3 Current Insights on the Role of Terpenoids as Anticancer Agents: A Perspective on Cancer Prevention and Treatment

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Contents

Abstract

Terpenoids are known to be a large family of secondary metabolites found ubiquitously in the plant kingdom and structurally composed of isoprenoid units. The diverse array of terpenoids has increased the interest in their commercial and pharmaceutical uses due to their antioxidative, anti-inflammation, and anticancer properties. Based on the structure, terpenoids are divided into six classes, namely monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyter-

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penes. Several terpenoids have been found to exhibit anticancer property via acting on different stages of tumor development, such as inhibition of the early initiation and progression of tumorigenesis by inducing cell cycle arrest, tumor cell differentiation, and apoptosis, and in the late stages, suppression of angiogenesis, invasion, and metastasis through the regulation of various intracellular signaling pathways. A relevant progress in the delineation of the detailed mechanism of their anticancer action has made these compounds as a promising therapeutic agents. Thus, the aim of this chapter is to present an updated overview of the current progress in the anticancer properties of terpenoids.

Keywords
Apoptosis · Angiogenesis · Chemoprevention · Metastasis · Terpenoids

3.1 Introduction

The chemo-diversity is a characteristic of biodiversity because the emergence of life on earth has witnessed the production of millions of different organic compounds in living organisms including plants. Several of these compounds have no perceptible function in the basic processes of growth and development in plants and have been termed as secondary metabolites. These secondary metabolites have been extensively studied for their numerous applications in medicine, agriculture, and industry.

Terpenoids, being the largest class of secondary metabolites have been known for their different roles in arbitrating antagonistic and positive interactions among organisms. They are involved in the defense of many plant species against herbivores, pathogens, and competitors (Gershenzon and Dudareva 2007). Terpenoids have been categorized on the basis of number and structural arrangement of carbons synthesized by the joining of isoprene units followed by cyclization and modifications (Zwenger and Basu 2008). The biosynthesis of sesqui- and triterpenoids in plants occurs through the mevalonate (MVA) pathway, which takes place in the cytosol; and mono-, di-, and tetraterpenoids are mainly synthesized from the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway, undergoing in plastids. Terpenoids have been reported to exhibit several biological activities, but currently their anticancer, anti-metastatic, and antiangiogenic properties have gained much attention (Cheng et al. 2007; Maffei et al. 2011).

Globally, cancer is an emergent and biggest challenge for human race and is the second leading cause of mortality after cardiovascular disease (Reddy et al. 2003). The process of carcinogenesis is interrupted by interfering with the three basic modulation steps (initiation, promotion, and progression) as well as the associated signal transduction pathways (Fresco et al. 2006). There are some kinds of cancer which are due to oxygen-centered free radicals and other reactive oxygen species because overproduction of such free radicals can cause oxidative damage to biomolecules (e.g., lipids, proteins, DNA) (Poulson et al. 1998). There are no extremely effective drugs to treat most cancers. As a result there is a general call for new drugs that are highly effective, possess low toxicity, and have a minor environmental impact too. Novel

natural products offer opportunities for innovation in drug discovery (Cai et al. 2004). Cancer chemoprevention by phytochemicals such as terpenoids may be one of the most feasible approaches for cancer control. Terpenoids can be easily obtained from vegetables, fruits, spices, teas, herbs, and medicinal plants and have been proven to suppress experimental carcinogenesis in various organs in preclinical models. Terpenoids consist of approximately 25,000 chemical structures thus far with potential practical applications in the fragrance and flavor industries and, particularly, in the pharmaceutical and chemical industries. Recent reports have indicated that mechanisms underlying chemopreventive potential of terpenoids may be a combination of antioxidant, anti-inflammatory, immune-enhancing, and hormone modulation effects along with effect on the expression of drug-metabolizing enzymes, influence on cell cycle progression and cell differentiation, induction of apoptosis, and suppression of proliferation and angiogenesis, thus playing roles in the initiation and secondary modification stages of neoplastic development. Although, terpenes as dietary agents have shown immense potential in cancer prevention in the last decade, they still need an elaborative preclinical and translational research. The aim of the present chapter is to present an overview of current progress in the anticancer properties of terpenoids.

3.2 Terpenoids

Terpenoids, also referred to as terpenes, are the largest group of natural compounds that play a variety of roles in many different plants. They are synthesized from combinations of several five-carbon-base (C_5) units called isoprene. Biochemical structural studies have revealed that all terpenoids are synthesized from two five-carbon building blocks. Based on the number of building blocks, terpenoids are commonly classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes. The biosynthesis of the terpenes consists of synthesis of the isopentenyl pyrophosphate (IPP) precursor, repetitive addition of IPPs to form the prenylpyrophosphate precursor of the various classes of terpenes, modification of the allylic prenylpyrophosphate by terpene-specific synthetases to form the terpene skeleton, and finally, secondary enzymatic modification (redox reaction) of the skeleton to attribute functional properties to the different terpenes. Over 40,000 different terpenoids have been isolated from plant, animal, and microbial species (Rohdich et al. 2005; Withers and Keasling 2007). A wide range of terpenoids has demonstrated pharmacological activity against human ailments such as cancer (taxanes from *Taxus brevifolia* and indole alkaloids, including vincristine and vinblastine, from *Catharanthus roseus*), human immunodeficiency virus (coumarins including calanolide A from *Calophyllum lanigerum*), and malaria (artemisinin from *Artemisia annua*) (Cragg and Newman 2003; Cragg and Newman 2005; Srivastava et al. 2005). Anticancer potentials of dietary and medicinal plant-derived substances, used in folk and traditional medicine, have been accepted currently as one of the main sources of cancer chemoprevention. A large and increasing number of patients in the world use medicinal plants and herbs for health purposes. Naturally occurring phytochemicals have shown enormous potential in the prevention and treatment of several cancers like breast, cervix, colon, liver, lungs, prostate, etc. (Cragg and Newman 2003).

3.2.1 Biosynthesis of Terpenes

Biosynthesis of terpenes is accomplished either by the mevalonate or the methylerythritol- 4-phosphate (MEP) pathway (which was originally named nonmevalonate pathway). The mevalonate pathway has been known for a long time and is located in the cytoplasm. By this pathway, sesquiterpenes, triterpenes, and polyterpenes are synthesized. The MEP pathway was discovered in the early 1990s and produces monoterpenes, diterpenes, sesterterpenes, and tetraterpenes. Their common intermediate is isopentenyl pyrophosphate (IPP; "activated isoprene") from which all terpenoids are formed. Catalyzed by prenyltransferases, IPP polymerizes to prenylpyrophosphates. In the third phase of synthesis, prenylpyrophosphates are finally converted to terpenes. These reactions are carried out by the large group of terpene synthases (Grassmann 2005).

3.2.2 Classification of Terpenes

The classification of terpenes is on the basis of number of isoprene units ranging from one to many. They are found present in the parent nucleus. The simplest type of terpenoids is hemiterpene, consisting of a single 5-C isoprene unit, rarely found and also not significant biologically. Monoterpenoids are classified into various subclasses on the basis of their cyclic carbon skeletons. Sesquiterpenoids are three isoprene unit compounds having 15 carbons in their structures. They occur in various forms ranging from simple acyclic, simple to macro monocyclic rings, as well as simple and complex bicyclic and tricyclic forms. Diterpenoids are 20 carbon compounds having 4 isoprene units in their structure. The diversity in their structure ranges from simple acyclic to complex polycyclic rings. Triterpenoids are the compounds which arise from the cyclization of an oxidized form of squalene. These are the compounds having 30 carbons in their structure (Table 3.1). Carotenes are the chief members of tetraterpenoids (Turina et al. 2006).

3.2.3 Biological Effects of Terpenes

3.2.3.1 Cytotoxicity

Cytotoxicity basically includes membrane damage. Various studies have suggested that essential oils can coagulate the cytoplasm and damage lipids and proteins (Ultee et al. 2002; Burt 2004). Damage to the cell wall and membrane can lead to the leakage of macromolecules (Gustafson et al. 1998; Cox et al. 2000; Oussalah et al. 2006). Consequently, cytotoxic nature of terpenoids made them an effectual chemotherapeutic agent against various carcinomas such as breast cancer, prostate cancer, colon cancer, cervical cancer, liver cancer, etc. (Di Pasqua et al. 2006; Turina et al. 2006).

Table 3.1 Classification of terpenoids

Class	No. of monomeric isoprene unit	Carbon atoms	Chemical formula
Monoterpenes	2	10	$C_{10}H_{16}$
Sesquiterpenes	3	15	$C_{15}H_{24}$
Diterpenes	4	20	$C_{20}H_{32}$
Triterpenes	6	30	$C_{30}H_{48}$
Tetraterpenes	8	40	$C_{40}H_{64}$
Polyterpenes	8	40	$(C_5H_8)_n$

3.2.3.2 Antimutagenic Properties

Up till now, various studies have suggested that the antimutagenic properties of terpenes are due to the inhibition of penetration of the mutagens into the cell inactivation of the mutagens by direct scavenging, antioxidant capture of radicals produced by a mutagen, or activation of cell antioxidant enzyme inhibition of metabolic conversion by P450 of promutagens into mutagens (Waters et al. 1996; Gomes-Carneiro et al. 1998). Less known is a possible antimutagenic interference with DNA repair systems after induction of genotoxic lesions. Some antimutagenic agents can either inhibit error-prone 0020 DNA repair or promote error-free DNA repair (Bronzetti et al. 1992; Vukovic-Gacic et al. 2006). The biochemistry of antimutagenic interference with promutagen metabolism to prevent mutagenesis is known and relatively well documented, as well as, during recent years, the role and reactions of ROS scavengers, such as glutathione, superoxide dismutase, catalase, N-acetylcystein, provitamins like retinoids, carotenoids and tocopherols, flavonoids and other polyphenols, etc. (Odin 1997; De Flora et al. 1999).

3.2.3.3 Anticancer Activity

Various studies have demonstrated that several dietary monoterpenes are effective in the prevention and treatment of cancer (Kris-Etherton et al. 2002; Table 3.2). Among these, monocyclic monoterpenes D-limonene and perillyl alcohol are known to inhibit the development of mammary, liver, skin, lung, colon, forestomach, prostate, and pancreatic carcinomas (Shi and Gould 2002). The metabolites such as oxygenated molecule of D-limonene and carvone have also been shown to have anticancer activities (Carvalho and Fonseca 2006). The anticancer mechanism of the monoterpene involves the inhibition of posttranslational isoprenylation of proteins regulating the growth of cells. Reports have suggested that terpenes such as geraniol possess chemotherapeutic activities toward human pancreatic cancers. Various studies have shown that betulinic acid is potent in inducing apoptosis against several human tumors such as melanoma and glioma, and ursolic acid and oleanolic acid reduced leukemia cell growth and inhibited the proliferation of several transplantable tumors in animals (Cipak et al. 2006). In addition to this, another diterpene paclitaxel, isolated from the bark of yew, is a potent antimitotic agent with excellent activity against breast and ovarian cancers (Long et al. 1998).

Table 3.2 Sources of terpenoids and their anticancer activity

Terpenoid class	Compounds	Sources	Cancer type
Monoterpenoids	Carvacrol	Thyme oil (*Thymus vulgaris* and *Origanum vulgare*)	Skin, bone, brain
	Carvone	Caraway oil (*Carum carvi*), spearmint oil (*Mentha spicata*)	Lung
	Thymol	Thyme oil (*Thymus vulgaris*)	Skin, bone, brain
	Thymoquinone	Black seed (*Nigella sativa*)	Skin, colon, lung, and breast
	Limonene	Citrus essential oils; orange (*Citrus sinensis*), lemon (*Citrus limon*), mandarin (*Citrus reticulata*), lime (*Citrus aurantifolia*), and grape (*Citrus paradisi*)	Prostate, breast, liver
	Linalool	Leaf oil (*Cinnamomum camphora*), coriander essential oil (*Coriandrum sativum*)	Cervical, leukemia, melanoma
	Menthol	Peppermint oil (*Mentha piperita*)	Prostate, bladder
	Myrcene	Verbena oil (*Lippia citriodora*), bay laurel oil (*Laurus nobilis*)	Lung, colon, cervical
	Perillyl alcohol (POH)	Grapefruit, caraway, bergamot, peppermint, spearmint, dill, tomato	Pancreatic, endothelial
	1,8-cineole (eucalyptol)	Eucalyptus leaf oil (*Eucalyptus globules*), rosemary (*Rosmarinus officinalis*)	Liver, cervical
	α- and β-pinene	*Pinus palustris*, *Pinus caribaea*, and *P. pinaster*	Lung, liver
	Terpinen-4-ol	Tea tree oil, oranges, mandarins, origanum, New Zealand lemonwood tree, Japanese cedar, and black pepper	Melanoma, liver
Sesquiterpenoids	Artemisinin	Sweet wormwood (*Artemisia annua*)	Colorectal, cervical, hepatocellular
	Parthenolide	Feverfew (*Tanacetum parthenium*)	Breast, cervical, lung, prostate
Diterpenoids	Acanthoic acid	*Acanthopanax koreanum*	Lung
	Carnosol	Sage (*Salvia carnosa*)	Melanoma, prostate, breast
	Ginkgolides	*Ginkgo biloba*	Ovarian, neuronian
	Tanshinone IIA	Danshen (*Salvia miltiorrhiza*)	Breast, cervical
	Taxol	Bark of the Pacific yew (*Taxus brevifolia*)	lung, breast, ovarian, colon, leukopenia and liver

(continued)

Table 3.2 (continued)

Terpenoid class	Compounds	Sources	Cancer type
Triterpenoids	Lupeol	Aloe (*Aloe vera*), carrot (*Daucus carota*), common fig (*Ficus carica*), tomato (*Lycopersicon esculentum*), olive (*Olea europaea*)	Breast, colon, prostate
	Ursolic acid	Holy basil (*Ocimum sanctum*), bilberry (*Vaccinium myrtillus*), rosemary (*Rosmarinus officinalis*)	ovarian, pancreatic, prostate, cervical, hepatic, breast, colorectal, leukemia, neuroma, colon
	Ginsenosides	Asian ginseng (*Panax ginseng*)	Lung, pancreatic, prostate, cervical, ovarian, melanoma
	Glycyrrhizin	Licorice (*Glycyrrhiza glabra*)	Cervical, colon
Tetraterpenoids	Lycopene	Tomato (*Lycopersicon esculentum*)	Breast, skin
	β-Carotene	Carrot (*Daucus carota*)	Skin
	Lutein	Spinach (*Spinacia oleracea*)	Skin

3.2.3.4 Anti-inflammatory Activity

A large number of terpenoids are known for their anti-inflammatory properties. Different reports have reported the anti-inflammatory potential of various monoterpenes such as linalyl acetate, 1,8-cineole, (−)-linalool, and its esters. Undoubtedly, 1,8-cineole has been reported to cure chronic ailments such as bronchitis, sinusitis, and steroid-dependent asthma or as a preventive agent in returning respiratory infections (Roussis et al. 1990). Several plant-derived triterpenoids, lupane, oleane, and ursane, and their natural and synthetic derivatives, have also been identified as anti-inflammatory agents (Recio et al. 1995).

3.2.3.5 Antiparasitic and Antibacterial Activity

A diverse range of terpenoids have been explored and successfully described as antiparasitic agents with high efficacy and selectivity (Hammer et al. 2003). The most extensively used parasitic drug in the world is the sesquiterpene lactone artemisinin extracted from *Artemisia annua*, an herb, which is native to China. This drug is used in China for more than 1000 years. The antimalarial property of artemisinin is because of the presence of a peroxide bridge, and also it possess a unique structure which lacks nitrogen-containing heterocyclic rings commonly found in most antimalarial compounds. Apart from artemisinin, betulinic acid has also been reported to possess antimalarial activity (Haynes 2003). Adding to this, thymols being a monoterpene phenol derivative of cymene also possess an anti-leishmanial potential (Robledo et al. 2005). Diterpenes extracted from *Salvia* species have exhibited antibacterial activities against a variety of organisms such as *S. aureus*, *S. epidermis*, *E. faecalis*, *B. subtilis*, *E. coli*, and *P. mirabilis*. Monoterpene mixtures

of terpinen-4-ol, R-terpineol, 1,8-cineole, and linalool have been shown to possess antibacterial activity against Gram-positive and Gram-negative bacteria isolated from the oral cavity, skin, and respiratory tract. The mechanism of antimicrobial action of terpenes is closely associated with their lipophilic character (Hada et al. 2003; Table 3.2).

3.2.3.6 Other Health Benefits

In addition to the aforesaid medicinal roles, terpenoids are also beneficial as skin penetration-enhancing agents and as supplementary agents in topical dermal preparations, cosmetics, and toiletries, which further broadens the applications of terpenes in other areas of human health care and medicine. There are several numbers of benefits which are provided by terpenes such as good penetration-enhancing abilities, low skin irritation effects, and low systemic toxicity (Williams and Barry 2004). Monoterpene such as 1,8-cineole has reported greatest penetration enhancement activity as compared to hydrocarbon or even alcohol or ketone functionalized terpenes (Williams and Barry 1991). Furthermore, monoterpenes such as linalool, carvone, and thymol have also been demonstrated to enhance the permeability of model drugs such as 5-fluorouracil (5-FU) through skin and mucous membranes. Conclusively, the uses of terpenoids as flavors and fragrances in foods and cosmetics (e.g., menthol, nootkatone, linalool, and sclareol) have been known for centuries. Monoterpenes have also found their useful application in industries as substitutes for ozone-depleting chlorofluorocarbons. Terpenes have also been proposed as substitutes for chlorinated solvents in applications such as cleaning electronic components and cables, degreasing metal, and cleaning aircraft parts (Brown et al. 1992).

3.3 Terpenoids: Prospective Candidate in Cancer Chemoprevention

3.3.1 Monoterpenoids

Monoterpenes are ten-carbon members belonging to the isoprenoid family of natural products. Their molecules represent nearly 90% of all the essential oils. They are often responsible for the characteristic odors of plants and are widely distributed in the plants. Monoterpenes are formed from the coupling of two isoprene units. They are commonly used as flavoring agent, in fragrances, and in pharmaceutical industries (Loza-Tavera 1999). Taxonomical studies have revealed that monoterpenes and their oxygenated derivatives have been reported in 46 families of the class Dicotyledones. Volatile monoterpenes have been reported in ascomycetes and algae (Arimura et al. 2004). Monoterpenoids play an imperative role in a broad range of ecological and biological processes, such as defense against insects and pathogens and attraction of the enemies of herbivores (Mateo and Jimenez 2000; Bezerra et al. 2013).

3.3.1.1 Carvacrol

Carvacrol or cymophenol (2-methyl-5-isopropyl phenol) is a monoterpene predominantly found in the essential oil of *Origanum*, *Satureja*, *Thymbra*, *Thymus*, and *Corydothymus* species belonging to Labiatae family. It has a characteristic pungent, warm odor of oregano and a pizza-like taste (Arcila Lozano 2004). The chemopreventive action of carvacrol involves the significant cytotoxic activity against mouse leukemia P388 and Hep-2 (Jafaari et al. 2007). Khan et al. have reported the chemopreventive potential of carvacrol in prostate cancer cells via mediating cell cycle arrest (Khan et al. 2017). Horvathova and collaborators found that carvacrol exerted cytotoxic effects in K562, $HepG_2$, and colonic Caco-2 cells and significantly reduced the level of DNA damage induced in these cells by the strong oxidant H_2O_2. Several reports have demonstrated that carvacrol displays cytotoxicity against B16-F10 melanoma cells, and this cytotoxicity is reduced by the addition of vitamin C and vitamin E. In the work of Stammati and collaborators, the authors compared the cytotoxic effects and molecular mechanisms of five monoterpenes: carvacrol, thymol, carveol, carvone, and isopulegol (Stammati et al. 1999). Yin and collaborators have proved the involvement of apoptosis in the cytotoxic effects of carvacrol on $HepG_2$ cells. Arunasree investigated the mechanism of carvacrol-induced cell death in MDA-MB 231 human metastatic breast cancer cells and demonstrated that this compound induced apoptosis in a dose-dependent manner (Arunasree 2010). The mechanism of action of carvacrol may in fact be related to its antioxidant activity and not associated with a DNA-damaging effect. Jayakumar and collaborators demonstrated that carvacrol protects the antioxidant system in DEN-induced hepatocellular carcinogenesis. It has been demonstrated that carvacrol induced cell cycle arrest at S phase and induced apoptosis in P815 tumor cell line (Jafaari et al. 2009). These results have suggested that the essential oil and carvacrol have pharmacological importance for the prevention of cancer because of its significant antimutagenic effect (Ipek et al. 2005). The carcinogenesis-reducing potential of carvacrol was demonstrated by Ozkan and Erdogan. Earlier carvacrol was also tested against lung tumors induced by dimethylbenz[ũFC;]anthracene (DMBA) in rats in vivo, and it was found to have strong antitumor activity at 0.1 mg/kg, ip (Zeytinoglu et al. 1998).

3.3.1.2 Carvone

Carvone being a monoterpene exhibits cytotoxicity and antiproliferative properties against various liver cancer cells. Carvone also presented a dose-dependent cytotoxic effect against HeLa cells (Mesa-Arango et al. 2009). Contrastingly, recently, Aydin and collaborators have reported that carvone could be a promising anticancer agent to improve brain tumor therapy. In the work of Jaafari and collaborators, the authors compared the cytotoxic effects and molecular mechanisms of five monoterpenes: carvacrol, thymol, carveol, carvone, and isopulegol. Although carvacrol induce cell cycle arrest in S phase, no effect on cell cycle was observed for carvone (Aydin et al. 2015).

3.3.1.3 Thymol

Thymol is a monoterpene, and its cytotoxic potential has been reported against various cancer cell lines such as Hep-2 cells, P815 mastocytoma cells, HepG2 human hepatoma cells, Caco-2 human colonic cells, and V79 hamster lung cells. Thymol has shown antioxidant activity and cytotoxic activity against the mouse leukemia P388 cell line (Bourgou et al. 2010). The cytotoxicity of thymol has been reduced by addition of vitamin C and vitamin E. Yin and collaborators demonstrated that thymol induced cell cycle arrest at G_0/G_1 phase. Deb and collaborators demonstrated that thymol induced apoptosis in HL-60 cells via caspase-dependent and caspase-independent pathways. Oskan and collaborators have demonstrated the antioxidant activity and carcinogenesis-reducing potential of thymol (Jafri et al. 2010).

3.3.1.4 Thymoquinone

Thymoquinone possesses antiproliferative and proapoptotic activities in several cell lines. Ivankovic and collaborators showed cytotoxicity and also antitumor activity of thymoquinone. Cecarini and collaborators (2010) demonstrated that thymoquinone induced time-dependent selective proteasome inhibition in glioblastoma cells and isolated enzymes and suggested that this mechanism could be implicated in the induction of apoptosis in cancer cells. The chemopreventive potential of thymoquinone against non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) cell lines alone and in synergistic combination with cisplatin (CDDP) has been evaluated (2010). They observed that thymoquinone inhibited cell proliferation, reduced cell viability, and induced apoptosis. These studies have concluded that thymoquinone inhibited cell proliferation by nearly 90% and also showed synergistic effects with cisplatin. Thymoquinone was able to induce apoptosis in NCI-H460 and NCI-H146 cell lines. Badary (1999) investigated the effects of thymoquinone on cisplatin-induced nephrotoxicity in mice and rats, and results revealed that thymoquinone induced amelioration of cisplatin nephrotoxicity and potentiated its antitumor activity. Thymoquinone has also been reported to decrease the ifosfamide-induced nephrotoxicity by improving its antitumor activity (Badary 1999). The chemosensitizing effect of thymoquinone on conventional chemotherapeutic agents was also demonstrated by Banerjee and collaborators. The mechanism of action involves downregulation of nuclear factor- B (NF- B), Bcl-2 family genes, and NF- B-dependent antiapoptotic genes (Banerjee et al. 2009). Sethi and collaborators (2008) evaluated the involvement of suppression of the NF- B activation pathway in apoptosis induced by thymoquinone. However, El-Najjar et al. (2010) demonstrated that thymoquinone triggered inactivation of the stress response pathway sensor CHEK1 and contributed to apoptosis in colorectal cancer cells. In human, multiple myeloma cells, thymoquinone inhibited proliferation, induced apoptosis, and induced chemo-sensitization, through suppression of the signal transducer and activator of transcription 3 (STAT3) activation pathway (Sethi et al. 2008). Reactive oxygen species were also involved in mediating thymoquinone-induced apoptosis in a panel of human colon cancer cells (Caco-2, HCT-116, LoVo, DLD-1, and HT-29) through activation of ERK and JNK signaling (El-Najjar et al.

2010). In prostate cancer cells, thymoquinone induced GSH depletion and increased ROS generation, but the mechanism of action of thymoquinone on cancer cells involves apoptosis and cell cycle arrest. Apoptosis and cell cycle arrest were evidenced in the $HepG_2$ hepatocellular carcinoma cell line and in the studies of El-Najjar et al. (2010) in primary mouse keratinocytes, papilloma (SP-1), and spindle carcinoma cells. Gurung and collaborators (2010) suggested that in glioblastoma cells thymoquinone induced DNA damage, telomere attrition through telomerase inhibition, and cell death. Abusnina and collaborators demonstrated that thymoquinone induces acute lymphoblastic leukemia cell apoptosis. Thymoquinone also has potential as a novel therapeutic agent against pancreatic cancer. Torres and collaborators (2010) demonstrated that thymoquinone downregulated MUC4 expression in pancreatic cancer cells and induced apoptosis by two different pathways. The activity of thymoquinone against multidrug-resistant (MDR) human tumor cell lines was also evaluated by Worthen and collaborators (Satooka and Kubo 2012), who showed that thymoquinone upregulated PTEN expression and induced apoptosis in doxorubicin-resistant human breast cancer cells. This study suggested that thymoquinone may not be an MDR substrate and that radical generation may not be critical to its cytotoxic activity. The encapsulation of thymoquinone into nanoparticles enhanced its antiproliferative and chemosensitizing effects (Abusnina et al. 2011). The structural modifications may contribute to the further clinical studies with thymoquinone. El-Najjar and collaborators (2010) showed that bovine serum albumin played a protective role against thymoquinone-induced cell death (Torres et al. 2010). Al-Shabanah and collaborators demonstrated that thymoquinone protected against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. Nagi and Almakki investigated a potential role for thymoquinone in protection against chemical carcinogenesis and toxicity by inducing quinone reductase and glutathione transferase in mice liver. Thymoquinone inhibited proliferation, induced apoptosis, and chemosensitized human multiple myeloma cells through suppression of the signal transducer and activator of transcription 3 (STAT3) activation pathway. Rajput and collaborators showed that molecular targeting of Akt by thymoquinone promoted G1 arrest through translation inhibition of cyclin D1 and induced apoptosis in breast cancer cells. Effenberger-Neidnicht and collaborators showed that thymoquinone boosted the anticancer effects of doxorubicin in certain cancer cell. Tundis and collaborators demonstrated the possible involvement of the PPAR-ũFE; pathway in the anticancer activity of thymoquinone in breast cancer cells. Thymoquinone enhances survival and activity of antigen-specific CD8-positive T cells in vitro, a result that can be useful in the cancer therapy (Salem et al. 2011). Exposure of cancer cells derived from lung, liver, colon, melanoma, and breast to increasing thymoquinone concentrations presented a significant inhibition of viability with an inhibition of Akt phosphorylation, DNA damage, and activation of mitochondrial proapoptotic pathways. Thymoquinone inhibited the invasive potential of various cancer cells. Moreover, thymoquinone synergizes with cisplatin to inhibit cellular viability. Tumor growth inhibition was associated with a significant increase in activated caspase-3. Odeh and collaborators described the encapsulation of thymoquinone into a liposome,

which maintained stability and improved bioavailability, while it maintained anticancer activity (Odeh et al. 2012). Das and collaborators showed that thymoquinone and diosgenin, alone and in combination, inhibited cell proliferation and induced apoptosis in squamous cell carcinoma. Alhosin and collaborators demonstrated that thymoquinone induced degradation of ūFC;- and β-tubulin proteins in human cancer cells without affecting their levels in normal human fibroblasts (Das et al. 2012).

3.3.1.5 Limonene

Limonene or D-limonene being a monoterpene is a dextrorotatory isomer that comprises of two isoprene units. D-Limonene is an abundantly present secondary metabolite in the essential oils of rind of various citrus fruits such as orange, lemon, mandarin, grapefruit, and lime (Schween et al. 1997). D-Limonene is a major constituent in several citrus oils, and a number of other essential oils have anticancer properties without toxicity on normal cells. Chemopreventive and chemotherapeutic studies have proven that D-limonene is effective against rodent mammary, liver, and pancreatic tumors (Elegbede et al. 1984). Limonene showed antioxidant and radical scavenging activities in several model systems and cytotoxicity against MCF-7, K562, PC 12, A-549, HT-29 cell lines, and HepG2 hepatocarcinoma cell lines (Manassero et al. 2013). Pattanayak and collaborators verified that limonene inhibited the activity of HMG-CoA reductase due to greater binding affinity with the receptor and thus reduced the possibility of cancer growth (Chen et al. 1998). Haag and collaborators demonstrated that limonene induced regression of mammary carcinomas, and when given in combination with 4-hydroxyandrostrenedione, it resulted in greater rat mammary tumor regression (83.3%) than either agent given alone (Chander et al. 1994). Chidambara and collaborators tested citrus volatile oil rich in D-limonene and verified that the oil induced apoptosis and acted as an antiangiogenic with a preventative effect on colon cancer. Elegbede and Gould investigated the effects of limonene at the initiation stage of aflatoxin B1-induced hepatocarcinogenesis and found that limonene significantly inhibited aflatoxin-DNA adduct formation in hepatocytes, which suggested that limonene may have potential as a chemopreventive agent against aflatoxin-induced liver cancer (Kawamori et al. 1996).

3.3.1.6 Linalool

Linalool is an acyclic monoterpene alcohol, isolated from nearly two thirds of the essential oil of *Coriandrum sativum* L. belonging to family Apiaceae. Linalool is also isolated from the essential oils of some other aromatic plants such as lavender (*Lavandula officinalis*) and sweet basil (*Ocimum basilicum*) (Burdock and Carabin 2009).

Reports have shown that linalool showed cytotoxic effects on C32 cells, BCC-1/KMC, AGS, RTCC-1/KMC, U2OS, HeLa, H520, H661, OSCC-1/KMC, J82, human leukemia and lymphoma cell lines, amelanotic melanoma C32 cells, and renal cell adenocarcinoma cells (Loizzo et al. 2008). Usta and collaborators have reportedly verified that linalool decreased HepG2 viability, increasing reactive oxygen species and decreasing ATP and GSH levels. Gu and collaborators through their experimental studies shown that linalool preferentially induced robust apoptosis of

a variety of leukemia cells by upregulation of p53 and cyclin-dependent kinase inhibitors. A study conducted by Ravizza and collaborators demonstrated that linalool reversed doxorubicin resistance in human breast adenocarcinoma cells. Maeda and collaborators demonstrated that linalool significantly suppressed HL60 cell proliferation, induced apoptosis, and promoted cell differentiation (Miyashita and Sadzuka 2013).

3.3.1.7 Menthol

Menthol is a naturally occurring compound predominantly present in the volatile oil of various species of mint plants such as peppermint and cornmint oil. Menthol is a cyclic terpene alcohol with three asymmetric carbon atoms (Eccles 1994). Various reports have suggested the cytotoxic nature of menthol in murine leukemia WEHI-3 cells in a concentration-dependent manner. In SNU-5 cells, menthol induced cytotoxicity by inhibiting the expression of topoisomerases I, II alpha, and II beta and promoting the expression of NF- B (Takemori and Ho 1988). This compound also enhances the antiproliferative activity of 1ūFC;,25-dihydroxyvitamin D3 in LNCaP cells. Wang and collaborators showed that menthol inhibited the proliferation and motility of prostate cancer DU145 cells. Li and collaborators have demonstrated that menthol induced cell death in a human bladder cancer cell line (Wang et al. 2012).

3.3.1.8 Geraniol

Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) is an acyclic monoterpene alcohol with the chemical formula C10H18O. Geraniol is one of the main components of geranium oil, and its content is about 20%, and it is extensively isolated from palmarosa oil (Bedoukian 1986; Clark 1998). Chemopreventive studies have shown that geraniol decreases the expression of p44/p42 ERK and has an antitumor effect in colon cancer cells. In addition, geraniol has a synergistic antitumor effect combined with 5-fluorouracil in TC-118 human colorectal tumors (Carnesecchi et al. 2004). Carnesecchi and collaborators demonstrated that this monoterpene sensitized human colonic cancer cells to 5-fluorouracil treatment in vitro. Bhattacharjee and Chatterjee promoted the identification of proapoptotic, anti-inflammatory, antiproliferative, anti-invasive, and potential antiangiogenic activities of geraniol by employing a dual reverse virtual screening protocol. Geraniol suppressed pancreatic tumor growth without significantly affecting blood cholesterol levels (Burke et al. 1997). Polo and de Bravo demonstrated multiple effects of geraniol on mevalonate and lipid metabolism in HepG2 cells that affected cell proliferation. Zheng and collaborators suggested that geraniol is a profitable chemopreventive agent because it showed strong GST-inducing activity in the mucosa of the small intestine and the large intestine. Ong and collaborators and Cardozo and collaborators suggested that geraniol showed promising chemopreventive effects against hepatocarcinogenesis (Wattenberg 1991). Burke et al. (2002) further investigated the mechanism of action of geraniol against pancreatic tumors. They reported that geraniol can induce apoptosis and increase expression of the proapoptotic protein Bak in cultured pancreatic tumor cells. Several reports have shown that geraniol

can inhibit proliferation, cell cycle progression, and cyclin-dependent kinase 2 activity in MCF-7 breast cancer cells.

3.3.1.9 Myrcene

Myrcene is an acyclic monoterpene which showed significant cytotoxic effects in crown gall tumors, MCF-7 breast carcinoma, HT-29 colon adenocarcinoma, and other cell lines. Silva and collaborators investigated the cytotoxicity of myrcene against HeLa (human cervical carcinoma), A-549 (human lung carcinoma), HT-29 (human colon adenocarcinoma), and Vero (monkey kidney) cell lines as well as mouse macrophages.

3.3.1.10 Perillyl Alcohol (POH)

POH derived from limonene is a naturally occurring dietary monoterpene, isolated from the essential oils of lavender, peppermint, and other plants. Stark and collaborators and Burke and collaborators demonstrated that perillyl alcohol has antitumor activity against pancreatic carcinomas at nontoxic doses. The antitumor activity of perillyl alcohol against pancreatic cancers may stem from its ability to inhibit the prenylation of growth-regulatory proteins other than K-Ras, including H-Ras (Stayrook et al. 1998). Furthermore, the antitumor activity of perillyl alcohol in pancreatic cancers may be due to preferential stimulation of Bak-induced apoptosis in malignant cells compared to normal cells. Further studies to evaluate the cytotoxicity mechanisms of perillyl alcohol against pancreatic cancer cells were conducted by Lebedeva and collaborators. Sundin and collaborators demonstrated that the perillyl alcohol inhibited telomerase activity in prostate cancer cells (Sundin et al. 2012). Yeruva and collaborators demonstrated that perillyl alcohol presented dose-dependent cytotoxicity with cell cycle arrest and apoptosis. Elevated expression of bax and p21 and increased caspase 3 activity were evidenced. Other studies revealed that perillyl alcohol sensitized cancer cells to cisplatin and radiation in a dose-dependent manner. Perillyl alcohol has shown its chemopreventive potential in vitro as it attenuates angiogenesis, modulated angiogenic factor production, and inhibited cell proliferation and survival in endothelial and tumor cells (Loutrari et al. 2004). Loutrari and collaborators also demonstrated that perillyl alcohol in addition to its anticancer activity may be an effective agent in the treatment of angiogenesis-dependent diseases. Sahin and collaborators demonstrated that perillyl alcohol selectively induced G0/G1 arrest and apoptosis in Bcr/Abl-transformed myeloid cell lines. Perillyl alcohol-mediated cell cycle arrest was found to precede apoptosis, which raised the possibility that the primary effect of perillyl alcohol is to induce G0/G1 arrest, with apoptosis as a consequence of this growth arrest (Clark et al. 2002).

3.3.1.11 1,8-Cineole (Eucalyptol)

1,8-Cineole (eucalyptol) is a bicyclic monoterpene, which comprises up to 90% of the essential oil of some species of the generic product *Eucalyptus* oil. The cytotoxicity of 1,8-cineole was investigated against various cancer cell lines. Reportedly, this monoterpene has moderate antioxidant and cytotoxic properties and pronounced

analgesic and antitumor activities. Also, eucalyptol exhibits apoptotic potential via mitochondrial stress and caspase activation as reported by Cha and collaborators. Bhattacharjee and Chatterjee have extensively reported the identification of pro-apoptotic, anti-inflammatory, antiproliferative, anti-invasive, and potential antiangiogenic activities of eucalyptol by employing a dual reverse virtual screening protocol (Wang et al. 2012).

3.3.1.12 α- and β-Pinene

α- and β-pinene isolated from pine needle oil are bicyclic monoterpenes. Alpha- and beta-pinene are hydrocarbon monoterpenes found in the essential oils of several aromatic species. Various chemopreventive studies have suggested that alpha- and beta-pinene showed cytotoxicity on tumor lymphocytes and in other different tumor and non-tumor cell lines (Chaverri et al. 2011). In the same cases, this cytotoxicity was comparable to doxorubicin. Alpha- and beta-pinene did not show antitumor activity in vivo using the Ehrlich ascites tumor model (Meadows et al. 2002). The cytotoxic potential of alpha-pinene was investigated in SK-OV-3, HO-8910, Bel-7402, and U937 cell lines. The cytotoxicity of alpha-pinene was comparable to doxorubicin (Cole et al. 2007). Bhattacharjee and Chatterjee promoted the identification of proapoptotic, anti-inflammatory, antiproliferative, anti-invasive, and potential antiangiogenic activities of alpha-pinene by employing a dual reverse virtual screening protocol. It have been demonstrated that these bicyclic monoterpenes can trigger oxidative stress and related signaling pathways in A549 and $HepG_2$ cells (Cole et al. 2007).

3.3.1.13 Terpinen-4-ol

Terpinen-4-ol is one of the primary active ingredients of the tea tree oil and is found in a variety of aromatic plants (oranges, mandarins, origanum, New Zealand lemonwood tree, Japanese cedar, and black pepper). It is a naturally occurring monoterpene found in the essential oils of many aromatic plants including *Melaleuca alternifolia* (tea tree oil), *Hajeb layoun arboreta* (Tunisia), and *Alpinia zerumbet* (Cha et al. 2007). Chemopreventive studies have suggested that terpinen-4-ol showed cytotoxicity against HepG2, HeLa, MOLT-4, K-562, CTVR-1, and human M14 melanoma cells. Bozzuto and collaborators demonstrated that this monoterpene interfered with the migration and invasion processes of drug-sensitive and drug-resistant melanoma cells. Terpinen-4-ol also induced necrosis and cell cycle arrest in murine cancer cell lines (Bozzuto et al. 2011).

3.3.2 Sesquiterpenoids

Sesquiterpenes are colorless lipophilic compounds, consist of 15-carbon skeleton, and are diverse in their structure. Most of the functional terpenoids are cyclic in nature. They are synthesized in endoplasmic reticulum in plants from three isoprene units via farnesyl pyrophosphate (FPP) (Yu and Utsumi 2009). The further modifications after sesquiterpene synthesis, such as oxidation and glycosylation, take

place which results in a vast number of structures (Lange and Lee 1987). Sesquiterpene lactones are most abundantly used in natural remedies although more than 7000 sesquiterpene structures have been characterized. Robles et al. have recently reported the pharmacological and ethnobotanical studies on some medicinal sesquiterpene lactones. Sesquiterpene lactones being a diverse group of plant compounds possess both medicinal activities and toxic effects, such as allergic and neurotoxic effects. Their medicinal properties include the prevention of inflammatory diseases and cancer. Recent studies have shown that these sesquiterpenes can inhibit NF-kB signaling, but still their molecular mechanisms are not clearly understood (Robles et al. 1995).

3.3.2.1 Parthenolide

Parthenolide is the most extensively studied sesquiterpene lactone abundantly present in the medicinal herb feverfew (*Tanacetum parthenium*). The herb is a popular remedy for migraine and some inflammatory diseases, such as arthritis (O'Hara et al. 1998). Several cell culture experimental reports have shown that the anti-inflammatory response by parthenolide is due to inhibition of NF-kB signaling. Sesquiterpene parthenolide also seems to have anticancer and anti-metastatic activities, apparently mediated by NF-kB signaling in certain cancer models. Sesquiterpene lactones have been intensively studied to understand the molecular mechanism of their inhibition of NF-kB signaling. Studies have also revealed that parthenolide alkylates cysteine-38 in the p65 subunit of NF-kB and inhibits DNA binding of NF-kB complex (Garcia-Pineres et al. 2001).

3.3.2.2 Helenalin A

Helenalin A is a sesquiterpene lactone which has been obtained from *Arnica* flos, mountain flowers. Arnica-based herbal tincture has been used locally to treat hematoma, rheumatic diseases, and skin inflammation. Lyss et al. have shown that the anti-inflammatory potency of helenalin A is again due to the inhibition of NF-kB signaling. They observed in their experiments that helenalin A can alkylate the p65 subunit of NF-kB complex and hence inhibit the DNA binding of that complex and the transcription of NF-kB-dependent genes (Lyss et al. 1998). However, the alkylation properties of helenalin A are indiscriminate, and it can also target other proteins, such as 5-lipoxygenase and leukotriene C4 synthase which affect inflammatory responses, too. In addition to its anti-inflammatory efficiency, helenalin A is also potent against infections. Helenalin A, as well as the other sesquiterpene lactones, has toxic effects which may limit its therapeutic use (Boulanger et al. 2007).

3.3.2.3 Artemisinin

Artemisinin is isolated from the leaves of *Artemisia annua*, a Chinese folk medicine and also known as qinghaosu. This diterpenoid also possesses anticancer, antiangiogenic, antifungal, and immunosuppressive properties and is also used as promising antimalarial drug, especially against multidrug-resistant malaria (Efferth 2007). Artemisinin, being an endoperoxide sesquiterpene lactone with complex polycyclic

rings, also functions via protein alkylation, a typical property of sesquiterpene lactones. There are a large number of alkylation targets in cells. Some appear to be specific only for distinct sesquiterpene lactones, and hence the lactones are effective only in certain diseases. The NF-kB transcription system may be one of the targets, since artemisinin inhibits the LPS-induced activation of NF-kB signaling. The exact mechanism is still unclear, but artemisinin has been reported to inhibit the DNA binding of NF-kB complex (Aldieri et al. 2003).

3.3.3 Diterpenoids

Diterpenes have basic structure of $C_{20}H_{32}$ and contain four isoprene units. Diterpenoids can be acyclic, but generally they appear as mono-, bi-, tri-, tetra-, or macrocyclic compounds. Oleoresin from the conifer species is a rich source of diterpenoids, and diterpenoids are also ingredients in many plant remedies. Aphidicolin, forskolin, gibberellins, phorbols, retinol derivatives, and taxanes are physiologically active diterpenoids. Although the molecular targets and functional mechanisms of these compounds are well known, still they have indirect effects on NF-kB signaling. For instance, taxol can activate NF-kB signaling via the TLR4 receptor complex. Moreover, there are diterpenoid compounds, such as abietic acid, which have both anti-inflammatory and other therapeutic effects, but involvement of the NF-kB system has still not verified (Keeling and Bohlmann 2006).

3.3.3.1 Acanthoic Acid

Acanthoic acid, isolated from *Acanthopanax koreanum* Nakai, is a pimarane diterpene. It has been extensively used as a sedative and antirheumatic remedy in Korean folk medicine. A series of acanthoic acid analogues have been synthesized by Chao et al. It has been reported in various research articles that these novel diterpenes inhibited the LPS-induced activation of IkBa phosphorylation and the nuclear DNA binding of NF-kB complex in Raw 264.7 cells. Moreover, acanthoic acid and its analogues reduced LPS-induced cytokine synthesis and pro-inflammatory response. They have been emerged as promising anti-inflammatory molecules because of the low toxicity of these compounds. It has been reported by Kang et al. that acanthoic acid can prevent fibrosis and nodular formation in rat lung (Chao et al. 2005).

3.3.3.2 Carnosol

Carnosol and carnosic acid are chiefly found in rosemary extracts (*Rosmarinus officinalis*), a well-known traditional herb remedy. These are an abietane type of diterpene constituents possessing anticancer and anti-inflammatory potential. It has been reported by Lo et al. that carnosol could inhibit the activation of the NF-kB system in LPS-activated RAW 264.7 macrophages. Studies have reported that carnosol also suppresses the metastatic potential of mouse melanoma cells. The anti-metastatic potential of carnosol is due to the suppression of metalloproteinase-9 expression via downregulation of NF-kB and c-Jun-mediated signaling.

The mechanism of inhibition of NF-kB signaling pathway is the antioxidant capacity of carnosol (Lo et al. 2002).

3.3.3.3 Ginkgolides

Ginkgolides are extracted from *Ginkgo biloba* leaves. These active diterpene trilactone extracts contain several flavonoids and terpenoids. The *Ginkgo* extract has also been regarded as one of the traditional Chinese plant remedies. It has been claimed that *Ginkgo* extract possesses therapeutic efficiency against various diseases, such as inflammatory diseases, vascular insufficiencies, ovarian cancer, and several neuronal disorders. Several studies have also reported that *Ginkgo* extract can inhibit NF-kB signaling and reduce the level of inflammatory response (Woo et al. 2003).

3.3.3.4 Tanshinone IIA

Tanshinone IIA is a major active diterpene quinone predominantly found present in the roots of *Salvia miltiorrhiza*. Tanshinone is a frequently used Chinese plant remedy against immunological disorders, osteoporosis, cardiovascular diseases, and breast cancer. Several studies have shown that tanshinone IIA can inhibit NF-kB signaling and inflammatory responses. Tanshinone IIA suppresses NF-kB signaling, inhibiting both the IKKa/b and NIK activation, and subsequently phosphorylation of IkBa protein and the nuclear translocation of NF-kB complex (Jang et al. 2006).

3.3.3.5 Taxol

Taxol, a complex polyoxygenated diterpene, is isolated from the bark of the Pacific yew tree, *Taxus brevifolia.* Taxol is a powerful anticancer compound which has been used clinically to combat several cancer diseases with the generic name of paclitaxel (Jordan and Wilson 2004). The anticancer mechanism of taxol suggests that it binds to the b-tubulin protein in microtubules, which increases the acetylation level of a-tubulin and suppresses microtubular dynamics. The excessive stabilization of the microtubules blocks mitosis, and this leads to the apoptotic cell death of proliferating cancer cells. Fascinatingly, taxol has other targets in cells which can activate NF-kB signaling and induce the expression of pro-inflammatory gene. The immunological effects of taxol have been reviewed by Fitzpatrick and Wheeler. Various scientific reports have demonstrated that taxol activates TLR4, the same receptor which is stimulated by bacterial LPS. Taxol binds to the CD18 protein, which in turn activates the multiprotein TLR4 complex and downstream signaling cascades including the NF-kB signaling. Plant-derived diterpenoids have several target proteins in cells. But most of the studied effects involve the inhibition of NF-kB signaling, although the diterpenoid target may be located at the NF-kB or IKK complexes or at sites upstream in the signaling cascade (Fitzpatrick and Wheeler 2003).

3.3.4 Triterpenoids

Triterpenes are formed from six isoprene units with 30 carbons, but in nature, triterpenes occur as complex cyclic structures called triterpenoids. Triterpenoids are the major substituents in several Chinese herbal remedies, such as ginseng and *Platycodon* (Bouvier et al. 2005).

3.3.4.1 Lupeol

Lupeol is a pentacyclic triterpenoid found in olives, mango, and fig and in several other medicinal herbs. Lupeol has therapeutic effects in some cancers and inflammation (Fernandez et al. 2001). Several studies have suggested that lupeol inhibits NF-kB signaling, including phosphorylation of IkBa protein, DNA binding of NF-kB complex, and NF-kB-dependent reporter gene activity (Lee et al. 2007). It seems that lupeol could inhibit several signaling pathways, such as Akt-dependent pathways, and in this way, it may possess anticancer and anti-inflammatory properties (Fernandez et al. 2001).

3.3.4.2 Ursolic Acid

Ursolic acid and its derivatives are pentacyclic triterpenes, extracted from the rosemary leaves that have been used in various folk remedies for a long time (Liu 1995). Various therapeutic studies have shown that these pentacyclic terpenes are effectual against inflammation, carcinogenesis, and hyperlipidemia. Shishodia et al. have observed that ursolic acid inhibited the activation of NF-kB signaling induced by a variety of carcinogenic agents in several cell lines. Ursolic acid inhibited IkBa kinase activation, IkBa protein phosphorylation and degradation, p65 nuclear translocation, and the DNA binding of NF-kB complex, as well as the NF-kB-dependent gene expression. Ursolic acid is one of the promising terpenoid-based drug candidates (Shishodia et al. 2003).

3.3.4.3 Ginsenosides

In West, ginseng has been probably known as the best traditional Chinese herbal remedy. There are various types of ginseng root products, but all refer to the perennial plant of *Panax* species. Chiefly grown in Asian countries, these *Panax* species include steroid-like triterpene, i.e., ginsenosides. There has been a widespread literature review on the structural diversity and pharmacology of ginseng products (Radad et al. 2006; Hofseth and Wargovich 2007). Ginsenosides have myriad of therapeutic effects used in inflammatory diseases, cancer, and neurodegenerative disorders. It has been suggested that the interaction between ginseng and signaling pathways regulates the inflammation-to-cancer cascades. Ginseng and ginsenosides inhibit NF-kB signaling, either directly or indirectly (Choi et al. 2007). It is likely that ginsenosides can affect the upstream components of the NF-kB signaling cascade since the JNK pathway and AP-1 binding activity are also inhibited by ginsenosides (Wu et al. 2007).

3.3.4.4 Glycyrrhizin

Glycyrrhizin, a triterpenoid glycosidic saponin extracted from the root extract of *Glycyrrhiza glabra*, is an active constituent in licorice. Chinese and Egyptian herbal medicines include licorice as an ancient traditional remedy for curing various diseases. Farooqui et al. have shown the chemopreventive potential of glycyrrhizin through cell culture experiments in cervical cancer cell lines. Fiore et al. have reviewed the therapeutic use of licorice in treating several diseases such as cardiovascular, gastrointestinal, and respiratory systems (Fiore et al. 2005). Various researches have shown that the glycyrrhizic acid, which is a chief constituent of glycyrrhizin, can inhibit the NF-kB signaling pathway along with other signaling pathways (Cherng et al. 2006).

3.3.5 Tetraterpenes

Tetraterpenes are pigmented terpenes with conjugated double bonds and consist of eight isoprenoid units. These conjugated double bonds are responsible for the strong light absorption and bright color of these compounds. Plant-derived carotenoids have various health benefits, and as a result, there have been numerous reviews concerned with the therapeutic effects of carotenoids in the prevention of diseases. Carotenoids have been emerged as a powerful antioxidant as they are effectual enough in treating the illnesses, such as cardiovascular disease and osteoporosis. In addition, carotenoids can modulate redox-sensitive signaling pathways, such as NF-kB signaling, and consequently provides protection against inflammatory responses and cancer (Krinsky and Johnson 2005).

3.3.5.1 Lycopene

Lycopene being an acyclic tetraterpene bestowed with a typical bright red color contains many conjugated carbon double bonds. It is the most commonly occurring carotenoid in the human body. The major dietary sources of lycopene are tomato and various other red vegetables. Lycopene blocks free radical attack during oxidative stress as it has been a powerful and better antioxidant than vitamin E. The molecular mechanisms involved in the action of lycopene and its therapeutic indications have been reviewed by Heber and Lu. It has been claimed that the risk of some chronic diseases, such as cardiovascular and inflammatory diseases, e.g., atherosclerosis and rheumatoid arthritis, has been decreased with the consumption of lycopene (Heber and Lu 2002). Moreover, lycopene seems to promote prostate health, especially preventing the development of prostate cancer. The presence of numerous double bonds in its structure makes lycopene an effective antioxidant. Reactive oxygen species (ROS) and oxidative stress activate NF-kB signaling, and hence all antioxidants, e.g., phytochemicals, can prevent NF-kB-dependent signaling. Furthermore, the inflammatory signaling induced by LPS and TNF cytokines is mediated via ROS-dependent signaling (Surh et al. 2005). For instance, lycopene can inhibit nuclear localization and DNA binding of NF-kB complex, as well as reducing macrophage activation. It seems that these properties are due to the

antioxidative activity of lycopene, such as that observed in inflammation and cancer cell proliferation (Huang et al. 2007).

3.3.5.2 β-Carotene

Carotenes are cyclic tetraterpenes including several isomers, of which β-carotene is the most common in nature. The orange color of carrots and many other fruits and vegetables is due to their β-carotene content. β-Carotene is stored in the liver and can be converted to vitamin A. The therapeutic actions of β-carotene have been widely studied, but there are still some controversies (Chew and Park 2004). The risk of cancer and cardiovascular diseases is reduced by the intake of beta-carotene. Various studies have been demonstrated that β-carotene has the potential to suppress LPS-induced NF-kB signaling and the expression of inflammatory genes in RAW 264.7 macrophages. It has been reported that beta-carotene can block the degradation of IkBa protein, the nuclear translocation of the p65 protein, and the DNA binding of NF-kB complex, as well as LPS-induced expression of iNOS, COX-2, TNF-a, and IL-1b expression (Bai et al. 2005). Interestingly, in cancer cells, β-carotene increased the production of ROS and simultaneously the DNA binding of NF-kB complex (Palozza et al. 2003). It seems that in tumor cells, β-carotene can have pro-oxidant characteristics, and in this way, it causes growth inhibition. This may be due to the oxidation of β-carotene and carotenoid-derived aldehyde production, which induces oxidative stress and apoptotic cell death, as has been observed in RPE cells (Kalariya et al. 2008).

3.3.5.3 Lutein

Lutein is a cyclic tetraterpene carotenoid with several conjugated double bonds which absorb blue light and endow a yellow-orange color to the molecule. This lipophilic xanthophyll is a dihydroxy derivative of β-carotene and widely present in fruits and vegetables but also in egg yolks. Clinical studies suggest that lutein has the potential to prevent several diseases, but the final conclusion still awaits more evidence (Ribaya-Mercado and Blumberg 2004). Lutein is also called a macular pigment since in the human body it is located at high concentrations in the macula area of retina, which takes care of fine vision. Dietary supplementation with lutein can elevate the macular lutein pigment concentration. There is evidence to indicate that lutein pigments can protect against oxidative stress and prevent age-related macular degeneration and cataract (Krinsky and Johnson 2005).

3.4 Conclusions and Future Prospects

Terpenoids are the diverse group of natural bio-active compounds, generally used in the traditional medicine, flavors and perfumes, food industries, plant defense mechanisms, and treatments of various ailments because of its minimal side effects. Moreover, it plays an important role in reducing the risk of cancer due to its low toxicity, bioavailability, and anticancer effects via modulation of the immune system, such as NF-kB signaling. However, the anticancer effects of these herbs can be

attributed to their effective modulation of multiple aspects of the patients, with the immune system being a major factor. Thus, in future more researches are desired to find out the exact underlying mechanisms and their mode of actions.

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