and their applications in nanomedicine. Int J Green Nanotechnol 5(1):1–15

Kim BH, Cho JY (2008) Anti-inflammatory effect of honokiol is mediated by PI3K/Akt pathway suppression 1. Acta Pharmacol Sin 29:113–122

Kim SH, Choi KC (2013) Anti-cancer effect and underlying mechanism(s) of kaempferol, a phytoestrogen, on the regulation of apoptosis in diverse cancer cell models. Toxicol Res 29:229–234

Kumar N, Pruthi V (2014) Potential applications of ferulic acid from natural sources. Biotechnol Rep 4:86–93

Kung HN, Lu KS, Chau YP (2014) The chemotherapeutic effects of lapacho tree extract: β-lapachone. Chemotherapy 3:1–5

Li Z, Liu Y, Zhao X et al (2008) Honokiol, a natural therapeutic candidate, induces apoptosis and inhibits angiogenesis of ovarian tumor cells. Eur J Obstet Gynecol Reprod Biol 140:95–102

Li QS, Li CY, Li ZL et al (2012) Genistein and its synthetic analogs as anticancer agents. Anti-Cancer Agents Med Chem 12:271–281

Liang Z, Yang Y, Wang H et al (2014) Inhibition of SIRT1 signaling sensitizes the antitumor activity of silybin against human lung adenocarcinoma cells in vitro and in vivo. Mol Cancer Ther 13:1860–1872

Lin Y, Shi R, Wang X et al (2008) Luteolin, a flavonoid with potentials for cancer prevention and therapy. Curr Cancer Drug Targets 8:634–646

Mahn A, Reyes A (2011) An overview of health-promoting compounds of broccoli (*Brassica oleracea* var. *italica*) and the effect of processing. Food Sci Tech Int 18:503–514

Mateen S, Tyagi A, Agarwal C et al (2010) Silibinin inhibits human nonsmall cell lung cancer cell growth through cell-cycle arrest by modulating expression and function of key cell-cycle regulators. Mol Carcinog 49:247–258

Merlin JJ, Prasad NR, Shibli SM (2012) Ferulic acid loaded poly-*d*,*l*-lactide-co-glycolide nanoparticles: systematic study of particle size, drug encapsulation efficiency and anticancer effect in non-small cell lung carcinoma cell line in vitro. Biomed Prev Nutr 2:69–76

Moudi M, Go R, Yien CYS et al (2013) Vinca alkaloids. Int J Prev Med 4:1231–1235

Nejati-Koshki K, Zarghami N, Pourhassan-Moghaddam M et al (2012) Inhibition of leptin gene expression and secretion by silibinin: possible role of estrogen receptors. Cytotechnology 64:719–726

Nishiyama N (2007) Nanomedicine: nanocarriers shape up for long life. Nat Nanotechnol 2:203–204

Orlikova B, Tasdemir D, Golais F et al (2011) Dietary chalcones with chemopreventive and chemotherapeutic potential. Genes Nutr 6:125–147

Pardee AB, Li Y, Li CJ (2002) Cancer therapy with β-lapachone. Curr Cancer Drug Targets 2:227–242

Park C, Lee WS, Go SI et al (2015) Morin, a flavonoid from Moraceae, induces apoptosis by induction of BAD protein in human leukemic cells. Int J Mol Sci 16:645–659

Prasad S, Yadav VR, Kannappan R et al (2011) Ursolic acid, a pentacyclin triterpene, potentiates TRAIL-induced apoptosis through p53-independent up-regulation of death receptors evidence for the role of reactive oxygen species and JNK. J Biol Chem 286:5546–5557

Qazi A, Pal J, Maitah MI et al (2010) Anticancer activity of a broccoli derivative, sulforaphane, in Barrett adenocarcinoma: potential use in chemoprevention and as adjuvant in chemotherapy. Transl Oncol 3:389–399

Rahman HS, Rasedee A, Yeap SK et al (2014) Biomedical properties of a natural dietary plant metabolite, zerumbone, in cancer therapy and chemoprevention trials. Biomed Res Int 2014:920742

Rawson NE, Ho CT, Li S (2014) Efficacious anti-cancer property of flavonoids from citrus peels. Food Sci Human Wellness 3:104–109

Ren KW, Li YH, Wu G et al (2017) Quercetin nanoparticles display antitumor activity via proliferation inhibition and apoptosis induction in liver cancer cells. Int J Oncol 50:1299–1311

Roohbakhsh A, Parhiz H, Soltani F et al (2015) Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. Life Sci 124:64–74

Shanmugam MK, Rajendran P, Li F et al (2011) Ursolic acid inhibits multiple cell survival pathways leading to suppression of growth of prostate cancer xenograft in nude mice. J Mol Med 89:713–727

Shanmugam MK, Dai X, Kumar AP et al (2013) Ursolic acid in cancer prevention and treatment: molecular targets, pharmacokinetics and clinical studies. Biochem Pharmacol 85:1579–1587

Shukla S, Gupta S (2010) Apigenin: a promising molecule for cancer prevention. Pharm Res 27:962–978
Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30
Singh RP, Deep G, Chittezhath M et al (2006) Effect of silibinin on the growth and progression of primary lung tumors in mice. J Natl Cancer Inst 98:846–855
Singh BN, Shankar S, Srivastava RK (2011) Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol 82:1807–1821
Srinivasan M, Sudheer AR, Menon VP (2007) Ferulic acid: therapeutic potential through its antioxidant property. J Clin Biochem Nutr 40:92–100
Steinmann P, Walters DK, Arlt MJ et al (2012) Antimetastatic activity of honokiol in osteosarcoma. Cancer 118:2117–2127
Steinmetz KA, Potter JD (1991a) Vegetables, fruit, and cancer. I. Epidemiology. Cancer Causes Control 2:325–357
Steinmetz KA, Potter JD (1991b) Vegetables, fruit, and cancer. II. Mechanisms. Cancer Causes Control 2:427–442
Subramaniam D, Ponnurangam S, Kwatra D et al (2015) Honokiol prevents colonic tumorigenesis and affects stem cell viability by affecting oncogenic YAP1 function. Cancer Res 75:1893
Subramanian AP, Jaganathan SK, Manikandan A et al (2016) Recent trends in nano-based drug delivery systems for efficient delivery of phytochemicals in chemotherapy. RSC Adv 6:48294–48314
Surai PF (2015) Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. Antioxidants 4:204–247
Syaefudin JA, Rosiyana L, Setyani A et al (2016) Nanoparticles of *Selaginella doederleinii* leaf extract inhibit human lung cancer cells A549. Earth Environ Sci 31:1–5
Tan W, Li Y, Chen M et al (2011) Berberine hydrochloride: anticancer activity and nanoparticulate delivery system. Int J Nanomedicine 6:1773–1777
Tang L, Zhang Y, Jobson EH et al (2006) Potent activation of mitochondria-mediated apoptosis and arrest in S and M phases of cancer cells by a broccoli sprout extract. Mol Cancer Ther 5:935–944
Tannock LR (2011) Ursolic acid effect on atherosclerosis: apples and apples, or apples and oranges? Atherosclerosis 219:397–398
Ting H, Deep G, Agarwal R (2013) Molecular mechanisms of silibinin-mediated cancer chemoprevention with major emphasis on prostate cancer. AAPS J 15:707–716
Tozer GM, Kanthou C, Parkins CS et al (2002) The biology of the combretastatins as tumour vascular targeting agents. Int J Exp Pathol 83:21–38
Varoni EM, Faro AFL, Sharifi-Rad J et al (2016) Anticancer molecular mechanisms of resveratrol. Front Nutr 3:1–15
Wang G, Yao S, Cheng L et al (2015) Antioxidant and anticancer effection of the volatile oil from various habitats of *Selaginella doederleinii* Hieron. Technol Health Care 23:S21–S27
Wei WT, Lin SZ, Liu DL et al (2013) The distinct mechanisms of the antitumor activity of emodin in different types of cancer. Oncol Rep 30:2555–2562
Woo CC, Kumar AP, Sethi G et al (2012) Thymoquinone: potential cure for inflammatory disorders and cancer. Biochem Pharmacol 83:443–451
Xu P, Yin Q, Shen J et al (2013) Synergistic inhibition of breast cancer metastasis by silibinin-loaded lipid nanoparticles containing TPGS. Int J Pharm 454:21–30
Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D, Jaggi M, Chauhan SC (2012) Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications. Int J Nanomedicine 7:1761
Yallapu MM, Khan S, Maher DM et al (2014) Anti-cancer activity of curcumin loaded nanoparticles in prostate cancer. Biomaterials 35:8635–8648
Yin H, Zhang H, Liu B (2013) Superior anticancer efficacy of curcumin-loaded nanoparticles against lung cancer. Acta Biochim Biophys Sin 45:634–640
Yuan Z, Liu H, Yan F et al (2009) Improved therapeutic efficacy against murine carcinoma by combining honokiol with gene therapy of PNAS-4, a novel pro-apoptotic gene. Cancer Sci 100:1757–1766

Zaman MS, Chauhan N, Yallapu MM et al (2016) Curcumin nanoformulation for cervical cancer treatment. Sci Rep 6:20051
Zhang HM, Zhao L, Li H et al (2014) Research progress on the anticarcinogenic actions and mechanisms of ellagic acid. Cancer Biol Med 11:92–100
Zhao Z, Moghadasian MH (2008) Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review. Food Chem 109:691–702