Phytoconstituents as apoptosis inducing agents: strategy to combat cancer

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Abstract Advancement in the field of cancer molecular biology has aided researchers to develop various new chemopreventive agents which can target cancer cells exclusively. Cancer chemopreventive agents have proficiency to inhibit, reverse and delay process of carcinogenesis during its early and later course. Chemopreventive agents can act as antioxidative, antimutagenic/antigenotoxic, anti-inflammatory agents or via aiming various molecular targets in a cell to induce cell death. Apoptosis is a kind of cell death which shows various cellular morphological alterations such as cell shrinkage, blebbing of membrane, chromatin condensation, DNA fragmentation, formation of apoptotic bodies etc. Nowadays, apoptosis is being one of the new approaches for the identification and development of novel anticancer therapies. For centuries, plants are known to play part in daily routine from providing food to management of human health. In the last two decades, diverse phytochemicals and various botanical formulations have been

characterized as agents that possess potential to execute cancer cells via inducing apoptosis. Data obtained from the research carried out globally pointed out that natural products are the potential candidates which have capability to combat cancer. In the present review, we surveyed literature on natural products which throws light on the mechanism through which these phytochemicals induce apoptosis in cancer cells.

Keywords Cancer chemoprevention · Phytochemicals · Apoptosis · Caspases · NF- κ B · ROS

Introduction

Cancer causes several million deaths all over the world. Among all the cancer deaths occurring in the world, about 60 % deaths happen in developing countries. It has been estimated that mortality due to cancer would increase up to 13.0 millions in 2030 along with 21.7 million new cancer cases (Cancer Facts & Figures, 2014 American Cancer Society). Most pilot studies on cancer prevention have been carried out in developed countries; hence the treatment strategies available are the outcome of research carried out in these countries. Developing countries are still lagging behind in the arena of cancer research (Disease Control Priorities Project). Cancer is a patho-physiological condition with multistage process consisting of three distinct phases: initiation,

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promotion and progression phases. Several factors such as mutations in genes, hypermethylation of various genes, silencing of some genes, overexpression and protein post-translational changes in various proteins lead to uncontrolled cell proliferation (Jones and Baylin 2002; Benz and Yau 2008). Several therapies which are used for cancer prevention includes radiation, chemotherapy, immunosuppression and surgery but all these strategies have one or other disadvantages. As mortality rate from cancer is increasing day by day, hence, there is requirement of new strategies for cancer prevention. Chemoprevention is the use of such agents which have potential to inhibit, reverse or retard tumorigenesis (Surh 2003). Use of natural plant products for cancer chemoprevention has gained considerable attention over the last few years (Surh 2003; Amin et al. 2009; Ji et al. 2014). Diet of people varies from place to place because of different lifestyles. Furthermore, it is estimated that 35 % of cancer deaths may be related to diet and dietary factors. In chemoprevention, various dietary biofactors, phytochemicals and even whole plant extracts are used to prevent cancer (Manson 2003; Doll and Peto 1981). Medicinal plants are used traditionally all over the world to cure several ailments including diabetes and cancer. According to the World Health Organization, 80 % of the world's population are dependent on medicinal plants for the treatment of several ailments (Calixto 2005). With the advancement in field of medicine, it has been observed that several novel therapies are now available in market for clinical use such as products of plants, animals and microbes. (Newman et al. 2003; Balunas and Kinghorn 2005; Tan et al. 2006; Gordaliza 2007). Now-a-days efforts are being made to understand the molecular targets of various dietary phytochemicals. These possess great potential to modulate expression of several genes via epigenetic modulatory mechanisms (Shukla et al. 2014). The use of plant extracts as anticancer agents is getting pace not only because they are inexpensive but also because of less side effects. Phytoconstituents in crude extracts of plants possess potential to inhibit or reverse the process of carcinogenesis (Ishiguro et al. 2007; Dahanukar et al. 2000; Rao 2003; Zhang and Tang 2007; Surh 2003). The identification and characterization of various phytochemicals in plants with anticancer properties has been gaining attention (Shu et al. 2010). Natural products and their synthetic analogues are largely

successful in their clinical trials as anticancer drugs (Pilatova et al. 2010). Several phytoconstituents such as vinblastine, vincristine, podophyllotoxin, camptothecins are potential candidates in anticancer drug development. Most of anticancer drugs available in market destroy cancer cells by inducing either apoptosis or necrosis (Kerr et al. 1972; McCarthy and Evan 1998). Numerous pure constituents and crude extracts from plants have been studied for apoptosis induction (Table 1, 2; Fig. 1). Apoptosis is a mechanism to eliminate precancerous and cancer cells and can be used as a novel target for cancer prevention studies (Kiechle and Zhang 2002; Nicholson 2000; Taraphdar et al. 2001). During the last decade, isolation of active constituents with anticancer activity obtained from natural plant products has been getting interest of researchers (Prasad et al. 2007). This review summarizes and covers basic aspects and some of the molecular mechanisms through which natural plant products induce apoptosis targeting cancer cells.

Mechanisms of apoptosis

Many natural products have been discovered which possess potential to regulate apoptosis. The term apoptosis was first introduced in 1972 by Kerr, Wyllie and Currie. Apoptosis is an energy dependent, asynchronous distinct form of cell death characterized by several features such as cell shrinkage, membrane blebbing and formation of apoptotic bodies, nuclear fragmentation, nuclear condensation etc. (Kerr et al. 1972; Debnath et al. 2005; Ratan et al. 1994). It is a mechanism which is very vital and necessary in the development, tissue homeostasis and guards against several viral infections (Kam and Ferch 2000; Bar 1996). During apoptosis, the cell separates itself from neighboring cells, followed by breakdown of nuclear material which is packed into membrane bounded vesicles known as apoptotic bodies and finally exocytosed. Another kind of cell death is necrosis which occurs synchronously in many cells during various pathological conditions, characterized by disruption of membrane integrity, cell and nucleus swelling and nuclear disintegration. It also causes inflammatory reactions (Thatte and Dahanukar 1997; Pritchard et al. 1997; Arends and Wyllie 1991; Wyllie 1997; Kam and Ferch 2000).

There are three different mechanisms by which a cell undergoes apoptosis. These include extrinsic

pathway, intrinsic pathway and perforin-granzyme apoptotic pathway (Elmore 2007). In the extrinsic pathway, death ligand binds with death receptor (such as TNF- α /TNFR1, FasL/FasR), interaction of ligand and receptor resulting in activation of caspase 8 from procaspase 8, which in-turn cleaves and activates caspases 3 from procaspase 3. Caspase 3 in-turn activates execution pathway which causes activation of endonucleases resulting in fragmentation of chromosomal DNA, breakdown of cytoskeletal proteins, nuclear condensation (pyknosis) leading to formation of apoptotic bodies (Fig. 2) (Wajant 2002; Kischkel et al. 1995; Rubio-Moscardo et al. 2005; Elmore 2007; Pan et al. 2008). Astragalus saponins induced apoptosis through the extrinsic pathway in HT-29 colon cancer cells (Auyeung et al. 2010). Apigenin induced apoptotic cell death via the extrinsic pathway in HER2-overexpressing breast cancer cells (Seo et al. 2012). Harmine is a beta-carboline alkaloid from the plant *Peganum harmala* which activates both intrinsic and extrinsic pathways of apoptosis (Hamsa and Kuttan 2011).

In the intrinsic pathway, different types of stimuli such as radiations, toxins, hypoxia, viral infections, free radicals and other factors alter inner mitochondrial membrane potential resulting in leaky membrane. This causes release of proapoptotic proteins such as cytochrome c (cyt c) which binds to Apoptotic protease activating factor (Apaf-1), procaspase 9 to form apoptosome activating caspase 3 which in-turn activates execution pathway as in case of the extrinsic pathway leading to apoptosis (Fig. 2) (Elmore 2007). Bcl-2 family proteins are of two types which are antagonistic in function and play a very crucial role in apoptotic cell death. Propapoptotic proteins include Bcl-10, Bax, Bak, Bid, Bad, Bim, Bik, and Blk while anti-apoptotic proteins are Bcl-2, Mcl-1, Bcl-x, Bcl-XL, Bcl-XS, Bcl-w, BAG. In case of cancer cells, balance between these two types of Bcl-2 family proteins alters which causes upregulation of anti-apoptotic members evading apoptosis (Oltvai et al. 1993; Reed 1997; Green and Reed 1998; Bossy-Wetzel and Green 1999; Kuwana et al. 2002; Martinou et al. 2000; Cory and Adams 2002; Schuler and Green 2001; Scorrano et al. 2003; Juin et al. 2004). Hence, inhibiting various anti-apoptotic proteins and upregulating proapoptotic proteins of the BCL-2 family can be targeted for cancer chemoprevention. *Strychnos nux-vomica* L. (SN) root extract was analyzed for

antiproliferative efficacy using the human multiple myeloma-cell line, RPMI 8226. Analysis of the apoptotic mechanism revealed that SN root extract exhibited mitochondrial dependent apoptosis. The anticancer activity was attributed to the presence of alkaloids strychnine and brucine (Rao et al. 2009). Medicinal mushroom *Ganoderma lucidum* and the herb *Duchesnea chrysanthra* extracts (GDE) synergistically induced mitochondrial damage and apoptosis in HL-60 cells (Kim KC et al. 2007). Salidroside isolated from plants of the *Rhodiola* genus was evaluated for apoptosis inducing ability. Authors concluded that salidroside induced the apoptosis of MCF-7 and MDA-MB-231 cells by suppressing anti-apoptotic proteins and involved mitochondrial pathway (Hu et al. 2010). Obacunone and obacunone glucoside (OG) isolated from the seeds of Marsh White grapefruit were evaluated for apoptotic inducing ability in on colon cancer (SW480) cells and reported that both limonoids induced apoptosis through the intrinsic apoptosis pathway (Chidambara Murthy et al. 2011). The apoptogenic activity of *Litchi chinensis* leaf extract against U937, K562 and HL-60 (leukemic cell lines) was reported by Roya et al. (2008) and showed that the extract induced apoptosis was mediated through the mitochondrial intrinsic pathway. Pal et al. (2010) evaluated 95 % ethanolic extract of *Inula racemosa* roots and its four fractions viz. n-hexane, chloroform, n-butanol and aqueous for their cytotoxic in vitro potential against various human cancer cell lines. Out of these fractions, n-hexane fraction which was investigated for apoptosis inducing ability in HL-60 cells was shown to induce apoptosis through intrinsic as well as extrinsic pathways. Liu et al. (2006) evaluated *Narcissus tazetta* var. chinensis for its apoptosis inducing ability. Results from the study indicated that the extract induced HL-60 cell apoptosis was regulated by the release of cytochrome c from the mitochondria leading to the activation of various proteins viz. caspase-8, -9, and -3 and Bax. Kwon et al. (2006) reported the antiproliferative effects of methanol extract of *Pterocarpus santalinus* in HeLa cell line. Extract induced apoptosis in the HeLa cell by the release of cytochrome c into cytoplasm, followed by activation of caspases and proteolytic cleavage of PARP. Studies carried out by Hsu et al. (2011) showed the cytotoxic potential of *Typhonium blumei* extract in A549 lung cancer cells. Flow cytometric analysis demonstrated that A549 cells were arrested at

the G2/M phase and apoptosis was induced by the mitochondrial pathway reducing the expression of Bcl-2 and Bcl-xL and enhancing the expression of Bax, Bad and Bak resulting in activation of caspase-9 and caspase-3. Aqueous extract of *Bryonia dioica* induced apoptosis through mitochondrial intrinsic pathway in BL41 Burkitt's lymphoma cells (Benarba et al. 2012). Extract caused upregulation of caspase-3 and -9, cleavage of PARP and decreased mitochondria membrane potential leading to apoptosis. Anticancer potential of ethanolic extract of mango peel (EEMP) was studied by Kim et al. (2012). It was reported that EEMP caused apoptotic cell death in human cervical carcinoma HeLa cells. EEMP treatment resulted in the increase of cell population in the sub-G1 phase. It also decreased the expression of Bcl-2 proteins, increased proteolytic cleavage of caspase-3, 7, 8, and 9 and cleaved the PARP protein. Both extrinsic and intrinsic pathways contributed in the apoptosis of HeLa cells induced by ethanolic extract of mango peel.

The third type of mechanism is perforin/granzyme induced apoptosis which is mainly used by cytotoxic T lymphocytes (CTLs). Target cells are killed during CTLs induced apoptosis through the extrinsic pathway and FASL/FasR interaction. Cytotoxic T lymphocytes (CTLs) also eliminate virus-infected or transformed cells using perforin and granzyme. Perforin proteins lead to the formation of pores in the membranes of the attacked cell which results in the entry of granzyme A and granzyme B into the cell. Granzyme B induces caspase-dependent apoptosis and granzyme A induces caspase-independent apoptosis (Brunner et al. 2003; Trapani and Smyth 2002; Lieberman and Fan 2003; Fan et al. 2002, 2003a, b; Elmore 2007). Earlier, it was believed that the cytotoxic potential of different anticancer drugs may be due to induction of DNA damage but now evidences are available that anticancer agents cause apoptosis. The induction of apoptosis in cancer cells is one of the vital strategies for the identification of potent anticancer drugs (Panchal 1998; McConkey et al. 1996; Hu and Kavanagh 2003).

Molecular targets of chemopreventive agents

Research in the field of cancer prevention has highlighted the use of various phytoconstituents possessing anticancer properties. Use of natural plant products for cancer chemopreventive studies has been gaining

attention among the scientific community all over the world. During the last few decades, several phytochemicals have shown anticancer effects by targeting NF- κ B (Alantolactone, Shikonin, Morusin and Xanthohumol), Caspases (Goniothalamine, Myriadenolide, Baicalein, Mahanine, Pyrayafoline D, Murrafoline-I and Dehydrocostus lactone, (–)-Anonaine, Corosolic acid, Casearin X and Pyranocycloartobioxanthone), AP-1 (Curcumin, Quercitrin, Parthenolide, Sulforaphane, Maslinic acid and Berberine), cell cycle (Rhodoxanthin, 4-nerolidylcatechol, Berberine, Haemanthine, Haemanthidine and Capsaicin), Reactive oxygen species (ROS) (Cinnamaldehyde, 6-Methoxydihydrosanguinarine, Pancratiastatin, Eugenol, Gallic acid, Curcumin, Butein, Icariin, Actinodaphnine, Saikosaponin-a & d, Flavokawain B, Plumbagin, β -Caryophyllene oxide, Goniothalamine, (–)-Epigallocatechin-3-gallate, Herbacetin and Piperlongumine) etc. (Tables 1, 2; Fig. 1). Understanding the mechanism of action of natural plant products in inducing cell death in cancer cells is very essential for searching lead molecules in the field of cancer chemoprevention.

Phytoconstituents as NF- κ B inhibitors

Sen and Baltimore (1986) were first to recognize nuclear factor kappaB (NF- κ B) in the nucleus. They found it to be bound to an enhancer element of the immunoglobulin kappa light chain gene in B cells. This transcription factor belongs to Rel family, and is involved in various processes such as immune response, inflammation process, cell adhesion molecules and growth factors. This family consists of five proteins viz. RelA (p65), RelB, c-Rel, NF- κ B1 (p50/p105) and NF- κ B2 (p52/100) (Lin and Karin 2003; Ghosh and Karin 2002; Baldwin 1996; Piette et al. 1997; Gilmore and Herscovitch 2006; Sen and Smale 2010; Shishodia and Aggarwal 2004). RelA, RelB, and c-Rel are formed as mature proteins while NF- κ B1 and NF- κ B2 are not formed directly as mature proteins. Initially, these are formed as p105 (105 kDa) and p100 (100 kDa), which later on following translation giving rise to DNA-binding subunits p50 and p52, respectively. These proteins in combination form homodimer/heterodimer proteins, which turn on different genes. Normally, NF- κ B remains inactive, owing to inhibitory action of inhibitors of NF- κ B (I κ Bs) such as I κ B α , I κ B β , I κ B ϵ , I κ B γ and Bcl-3

Table 1 Plant extracts possessing apoptosis inducing effects

S. no.	Botanical name/common name	Plant part used	Cell line/animal model used	Targets	References
1.	<i>Allium sativum</i>		Colo 205	Caspase-3 (↑); Bcl-2 (↓); Bax (↑); cytochrome c (↑)	Su et al. (2006)
2.	<i>Annona squamosa</i>	Seeds	BC-8	Bcl-2 (↓); Bcl _{xl} (↓); caspase-3 (↑); ROS (↑); GSH (↓)	Pardhasaradhi et al. (2004)
3.	<i>Azadirachta indica</i>	Leaves	Hamster buccal pouch carcinoma	Bim (↑); caspase 8 (↑); caspase 3 (↑); Bcl-2 (↓)	Subapriya et al. (2005)
4.	Blackberry	Fruits	A549 cells JB6 P+ cells	AP-1 (↓)	Feng et al. (2004)
5.	<i>Bryonia dioica</i>	Roots	BL41	Caspase-3, -9 (↑); Cleavage of PARP; mitochondria membrane potential (↓)	Benarba et al. (2012)
6.	<i>Camellia sinensis</i>	Leaves	HT-29	Caspase-3, -8, and -9 (↑)	Hajiaghaalipour et al. (2015)
7.	<i>Citrus grandis Osbeck</i>	Immature fruits	U937	Caspase-3 (↑); Bcl-2 (↓); Bax (↑); PARP degradation	Lim et al. (2009)
8.	<i>Cinnamomum cassia</i>	Bark	In vitro: B16F10 In vivo: Mouse melanoma model	NFκB (↓); API(↓)	Kwon et al. (2010)
9.	<i>Codonopsis lanceolata</i>	Roots	HT-29	ROS (↑); Polyamine depletion; JNK activation; G0/G1 phase arrest; Bax (↑); Bcl-2 (↓); survivin (↓); Caspases 3 (↑); p53 activation (↑)	Wang et al. (2011)
10.	<i>Commiphora mukul</i>	Gum guggul resin	LNCaP (androgen-dependent) C81 androgen-independent variant	PARP cleavage; ROS (↑); Bax and Bak (↑); Bcl-2 (↓); JNK (↑)	Xiao et al. (2011)
11.	<i>Coptis japonica</i> var. dissecta	Roots	SNU-668	Bcl-2 (↓); Bax (↑); Caspase 3 (↑)	Park et al. (2005)
12.	<i>Crenanthodium humile</i>	Flowers	Hela	Cytochrome c (↑); mitochondrial membrane potential (↓); Caspases-3 (↑); Caspases 7 (↑); Caspases 9 (↑); ROS (↑)	Li et al. (2007)
13.	<i>Crocus sativus</i>	Stigmas	MCF-7	Bax (↑)	Mousavi et al. (2009)
14.	<i>Cyathula prostrata</i>	Whole plant	HeLa U937	Caspases 8 (↑); G0/G1 arrest	Schnablegger et al. (2013)
15.	Dandelion	Roots	Jurkat cells	Caspase 3 (↑); caspase-8 (↑)	Ovadje et al. (2011)
16.	<i>Dianthus superbus</i>	Aerial parts	HepG2	Cytochrome c release; Bcl-2 (↓); NF-κB (↓); caspase-9, -3 (↑)	Yu et al. (2012)

Table 1 continued

S. no.	Botanical name/common name	Plant part used	Cell line/animal model used	Targets	References
17.	<i>Ficus hirta</i>	Roots	HeLa	Sub-G1 phase increase	Zeng et al. (2012)
18.	Fresh Gala apples	Peels	In vitro: JB6 cells In vivo: AP-1-luciferase reporter transgenic mice	AP-1 (↓)	Ding et al. (2004)
19.	<i>Ganoderma lucidum</i>	Fresh fruiting bodies	HL-60	Bcl-2 (↓); translocation of Bax to mitochondria; cytochrome c (↑); caspase 3 (↑)	Kim KC et al. (2007)
20.	<i>Duchesnea chrysantha</i> (tested in combination)	Whole parts	HL-60		
21.	<i>Inula racemosa</i>	Roots	HL-60	ROS generation; cytochrome c release; translocation of Bax; PARP cleavage; caspases-3, -6, -8 & -9 (↑)	Pal et al. (2010)
22.	<i>Litchi chinensis</i>	Leaves	U937 K562 HL-60	Cytochrome c release; caspase 9 (↑), caspase 3 (↑); G2-M phase arrest (U937 and K562 cell lines); G1 phase arrest (HL-60 cell line)	Roya et al. (2008)
23.	<i>Luffa echinata</i>	Fruits	HT-29	ROS (↑); mitochondrial membrane potential (↓); G2/M phase arrest, Bcl _{xl} (↓); Bax (↑); Bcl-2 (↓); caspases 3 (↑)	Shang et al. (2012)
24.	<i>Mangifera indica</i>	Fruit Peels	HeLa	Bcl-2 expression (↓); caspase-3, 7, 8, and 9 (proteolytic activation); PARP cleavage	Kim et al. (2012)
25.	<i>Memecylon edule</i>	Leaves	MKN-74 and NUGC	Cytochrome c release; mitochondrial membrane potential loss; caspases 3 (↑); Bcl-2 (↓)	Naidu et al. (2013)
26.	<i>Narcissus tazetta</i> var. chinensis	Stems and leaves	HL-60 K562 KT1/A3 A3R	For HL-60 cells: Cytochrome c release; caspases-8, -9, and -3 (↑); Bax (↑)	Liu et al. (2006)
27.	<i>Phyllanthus watsonii</i>	Leaves	MCF-7	Caspase 3 (↑); S phase arrest	Ramasamy et al. (2013)
28.	<i>Physalis peruviana</i>	Leaves	H661	S phase arrest; p53 (↑); cytochrome c release; caspase-3 (↑); PARP cleavage; Bax (↑); inhibitor of apoptosis protein (IAP) (↓)	Wu et al. (2009)

Table 1 continued

S. no.	Botanical name/common name	Plant part used	Cell line/animal model used	Targets	References
29.	<i>Pistacia atlantica sub kurdica</i>	Pericarp	HT29	S phase delay; cyclin A (↓)	Rezaei et al. (2012)
30.	<i>Plocamium telfairiae</i>	Sea weed	HT-29	Caspases-8, -9, -3, and -7 (↑); proteolytic cleavage of PARP	Kim JY et al. (2007)
31.	<i>Propolis</i>	–	MCF-7	Caspase-8 (↑); caspase-9 (↑); caspase-6 (↑)	Vatansever et al. (2010)
32.	<i>Psidium cattleianum</i>	Leaves	SNU-16	Cleaved caspase 3 (↑); cleaved caspases 8 (↑); Bcl-2 (↓); proteolytic cleavage of PARP; sub-G1 phase accumulation	Moon et al. (2011)
33.	<i>Rhodiola imbricata</i>	Rhizomes	K-562	ROS (↑); G2/M phase arrest	Mishra et al. (2008)
34.	<i>Rubus coreanum</i>	Incompletely ripened fruit	HT-29	Caspase 3 (↑)	Kim et al. (2005)
35.	<i>Sapindus rarak</i>	Fruit pulp	A549 cells	Caspase 3 (↑); caspase 9 (↑)	Kummalu et al. (2011)
36.	<i>Strychnos nux-vomica</i>	Roots	RPMI 8226	Mitochondrial membrane potential (↓); Cytochrome C release; sub-G0/G1 cell population accumulation	Rao et al. (2009)
37.	<i>Tinospora cordifolia</i>	Stems	Ehrlich ascites tumor	Caspases 3 (↑); Bcl-2 (↓); Bax (↑)	Thippeswamy and Salimath (2007)
38.	<i>Tripterygium hypoglaucum</i>	Roots	HL-60 cell	Genes linked to NF-κB signaling pathway (↑); Cell apoptosis genes (such as NFKB1B, PRG1 and B2M) (↑); caspase-3 (↑); caspase-8 (↑)	Zhuang et al. (2004)
39.	<i>Typhonium blumei</i>	Leaves	A549 LNCaP MCF-7	For A549 cells: G2/M phase arrest; Bcl-2 and Bcl-xL (↓); Bax, Bad and Bak (↑); caspase-9 (↑); caspase-3 (↑)	Hsu et al. (2011)

Table 2 Phytochemicals with apoptosis inducing effects

S. no.	Compound	Cell line/animal model used	Targets	References
1.	Actinodaphnine (aporphine alkaloid)	Mahlavu	Caspases 3/7, 9 activities (↑); NF-κB (↓); NO (↑); ROS (↑); loss of mitochondrial membrane potential	Hsieh et al. (2006)
2.	Alantolactone (sesquiterpene lactone)	HepG2 Bel-7402 SMMC-7721	For HepG2 cell line G ₂ -M arrest; activate caspase 8, 9, 3 (↑); cytosolic cytochrome c (↑); NF-κB/p65 (↓); p53 (↑); PARP (cleaved); Bax (↑); Bak (↑); Bcl-2(↓); t-Bid (↑); p53 (↑)	Lei et al. (2012)
3.	(–)-Anonaine (alkaloid)	HeLa	p53 (↑); Bax (↑); caspase 3,7,8,9 (↑); PARP cleavage; ROS (↑); NO (↑); GSH (↓); mitochondrial membrane potential (↓)	Chen et al. (2008)
4.	Baicalein (flavone)	HL-60	Caspases 3 (↑), PARP (Cleavage)	Li et al. (2004)
5.	Berberine (alkaloid)	HPV16 positive SiHa cells HPV18 positive HeLa cells	In SiHa: AP-1 DNA binding activity (↓); cFos (↓); JunD (reduced by 12 h, recovered by 24 h) In HeLa: AP-1 DNA binding activity (↓); cFos (↓); cJun (↓) In both cell lines: HPV16E6 (↓); HPV16E7 (↓); HPV18E6 (↓); HPV18E7 (↓); p53 (↑), Rb (↑); hTERT (↓); caspase 3 (↑); PARP (cleavage); loss of mitochondrial membrane potential	Mahata et al. (2011)
6.	Berberine (alkaloid)	HL-60	Accumulation of cells in S phase, cyclin D1 (↓); phosphorylation and degradation of Cdc25A; Chk2 activation, p21waf (↑)	Khan et al. (2010)
7.	Butein (chalcone)	HepG2 Hep3B	In both cell lines: SOD activity (↑); Cdc25C (↓); Cdc2 (↓); Cdc2 kinase activity (↓); p-Cdc2 (↑); p-Chk1 (↑); p-Chk2 (↑); p-ATM (↑); p-JNK (↑); Bax/Bcl-2 ratio (↑); caspase 3 activity (↑); G2/M phase arrest; ROS (↑); Bax (↑); Bcl2 (↓); PARP cleavage	Moon et al. (2010)
8.	Capsaicin (alkaloid)	KB	G2/M phase arrest; caspase 3, 9 (↑), PARP (cleaved); mitochondrial membrane potential depolarization	Lin et al. (2013)

Table 2 continued

S. no.	Compound	Cell line/animal model used	Targets	References
9.	β -caryophyllene oxide (sesquiterpene)	PC-3 MCF-7	In both cells: p-P13K ($\downarrow$); p-AKT ($\downarrow$); p-mTOR ($\downarrow$); p-S6K1 ($\downarrow$); p-JNK ($\uparrow$); p-ERK ($\uparrow$); p-p38 ($\uparrow$) In PC-3 cells: cyclin D1 ($\downarrow$); Bcl-2 ($\downarrow$); Bcl-xL ($\downarrow$); survivin ($\downarrow$); IAP-1 ($\downarrow$); IAP-2 ($\downarrow$); COX-2 ($\downarrow$); VEGF ($\downarrow$); p53 ($\uparrow$); p21 ($\uparrow$); procaspase 3 ($\downarrow$); cleaved caspase 3 ($\uparrow$); cleaved PARP ($\uparrow$); p21 ($\uparrow$); p53 ($\uparrow$); cyt. c release ($\uparrow$); ROS ($\uparrow$)	Park et al. (2011)
10.	Casearin X (clerodane diterpenes)	HL-60	Caspases 3/7 activation ($\uparrow$), mitochondrial depolarization	Ferreira et al. (2010)
11.	Corosolic acid (triterpene)	HeLa	Bax ($\uparrow$); caspase 8, 9, 3 ($\uparrow$); Cytosolic cytochrome C ($\uparrow$); decrease in mitochondrial membrane potential	Xu et al. (2009)
12.	Chrysin (flavone)	HCT-116	PARP cleavage; caspase 8, 3 ($\uparrow$); inhibition of degradation of Inhibitor of kappaB (I κ B); inhibition of nuclear translocation of p65; c-FLIP-L ($\downarrow$) [on treatment with chrysin along with TNF- α]	Li X et al. (2010)
13.	Cinnamaldehyde (aromatic aldehyde)	HL-60	Cytochrome c release; mitochondrial membrane potential loss; ROS ($\uparrow$); procaspase 9, 3 ($\downarrow$); GSH ($\downarrow$); protein thiols ($\downarrow$)	Ka et al. (2003)
14.	Curcumin (diarylhepanoid)	HL-60	I κ B α degradation (blocked); nuclear translocation of p65 (inhibited); binding of NF- κ B and AP-1 to their consensus DNA sequences ($\downarrow$)	Han et al. (2002)
15.	Curcumin (diarylhepanoid)	L929	ROS ($\uparrow$), mitochondrial AIF ($\downarrow$); cytosolic and nuclear AIF ($\uparrow$); mitochondrial cytochrome c ($\downarrow$); cytosolic cytochrome c ($\uparrow$); PARP cleavage; p53 ($\uparrow$); p21 ($\uparrow$); Rb ($\downarrow$); cyclin D1,D3 ($\downarrow$); caspase 3 activity ($\uparrow$)	Thayyullathil et al. (2008)
16.	Dehydrocostus lactone (sesquiterpene lactone)	DU145	Cleaved caspase 8,9,7,3 ($\uparrow$); PARP cleavage; Bcl-XL ($\downarrow$); Bax ($\uparrow$); Bak ($\uparrow$); Bok ($\uparrow$); Bkl ($\uparrow$); Bmf ($\uparrow$); t-Bid ($\uparrow$); cytochrome c release; mitochondrial membrane permeability ($\uparrow$)	Kim et al. (2008)

Table 2 continued

S. no.	Compound	Cell line/animal model used	Targets	References
17.	(-)-Epigallocatechin-3-gallate (polyphenol)	Ishikawa Human primary endometrial cancer cells	In both cell lines: ER α ($\downarrow$); PR ($\downarrow$); PCNA ($\downarrow$); cyclin D1 ($\downarrow$); Bax/Bcl-2 ratio ($\uparrow$) In Ishikawa cells: GSH ($\downarrow$); p38 ($\uparrow$); ERK ($\downarrow$); c-jun ($\downarrow$); c-fos ($\downarrow$); cleaved PARP ($\uparrow$); cleaved caspase 3 ($\uparrow$); ROS ($\uparrow$)	Manohar et al. (2013)
18.	Eugenol (phenylpropanoid)	HL-60 3LL Lewis U-937 SNU-C5 HepG2 HL-60	In HL-60 cells: ROS ($\uparrow$); cytosolic cytochrome <i>c</i> ($\uparrow$); mitochondrial cytochrome <i>c</i> ($\downarrow$); Bcl-2 ($\downarrow$); protein thiols ($\downarrow$); GSH ($\downarrow$); procaspase 9, 3 ($\downarrow$); cytosolic Bax ($\downarrow$); mitochondrial Bax ($\uparrow$)	Yoo et al. (2005)
19.	Eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone)	HepG2 HL-60	Caspase 9, 3, 7 (proteolytic activation); cytosolic cytochrome <i>c</i> ($\uparrow$); PARP (cleaved)	Seo and Surh (2001)
20.	Flavokawain B (chalcone)	HCT116	GADD153 ($\uparrow$); Bcl-2 ($\downarrow$); Bim EL, L, S ($\uparrow$); PARP cleavage; p-p38 ($\uparrow$); ROS ($\uparrow$); mitochondrial membrane potential loss; cytochrome <i>c</i> release	Kuo et al. (2010)
21.	Gallic acid (phenolic acid)	DU145 LNCaP PC-3	In DU145 cells: Bcl _{XL} ($\downarrow$); Bax ($\uparrow$); PARP cleavage; caspase 9, 3 activation; cyclin B1 ($\downarrow$); Cdc2 ($\downarrow$); Cdc25C ($\downarrow$); p-Cdc2(Tyr15) ($\uparrow$), p-Cdc25C(Ser216) ($\uparrow$), p-Chk1(Ser345) ($\uparrow$), p-Chk2(Ser516) ($\uparrow$); cytosolic cytochrome <i>c</i> ($\uparrow$); mitochondrial cytochrome <i>c</i> ($\downarrow$); loss of mitochondrial membrane potential; ROS ($\uparrow$)	Chen et al. (2009)
22.	Goniothalamin (styrylpyrone derivative)	Jurkat T-cells	Caspases 3, 7 (cleavage); PARP (cleaved)	Inayat-Hussain et al. (1999)
23.	Goniothalamin (styrylpyrone derivative)	Ca9-22	ROS ($\uparrow$); DNA damage (double strand breaks); depolarization of mitochondrial membrane; increase in sub-G1 population	Yen et al. (2012)
24.	Haemanthamine (alkaloid) Haemanthidine (alkaloid)	Jurkat (p53 mutant E6.1)	p16 expression ($\uparrow$); Chk1 Ser345 phosphorylation, activation of caspase 3/7, 8, 9 ($\uparrow$); loss of mitochondrial membrane potential; accumulation of cells at G1 and G2 phase	Havelek et al. (2014)

Table 2 continued

S. no.	Compound	Cell line/animal model used	Targets	References
25.	Herbacetin (flavonoid)	HepG2	p-Akt (↓); PARP cleavage (↑); Bcl-2 (↓) Bax (↑); cleaved caspase 3 (↑); PGC-1α (↑); cytosolic cytochrome <i>c</i> (↑); ROS (↑)	Qiao et al. (2013)
26.	Hyperforin (prenylated phloroglucinol derivative)	K562 U937 LN229	In K562: caspases 8, 3 (↑) In U937: caspases 9, 3 (↑)	Hostanska et al. (2003)
27.	Icariin (flavonol glycoside)	SMMC-7721	p-JNK (↑); Bax/Bcl-2 (↑); cleaved caspase 9, 3 (↑); cleaved PARP (↑); XIAP (↓); mitochondrial cyt. <i>c</i> (↓); cytosolic cyt. <i>c</i> (↑); ROS (↑)	Li S et al. (2010)
28.	Magnolol (lignin)	U937 HeLa HL-60 MCF-7	NF-κB p65 (↓); MMP-9 (↓); IL-8 (↓); MCP-1 (↓); MIP-1α (↓); TNF-α (↓); inhibition of IκBα phosphorylation and breakdown; (inhibited); IKK (IκB kinases) activity (inhibited)	Tse et al. (2007)
29.	Mahanine pyrayafoline-D, murrafoline-I (carbazole alkaloids)	HL-60	Caspase 9, 3 (↑); mitochondrial membrane potential (↓)	Ito et al. (2006)
30.	Mannose/sialic acid-binding lectin (lectin)	A375	Bax (↑), Bcl _{XL} (↓); Bcl-2 (↓); cytosolic cytochrome <i>c</i> (↑); active caspase 9, 3 (↑); procaspase 9, 3 (↓); ICAD (↓); Cleaved PARP (↑); GSH content (↓); GPX enzyme activity (↓); p-p38 (↑); p-p53 (↑); ROS (↑)	Liu et al. (2009)
31.	Maslinic acid (triterpenoid)	Raji	COX-2 (↓); AP-1 DNA binding activity (↓); nuclear NF-κB p65 (↓); NF-κB DNA binding activity (↓)	Hsum et al. (2011)
32.	6-Methoxydihydrosanguinarine (benzophenanthridine alkaloid)	HepG2	p53 (↑); Bax (↑); Bcl2 (↓); caspase 3, 8, 9 activity (↑); cytosolic cytochrome <i>c</i> (↑); PARP cleavage	Yin et al. (2005)
33.	4- <i>O</i> -methyllhonokiol (neolignan)	SW620 HCT-116	NF-κB (↓); cdk4 (↓); cdk4 (↓); cyclin D1 (↓); cyclin E (↓); p21 (↑); p53 (increased in HCT-116, not present in SW620); <i>Rb</i> (↓); Bcl-2 (↓); cIAP1 (↓); cIAP2 (↓); survivin (↓); GSK-3β (↓); Bax (↑); cleaved caspases 9, 3 (↑); COX-2 (↓); iNOS (↓); G ₀ -G ₁ phase arrest	Oh et al. (2012)

Table 2 continued

S. no.	Compound	Cell line/animal model used	Targets	References
34.	Morusin (isoprenylated flavone)	HT-29	IκBα (↑); caspase 8, 9, 3 (↑); NF-κB (↓); Ku70 (↓); XIAP (↓); mitochondrial tBid (↑); mitochondrial Bax (↑)	Lee et al. (2008)
35.	Myriadenolide (diterpene)	Jurkat; THP-1	Caspase 8, 9, 3 (↑); Bid (cleaved)	Souza-Fagundes et al. (2003)
36.	Pancreatistatin (alkaloid)	SHSY-5Y	Mitochondrion membrane permeability (↑); ROS (↑); ATP concentration (↓); caspase-3 and proteasome activity (↑)	McLachlan et al. (2005)
37.	Parthenolide (sesquiterpene lactone)	UVB-induced skin cancer; JB6	Suppression of AP-1 and MAPK In UVB induced cancer: AP-1 DNA binding activity (↓); JNK (↓); p38 (↓) In JB6 cells: AP-1 luciferase (↓)	Won et al. (2004)
38.	Piperlongumine (alkaloid)	PANC-1 MIA PaCa-2 BxPC-3 Xenograft mouse model (Pancreatic cancer)	ROS (↑), caused DNA damage Ki-67(↓), increased 8-OHdG expression (↑) (in mouse model)	Dhillon et al. (2014)
39.	Plumbagin (quinone)	K562	ROS (↑); TRAIL receptors DR4 and DR5 (↑)	Sun and Mckallip (2011)
40.	Plumbagin (quinone)	NB4 tumor xenograft in NOD/SCID mice	ROS (↑); loss of mitochondrial membrane potential; caspase 9,3,8 activities (↑); Bax (↑); Bak (↑); Bcl _{XL} (↓)	Xu and Lu (2010)
41.	Pyranocycloartobioxanthone A (xathone)	MCF-7	Bcl-2 (↓); Bax (↑); cytosolic cytochrome c (↑); NF-κB translocation to nucleus (Inhibited); caspases 3/7, 9, 8, (↑)	Mohan et al. (2012)
42.	Quercitrin (glycosylated flavonoid)	JB6	UVB and TPA induced nuclear translocation of AP-1 and NF-κB (↓); phosphorylation of MAPKs including ERKs, p38 kinase and JNKs (↓); nuclear Nrf2 (↑); GST ARE-luciferase activity (↑); nuclear translocation of p65 and c-jun (blocked); activity of detoxifying enzymes GSH and NQO1 (↑)	Ding et al. (2010)
43.	Saikosaponin-a and -d (triterpene saponins)	HeLa	Caspase 3 (↑); PARP cleavage (↑); ROS (↑) [Saikosaponins along with cisplatin]	Wang et al. (2010)

Table 2 continued

S. no.	Compound	Cell line/animal model used	Targets	References
44.	Shikonin (naphthoquinone)	Huh7 BEL 7402	c-FLIPL (↓); Bcl-2 (↓); Mcl-1 (↑); Akt (↓); p-Akt (↓); RIP1 (↓); p65 (↓); p50 (↓); NF-κB reporter luciferase (↓); ROS (↑); cleavage of caspase 8, 9; PARP (Cleavage)	Gong and Li (2011)
45.	Sulforaphane (isothiocyanate)	UVB-induced squamous cell carcinoma mouse model	AP-1 luciferase (↓); cFos binding to MMP-1 TRE(↓); Binding of nuclear AP-1 to the TRE (↓)	Dickinson et al. (2009)
46.	Ursolic acid (triterpene)	B16F-10	Caspase 3 (↑); p53 (↑); TNF-α (↓); IL-1β (↓); IL-6 (↓); GM-CSF (↓); Bcl-2 (↓)	Manu and Kuttan (2008)
47.	Xanthohumol (prenylflavonoid)	BPH-1	NF-κB (↓); Bax (↑); p53 (↑); Bcl-2 (↓)	Colgate et al. (2007)

(Hayden and Ghosh 2004). There are two different pathways involved in activation of NF-κB transcription factor, (a) the first one is the canonical or standard pathway (involved in innate immunity) and (b) the second one is the alternative or non-canonical pathway (involved in adaptive immunity and lymphoid organ development). In canonical pathway, in response to cell stimuli (TNF-α, LPS or IL-1β), IκBs get phosphorylated by IκB kinase (IKK) complex [two catalytic subunits IKKα and IKKβ and a regulatory subunit IKKγ or NF-κB essential modulator (NEMO)] and undergoes proteosomal degradation. In this mechanism, the main role is played by IKKβ, which causes translocation of NF-κB dimer to nucleus, henceforth triggering the target genes. In the second pathway, various stimuli such as B cell activated factor (BAFF), lymphotoxin-β (LTβ), CD40 ligand are involved in activating several factors (TNF receptor-associated factor) that in turn activate cellular inhibitors of apoptosis 1 and 2 (cIAP1 and cIAP2) and NF-κB inducing kinase (NIK). NF-κB inducing kinase then triggers the activation and phosphorylation of the IKKα catalytic subunit. IKKα in turn phosphorylates NF-κB2/p100. Finally, NF-κB is translocated to the nucleus regulating the expression of target genes. (Chen and Greene 2004; Lin and Karin 2003; Grimm and Baeurle 1993; Chen and Ghosh 1999; Zarnegar et al. 2004, 2008). NF-κB is involved in promotion and progression of cancer via regulating anti-apoptotic and apoptotic genes expressions (Fig. 3). It was noticed that NF-κB constitutively gets activated in cancer cells (Tse et al. 2007; Aggarwal 2004; Pikarsky et al. 2004; Dolcet et al. 2005; Wang et al. 1998; Suh and Rabson 2004; Garg and Aggarwal 2002; Oh et al. 2012; Manu and Kuttan 2008). Thus, suppression or inhibition of NF-κB is one of the novel target that can be used in cancer drug development. In last two decades, numerous plant extracts and plant constituents (such as Alantolactone, Shikonin, Morusin and Xanthohumol) have been studied for their potential to inhibit NF-κB, thus preventing cancer (Tables 1, 2; Fig. 1).

Alkaloids from *Tripterygium hypoglaucum* root were prepared and evaluated for their apoptosis inducing potential in HL-60 cell (Zhuang et al. 2004). It was found by cDNA microarray technology that there was increased expression of genes related to the NF-κB signaling pathway along with different genes viz. NFKBIB, PRG1 and B2M (cell apoptosis genes). Beside these, it also regulated

Fig. 1 Phytochemicals with antiproliferative and apoptosis inducing potential

(-)-Epigallocatechin-3-gallate

Molecular Weight: 458.37

Molecular Formula: $C_{22}H_{18}O_{11}$ **Eugenol**

Molecular Weight: 164.20

Molecular Formula: $C_{10}H_{12}O_2$ **Eupatilin**

Molecular Weight: 344.32

Molecular Formula: $C_{18}H_{16}O_7$ **Flavokawain B**

Molecular Weight: 284.31

Molecular Formula: $C_{17}H_{16}O_4$ **Gallic acid**

Molecular Weight: 170.12

Molecular Formula: $C_7H_6O_5$ **Goniotalamin**

Molecular Weight: 200.23

Molecular Formula: $C_{13}H_{12}O_2$ **Haemanthidine**

Molecular Weight: 317.34

Molecular Formula: $C_{17}H_{19}NO_5$ **Haemanthamine**

Molecular Weight: 301.34

Molecular Formula: $C_{17}H_{19}NO_4$ **Harmine**

Molecular Weight: 212.25

Molecular Formula: $C_{13}H_{12}N_2O$ **Herbacetin**

Molecular Weight: 302.24

Molecular Formula: $C_{15}H_{10}O_7$ **Hyperforin**

Molecular Weight: 536.78

Molecular Formula: $C_{35}H_{52}O_4$ **Icariin**

Molecular Weight: 676.66

Molecular Formula: $C_{33}H_{40}O_{15}$ **Fig. 1** continued

Mahanine
Molecular Weight: 347.45
Molecular Formula: $C_{23}H_{25}NO_2$

Magnolol
Molecular Weight: 266.33
Molecular Formula: $C_{18}H_{18}O_2$

Maslinic acid
Molecular Weight: 472.7
Molecular Formula: $C_{30}H_{48}O_4$

6-methoxydihydrosanguinarine
Molecular Weight: 363.36
Molecular Formula: $C_{21}H_{17}NO_3$

4-O-Methylhonokiol
Molecular Weight: 280.36
Molecular Formula: $C_{19}H_{20}O_2$

Morusin
Molecular Weight: 420.45
Molecular Formula: $C_{25}H_{24}O_6$

Murrafoline-I
Molecular Weight: 618.72
Molecular Formula: $C_{38}H_{38}N_2O_6$

Myriadenolide
Molecular Weight: 334.45
Molecular Formula: $C_{20}H_{30}O_4$

4-Nerolidylcatechol
Molecular Weight: 314.46
Molecular Formula: $C_{21}H_{30}O_2$

Obacunone
Molecular Weight: 454.51
Molecular Formula: $C_{26}H_{30}O_7$

Parthenolide
Molecular Weight: 248.32
Molecular Formula: $C_{15}H_{20}O_3$

Pancratistatin
Molecular Weight: 325.27
Molecular Formula: $C_{14}H_{13}NO_8$

Fig. 1 continued

Fig. 1 continued

expression of c-myc binding protein and apoptosis-related cysteine proteases, caspase-3 and caspase-8. Involvement of c-myc and NF- κ B signaling

pathways were responsible for apoptotic cell death. Xanthohumol (prenylflavonoid) was found to exert an antitumor effect on BPH-1 (Benign Prostate

Fig. 2 Diagrammatic representation of extrinsic and intrinsic pathways of apoptosis

Hyperplasia) cells. It was reported that xanthohumol and its oxidation product (xanthoaurenal) possess potential to induce apoptosis and down-regulate NF- κ B expression in BPH-1 cells (Colgate et al. 2007). Magnolol (lignin) from plant *Magnolia officinalis* lessens TNF- α induced NF- κ B p65 activation. Results suggested that magnolol possessed potential to induce apoptosis and can be further exploited in cancer chemoprevention studies (Tse et al. 2007). Morusin isolated from root bark of *Morus australis* (Moraceae) effectively induced apoptosis in human colorectal cancer (HT-29) cells. Morusin prevented the phosphorylation of IKK- α , IKK- β and I κ B- α and thus stops the movement of NF- κ B into the nucleus. Morusin induced apoptosis in HT-29 cells through activation of caspases and suppressive effect on NF- κ B (Lee et al. 2008). Manu and Kuttan (2008) reported that ursolic acid

induced apoptosis via inactivating NF- κ B and bcl-2 (anti-apoptotic proteins). Ursolic acid also increased expression of p53 and caspase 3, thus turning on the pro-apoptotic pathways in B16F-10 cells. Chrysin (5,7-dihydroxyflavone) in combination with TNF- α induced apoptosis in HCT-116 via suppressing the expression of NF- κ B and also c-FLIP-L (an anti-apoptotic gene) (Li X et al. 2010). Shikonin, a naphthoquinone demonstrated apoptotic cell death in hepatocellular carcinoma cell lines. ROS/Akt and RIP1/NF- κ B signaling pathways were found to be the chief players in inducing apoptotic cell death in hepatic cancer cell lines (Gong and Li 2011). Gambari et al. (2012) reported that Corilagin found in *Phyllanthus urinaria* and some other plant species prevents NF- κ B/DNA interactions and thus modulates expression of IL-8 gene cystic fibrosis IB3-1 cells treated with TNF- α . The apoptosis

inducing effects of 4-*O*-methylhonokiol on colon cancer cells were investigated by Oh et al. (2012). It effectively downregulated nuclear factor NF- κ B DNA binding activity and suppressed the proliferation of SW620 and HCT116 cancer cells. Alantolactone (sesquiterpene lactone) was found to inhibit the growth of HepG2 human liver cancer cell line (Lei et al. 2012). Alantolactone treatment targeted downregulation of NF- κ B/p65. *Dianthus superbus* L. was explored for anticancer potential by Yu et al. (2012). Ethyl acetate fraction of ethanol extract of *D. superbus* induced apoptosis of

HepG2 cells through the mitochondrial intrinsic pathway involving downregulation of Bcl-2 and NF- κ B and upregulation of caspase-9 and -3.

Phytoconstituents as caspases activators

Caspases play a potential role in apoptosis and inflammatory signaling pathways (Nicholson 1999). Caspases are enzymes (cysteine proteases) possessing aspartate substrate specific activity (Alnemri et al. 1996). Human caspases show resemblance with cysteine proteases produced by CED-3 gene of *Caenorhabditis elegans* (Yuan et al. 1993). Fourteen different caspases are identified in mammals, out of which 11 belong to human. Caspases are found as procaspases i.e. zymogenic form, which require activation before carrying out their function. Caspases also possess ability of self activation and to activate some other caspases. Caspases plays an essential role in apoptosis. These have been divided into (a) Activator caspases (Caspases 2, 8, 9, 10) also known as initiator caspases (b) Executioner or effector caspases (Caspases 3, 6, 7) and (c) Inflammatory caspases (Caspases 1, 4, 5, 11, 12, 13, 14) (Fig. 4) (Grütter 2000; Kumar and Vaux 2002; Salvesen 2002; Lü et al. 2003; Lippens et al. 2000; Deveraux et al. 1998; Chowdhury et al. 2008; Pistritto et al. 2002). In the last few decades, several plant extracts and their constituents (Goniothalamin, Myriadenolide, Baicalein, Mahanine, Pyrayafoline D, Murrafoline-I and Dehydrocostus lactone, (–)-Anonaine, Corosolic acid, Casearin X and Pyranocycloartobiloxanthone) have been screened for apoptosis inducing ability via upregulating caspases activity (Tables 1, 2; Fig. 1).

Fig. 3 Role of NF- κ B pathway in cancer progression

Fig. 4 Various types of caspases

Goniothalamine, a styrylpyrone derivative isolated from the plant *Goniothalamus andersonii* caused apoptosis in Jurkat T-cells by upregulating effector caspases 3 and 7 (Inayat-Hussain et al. 1999). Seo and Surh (2001) reported teupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone) from *Artemisia asiatica* for its apoptosis-inducing potential in HL-60 cells via caspases dependent pathways and also that it regulated the expression of Bcl-2 and Bax-2 proteins. Hyperforin found in the plant *Hypericum perforatum* L. was investigated for its cytotoxic potential against leukemia K562 and U937 cells, brain glioblastoma cells LN229 and normal human astrocytes. It upregulated the expression of caspase-9 and caspase-3 in leukemia U937 cells and caspase-8 and caspase-3 in K562 cells (Hostanska et al. 2003). Authors concluded that hyperforin induced apoptosis via caspase-dependent mechanism. Myriadenolide isolated from *Alomia myriadenia* (Asteraceae) exhibited caspases regulated antiproliferative potential against human leukemia cells viz. lymphocytic (Jurkat) and monocytic (THP-1) (Souza-Fagundes et al. 2003). Investigations on apoptotic activity of Baicalein on human promyelocytic leukemia HL-60 cells were carried by Li et al. (2004). From the results, it was concluded that baicalein induced activation of caspase-3 activity which causes cleavage of poly-ADP-ribose polymerase resulting in DNA breakage/fragmentation which is the hallmark of apoptosis. *Coptis japonica* roots were evaluated for antiproliferative potential and results obtained showed that caspase 3 activity was enhanced. Downregulation in Bcl 2 expression and upregulation in Bax expression was also seen, when SNU-668 human gastric cancer cells were treated with *Coptis japonica* roots extract (Park et al. 2005). The incompletely ripened fruit of *Rubus coreanum* extract inhibited HT-29 cell growth. Aqueous extract induced apoptosis in HT-29 cells by enhancing the caspase-3 activity (Kim et al. 2005). Subapriya et al. (2005) reported that ethanolic neem leaf extract regulated Bcl-2 (downregulation) and Bim, caspase 8, caspase 3 expression (upregulation) and caused apoptosis in the hamster buccal pouch carcinoma. The crude extract of garlic caused apoptosis in Colo 205 cells through upregulation of caspase-3 activity (Su et al. 2006). Ito et al. (2006) isolated different carbazole alkaloids from *Murraya koenigii* and tested for antiproliferative potential in HL-60 cells and results demonstrated that three alkaloids (mahanine,

pyrayafoline-D and murrifoline-I) induced apoptosis in HL-60 cells via the mitochondria dependent pathway involving activation of the caspase-9/caspase-3. *Plocamium telfairiae* (Marine sea weed) methanol extract induced apoptosis via the caspase-dependent pathway in HT-29 cells (Kim JY et al. 2007). Dehydrocostus lactone, pure constituent from *Saussurea lappa* dose-dependently induced apoptosis in DU145 cells via upregulating caspases and modulated the expression of various apoptotic and anti-apoptotic proteins resulting in the cell death pathway (Kim et al. 2008). Chen et al. (2008) explored the mechanisms of apoptosis induced by (–)-anonnaine in human HeLa cancer cells and reported that apoptotic cell death resulted from upregulation of p53, Bax and caspases proteins.

Corosolic acid promoted cell death in HeLa cells in dose dependent manner. Results suggested the role of caspases involving mitochondrial pathway was responsible for cell death (Xu et al. 2009). Immature *Citrus grandis* Osbeck fruit extract was evaluated for apoptosis inducing ability in U937 human leukaemia cells. Activation of caspase-3 activity led to activation of mitochondria-mediated signaling pathway resulting in inducing apoptosis in leukaemia cells (Lim et al. 2009). *Crocus sativus* commonly known as Saffron (spice) was evaluated for apoptosis inducing ability in MCF-7 cells and reported that saffron induced apoptosis by the caspase-dependent pathway along with increased expression of Bax protein (Mousavi et al. 2009). Vatansever et al. (2010) investigated the apoptotic activity of propolis extracts on the MCF-7 cells. It was reported that it activated caspase-8, caspase-9 and caspase-6, thus causing death by caspase dependent pathway. Casearin L (Cas L), O (Cas O) and X (Cas X) and (–)-hardwickiic acid were isolated from *Casearia sylvestris* and tested for antiproliferative activity in human leukemia cell lines viz. HL-60, K-562, and CEM (Ferreira et al. 2010). Cas X was found to be most potent antiproliferative constituent that stimulated apoptosis in HL-60 involving effector caspases 3/7 and loss of mitochondrial membrane potential. This has the potential to be used for cancer chemoprevention studies for development of anticancer drugs. The *Sapindus rarak* DC extract caused cell death in A549 cells via the caspase dependent pathway involving caspase 3 and 9 upregulation (Kummalu et al. 2011). The antiproliferative activity of the chloroform fraction of *Psidium*

cattleianum Sabine leaf extract was analyzed in SNU-16 (human gastric cancer cell line). Findings showed that this fraction targeted various mechanisms which resulted in caspase upregulation leading to apoptosis in SNU-16 cells (Moon et al. 2011). They further identified ferulic acid, genistein, 3', 4', 5' trimethoxy flavone, phlorizin, and oleanolic acid which might be responsible for the above activities. Dandelion root extract induced apoptosis in human leukemia cells (Jurkat) via upregulation of caspase 8 and caspase 3 expression (Ovadjie et al. 2011).

Pyranocycloartobioxanthone A isolated from *Artocarpus obtusus* induced cell death of MCF-7 cells. It induced apoptosis by modulating Bcl 2 (increased expression) and Bax (decreased expression) protein expressions resulting in stimulation of cytochrome c release which initiated the caspases cascade leading to apoptosis. NF- κ B was also reported to be involved in inducing apoptosis by Pyranocycloartobioxanthone A (Mohan et al. 2012). The apoptosis inducing potential of ethyl acetate extract of *Memecylon edule* leaves in MKN-74 and NUGC (gastric cancer cell lines) was investigated by Naidu et al. (2013). Extract treatment caused cytochrome c release, mitochondrial membrane potential loss, upregulation of caspase 3, decreased expression of Bcl-2 which pointed out the involvement of The intrinsic pathway in inducing apoptosis. *Cyathula prostrata* extract caused apoptosis in Hela and U937 cells by the extrinsic apoptotic pathway via upregulating the expression of caspase 8 and cell cycle arrest at G0/G1 phase of the cell cycle (Schnablegger et al. 2013). Ramasamy et al. (2013) studied the apoptosis inducing potential of different extracts obtained from the leaves of the endemic plant *Phyllanthus watsonii* Airy Shaw (Phyllanthaceae) on MCF-7 human breast cancer cells. Findings suggested that *P. watsonii* induced cytotoxic effects via modulating expression of proteins like caspase 3 and arresting growth of MCF-7 cells in S phase of cell cycle. White tea (*Camellia sinensis*) showed antiproliferative effects in HT-29 cells. It was observed that HT-29 cells on treatment with White tea extract demonstrated upregulation of caspase-3, -8, and -9 (Hajiaghaalipour et al. 2015).

Phytoconstituents as AP-1 inhibitors

AP-1 (activating protein-1) is a sequence-specific transcription factor made up of Jun, Fos, ATF and

some Maf proteins which forms homodimers and heterodimers (Angel et al. 1987; Bohmann et al. 1987; Vogt and Bos 1990; Angel and Karin 1991; Shaulian and Karin 2001). Heterodimers include the member of the Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra-1 and Fra-2) families. However, homodimers are made up of Jun–Jun proteins. About 18 different combinations of Jun & Fos proteins undergo dimerization to produce AP-1 transcription factor. Earlier, it was known by the name “12-O-tetradecanoylphorbol-13-acetate” (TPA) inducible transcription factor as it binds to TPA response element (TRE) (Angel et al. 1987). Cellular proliferation, differentiation, apoptosis, genes activation are regulated by AP-1. Various stimuli activate AP-1 factor such as stress condition, growth factors, UV radiation, hormones, alkylating agents and other pathological conditions. It may also be involved in malignant transformation and development of cancer. AP-1 can promote apoptosis as well as survival depending on its post translational modifications and various interacting factors. MAPK (mitogen-activated protein kinases) are also found to be implicated in the regulation of AP-1 transcription factor (Huang et al. 1998; Dorai and Aggarwal 2004). Mitogen activated protein kinases (MAP kinases) are identified as proline-directed serine/threonine kinases responsible for passing extracellular signals to nucleus. MAP kinases require phosphorylation at both threonine and tyrosine residues i.e. dual phosphorylation for their activation. ERK, JNK, and p38 are three signaling molecules of MAP kinases characterized in mammalian cells. Activated MAPK phosphorylates various transcription factors which in-turn modulate expression of various genes (Cano and Mahadevan 1995; Kyriakis and Avruch 1996; Chen et al. 1996; Whitmarsh and Davis 1996). One of the targets of MAP kinases signaling cascade is AP-1. Numerous plant constituents (Curcumin, Parthenolide, Quercitrin, Sulforaphane, Maslinic acid and Berberine) exhibited potential to modulate expression of AP-1 and MAP kinases (Tables 1, 2; Fig. 1)

Han et al. (2002) showed curcumin as a potential inhibitor of TPA-induced activation of NF- κ B and AP-1 which points toward chemopreventive potential of curcumin. Apple peel extracts possessed a potential to suppress the AP-1 activation in tumorigenesis (in vivo as well as in vitro). Regulation of AP-1 along with other signaling molecules such as MAP kinases, ERKs and JNK suggesting potential

of apple peels as good candidate for cancer chemoprevention (Ding et al. 2004). Fresh blackberry extracts were tested for antiproliferative potential against A549 cells and inhibition of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced neoplastic transformation. Authors reported that blackberry extract inhibited cancer cell proliferation and prevented neoplastic proliferation by inhibiting AP-1 and MAPK activation (Feng et al. 2004). Won et al. (2004) reported anticancer effects of Parthenolide (major sesquiterpene lactone) found in *Tanacetum parthenium* and reported the suppression of AP-1 and mitogen-activated protein kinases (MAPK). Dickinson et al. (2009) were first to report that Sulforaphane downregulates AP-1 activity in UVB-induced squamous cell carcinoma in mouse. Results pointed that inhibition of AP-1 activity by Sulforaphane can be used as a target for prevention of squamous cell carcinoma.

Cinnamon extract showed an antiproliferative potential in different cancer cell lines in vitro and also inhibited melanoma progression in vivo. The extract inhibited the growth of cancer via inhibiting NF-κB and AP1 and modulating expression of anti-apoptotic and proapoptotic genes (Kwon et al. 2010). Ding et al. (2010) studied the inhibitory potential of quercitrin on tumor promotion in mouse JB6 cells and explored the molecular mechanism involved in inducing chemopreventive activity. It was demonstrated that inhibition of MAPKs, AP-1, NF-κB signaling pathways and activation of antioxidant system might be responsible for the chemopreventive activity. Maslinic acid, a triterpenoid suppressed COX-2 expression and also inhibited binding activity of NF-κB and AP-1 in Raji cells. Researchers concluded that NF-κB and AP-1 signaling pathways might be responsible for the suppression of COX-2 (Hsum et al. 2011). Mahata et al. (2011) carried out investigations on berberine (an alkaloid) regarding its effect on Human Papilloma virus 16 (HPV16)-positive cervical cancer cell line (SiHa) and HPV18-positive cervical cancer cell line (HeLa). Berberine efficiently inhibited AP-1 along with obstructing the expression of viral oncoproteins E6 and E7. Thus AP-1 down-regulation by berberine might be accountable for the anti-HPV effect. 1α, 25-dihydroxyvitamin D3 was evaluated for anticancer effects in MCF-7 and tamoxifen-resistant MCF-7/TAM^R-1, MCF-7/TAM^R-4,

MCF-7/TAM^R-7, MCF-7/TAM^R-8 cells and reported that the compound induced antiproliferative effects via inhibiting the NF-κB pathway (Lundqvist et al. 2014).

Phytoconstituents as ROS inducers

Reactive oxygen species are of two types (a) radicals (hydroxyl radicals, superoxide anion radicals, alkoxyl radicals, nitrosyl radicals etc.), (b) non radicals [hydrogen peroxide, organic hydroperoxides (ROOH), hypochlorous acid (HOCl) etc.]. These ROS are usually generated as a result of various metabolic actions occurring in the cell. It has been seen that at low concentration, they take part in signaling processes while in pathological condition (excessive production), they may damage different biomolecules including DNA, proteins, lipids etc. (Circu and Aw 2010; Halliwell and Cross 1994; Simon et al. 2000). There are several organelles in the cells which account for ROS generation as mitochondria, endoplasmic reticulum and peroxisomes (Ames et al. 1993; Turrens 2003; Fritz et al. 2007; Zangar et al. 2004). Any perturbation in DNA resulting from oxidative stress leads to the induction of various signaling pathways by causing changes in different key regulatory proteins. Oxidative stress may also result in carcinogenesis (Klaunig and Kamendulis 2004; Guyton et al. 1996; Bae et al. 1997; Manna et al. 1998; Kong et al. 2000; D'Autreaux and Toledano 2007; Szatrowski and Nathan 1991; Petros et al. 2005). Generally, the level of ROS in cancerous cells is higher than that of normal cells. Further, ROS enhancement up to lethal levels can cause cell death. Certain plant products possess potential to induce ROS generation associated with a decrease in mitochondrial membrane potential followed by release of apoptogenic proteins into cytosol which causes caspases cascades leading to apoptosis (Schumacker 2006; Jeong and Seol 2008; Fruehauf and Meyskens 2007; Vercesi and Hoffman 1993; Conklin 2004; Pelicano et al. 2004; Behrend et al. 2003; Kirshner et al. 2008; Circu and Aw 2010; Simon et al. 2000). As ROS targets cancer cells by inducing apoptosis, this strategy can be used in anticancer therapies (Fig. 5). Several natural plant constituents (Cinnamaldehyde, 6-Methoxydihydrosanguinarine, Pancratistatin, Eugenol, Gallic acid, Curcumin,

Fig. 5 Role of reactive oxygen species in apoptosis

Butein, Icariin, Actinodaphnine, Saikosaponin-a & d, Flavokawain B, Plumbagin, β -Caryophyllene oxide, Goniotalamin, (–)-Epigallocatechin-3-gallate, Herbacetin and Piperlongumine) have been reported to induce apoptosis by ROS mediated mechanism (Tables 1, 2; Fig. 1).

Ka et al. (2003) examined the potential of cinnamaldehyde for anticancer effects in human promyelocytic leukemia cells. It has been found that cinnamaldehyde caused massive ROS accumulation which altered mitochondrial membrane permeability resulting in cytochrome c release initiating a signaling cascade causing cell death. *Annona squamosa* seed extracts were investigated for tumor inhibitory potential in rat histiocytic tumor cell line (AK-5). Treatment with extracts modulated the expression of various proteins as Bcl-2 and Bcl_{xL} (upregulated) and caspase-3 (downregulated) along with the generation of ROS which were involved in a signaling cascade inducing apoptosis (Pardhasaradhi et al. 2004). 6-Methoxydihydrosanguinarine, a benzophenanthridine alkaloid from *Hylomecon* species was tested for apoptosis inducing ability in HepG2 cells. Apoptotic effects induced in hepatocellular carcinoma cells by 6-methoxydihydrosanguinarine was due to excess generation of reactive oxygen species. Further,

preincubation of HepG2 cells with vitamin C lowered down the expression of p53 and bax levels, inhibited the release of cytochrome c and the whole signaling cascades preventing cell death inducing effects by 6-methoxydihydrosanguinarine (Yin et al. 2005). Pancratistatin, a phytochemical from Spider lily (*Pancratium littorale*) was found to induce apoptosis specifically in Human Neuroblastoma (SHSY-5Y) cells. The compound targeted mitochondria as revealed by detailed studies done regarding mitochondrion membrane potential, ROS generation and ATP concentration. Comet assay results showed that SHSY-5Y cells on treatment with pancratistatin showed apoptotic DNA cleavage (McLachlan et al. 2005)

Yoo et al. (2005) reported that eugenol isolated from *Eugenia caryophyllata* increased ROS accumulation which in turn altered mitochondrial membrane potential leading to cytochrome c release resulting in activating signaling cascade causing apoptosis in HL-60 cells. Actinodaphnine, an aporphine alkaloid from *Cinnamomum insularimontanum* was examined for inducing apoptosis in human hepatoma Mahlavu cells. Findings suggested that ROS and NO may be responsible for the altered mitochondrial membrane potential which in turn activates caspases 3 and 7 resulting in

cell death. It also decreased the expression of NF- κ B (Hsieh et al. 2006). Apoptosis in HeLa cells was induced by ether extract from *Cremanthodium humile* by altering mitochondrial membrane potential leading to the release of cytochrome c from mitochondria resulting in the upregulation of caspase-3/7 and -9. Reactive oxygen species (ROS) were also accumulated in HeLa cells upon treatment with extract which suggests apoptotic cell death of HeLa cells through a ROS regulated mitochondria dependent pathway (Li et al. 2007). Mishra et al. (2008) evaluated *Rhodiola imbricata* aqueous extract for antiproliferative activity in K-562 (human erythroleukemia cell line). The extract decreased cell growth after 72 h incubation in K-562 cell line but no cytotoxicity was noticed in normal human peripheral blood lymphocytes or mouse macrophage cell line RAW-264.7. Treatment with extract stimulated intracellular ROS generation in K-562, which can be the possible cause for apoptotic cell death. Thayyullathil et al. (2008) investigated curcumin for inducing apoptotic cell death pathways in mouse fibroblast L929 cells. Results pointed that ROS generation is responsible for curcumin-induced apoptosis via targeting caspases dependent/caspases independent apoptosis in L929 cells. Gallic acid isolated from *Toona sinensis* leaf extracts was examined for anticancer effects in DU145 prostate cancer cells. Mechanistic analysis of apoptotic pathway revealed that gallic acid inhibited growth of DU145 prostate cancer cells by accumulating reactive oxygen species (ROS) and mitochondria-mediated signaling. It also exhibited synergism with doxorubicin in causing apoptosis. Studies are required to exploit gallic acid for prostate cancer treatment (Chen et al. 2009). Liu et al. (2009) reported that Polygonatum cyrtonema lectin (mannose/sialic acid-binding lectin) suppressed the growth of cancerous cells (human melanoma A375 cells) via mitochondrial mediated ROS accumulation and p38-p53 activation pathway. Butein (3,4,2',4'-tetrahydroxychalcone) was investigated for antiproliferative activity in two hepatoma cancer cell lines (HepG2 and Hep3B) and concluded that cell cycle arrest in G2/M phase, ROS production, JNK activation along with modulation of other proteins were responsible for butein induced apoptosis (Moon et al. 2010). Li S et al. (2010) investigated Icarin, a flavonol glycoside for antiproliferative potential against SMMC-7721 cells (human hepatoma cell line). The authors concluded that apoptosis

induction by Icarin was regulated by ROS generation and JNK activation which in-turn is responsible for activation of the mitochondrial cell death pathway. Furthermore, when Icarin was administered to the mice, it significantly suppressed the growth of tumors induced by SMMC-7721 cells in a nude mouse.

Saikosaponin-a and -d found in *Bupleurum radix* were investigated for chemosensitization effect on the cytotoxicity induced by cisplatin in two cervical cancer cell lines (HeLa and SiHa), an ovarian cancer cell line (SKOV3) and non-small cell lung cancer cell line (A549). Results demonstrated that various combinations of cisplatin and both saikosaponins synergistically sensitized cancer cells to cisplatin via ROS regulated cell death (Wang et al. 2010). A novel chalcone Flavokawain B isolated from *Alpinia pricei* Hayata was found to inhibit the proliferation of colon cancer cells (HCT116). It has been found that Flavokawain B effectively induced apoptosis through ROS generation and upregulation of GADD153 which stimulated mitochondria dependent apoptosis by modulating expression of Bcl-2 family proteins (Kuo et al. 2010). Xu and Lu (2010) elucidated that plumbagin checked tumor growth in acute promyelocytic leukemia mouse model (NB4 tumor xenograft in NOD/SCID mice). Further, it was noticed that it did not induce any toxicity and ROS played a chief role in inducing mitochondria-dependent apoptosis of tumor cells.

Sun and Mckallip (2011) reported that Plumbagin induced apoptosis in human K562 leukemia cells via enhancing ROS generation and increased expression of the TRAIL (TNF-related apoptosis-inducing ligand) receptor. *n*-Butanol fraction of *Codonopsis lanceolata* was tested against human colon cancer HT-29 cell for antiproliferative activity and induction of apoptosis. The fraction stimulated ROS accumulation, polyamine depletion and activated JNK in turn initiating mitochondrial apoptotic signaling pathway via modulating Bax/Bcl-2 proteins (Wang et al. 2011). Investigations on the β -caryophyllene oxide (CPO), a sesquiterpene isolated from essential oils of medicinal plants to inhibit human prostate (PC-3) and breast (MCF-7) cancer cells proliferation has been carried out by Park et al. (2011). Findings obtained from the study demonstrated that β -Caryophyllene oxide suppressed the constitutive PI3K/AKT/mTOR/S6K1 signaling cascades, upregulated ROS-mediated MAPKs leading to apoptotic cell death. It also decreased the expression of different genes involved in cell

proliferation (cyclin D1), survival (bcl-2, bcl-xL, survivin, IAP-1, and IAP-2), metastasis (COX-2), angiogenesis (VEGF), and enhanced p53 and p21 expressions. Studies were carried out to evaluate the gugulipid extract of medicinal plant (*Commiphora mukul*) for anticancer potential against prostate cancer using cancer cell line LNCaP (androgen-dependent) and its androgen-independent variant (C81) (Xiao et al. 2011). Gugulipid was found to be a potent inhibitor of prostate cancer cells. It was seen that the extract caused ROS-dependent apoptosis in prostate cancer cell lines mediated by JNK signaling pathway. Anticancer effects of the fruits of *Luffa echinata* Roxb. (LER) against HT-29 (human colon cancer cells) were explored by Shang et al. (2012). Results showed that treatment with extract alters the level of Bax and Bcl-2 genes and induced high level of ROS in cells which points that reactive oxygen species may be responsible for induction of apoptosis. Growth inhibitory potential of goniotalamin on the Ca9-22 oral cancer cell line were tested by Yen et al. (2012). Results obtained from this study demonstrated that goniotalamin inhibited growth via ROS induction, DNA damage and mitochondria dysfunction and further studies are required to tap the potential of goniotalamin for the development of a drug against oral cancer.

Green tea polyphenol, (–)-Epigallocatechin-3-gallate exhibited antiproliferative activity in human endometrial cancer cells (Ishikawa cells) and primary endometrial adenocarcinoma cells. ROS and p38 MAP kinase pathway activation and inhibition of ERK activation play a critical role in (–)-Epigallocatechin-3-gallate induced apoptosis (Manohar et al. 2013). Herbacetin (flavonoid) from *Ramose Scouring Rush* Herb was assessed for apoptosis inducing ability in HepG2 cells. Herbacetin induced apoptosis in HepG2 cells by PI3K/Akt and ROS-mediated mitochondria-dependent pathway (Qiao et al. 2013). Dhillon et al. (2014) studied the effect of Piperlongumine on pancreatic cancer cells in vivo as well as in vitro. The authors reported that the compound effectively inhibited growth of cancer cells via the mechanism of increased ROS generation and DNA damage.

Phytoconstituents as cell cycle inhibitors

Cell cycle is one of the most important processes responsible for growth. Equilibrium exists between

apoptosis (cell death) and cell division (proliferation) under normal physiological conditions which maintain normal number of cells. Any irregularity in these two processes i.e. apoptosis and cell division may lead to abnormal growth leading to less growth (atrophy) or tumor formation (hyperplasia). All the events occurring in the cell cycle are being controlled by the cell cycle check points occurring at the G1/S phase boundary, in the S phase, and during the G2/M phases. These check points prevent any perturbation that may result during cell cycle. The cyclin dependent protein kinases (CDKs) and the cyclins are proteins that act as key players in controlling and regulating cell cycle. CDKs work in the presence of activating subunits (cyclins) by phosphorylation on threonine/tyrosine residues and are activated at precise points of the cell cycle (MacLachlan et al. 1995; Donzelli and Draetta 2003; Peters 2002). There are nine different types of CDK's which are known to us, out of these only five are found to be active during different phases of the cell cycle [G1 (CDK4, CDK6 and CDK2), S (CDK2), G2 and M (CDK1)] (Vermeulen et al. 2003). Expression of various proteins such as CDKs, CDK activating proteins, check point proteins and cyclins is disturbed in the cancer cells (Sherr 1996; McDonald and El-Deiry 2000). Regulation of expression of these proteins and the cell cycle arrest can be used as potential target for cancer prevention. Phytoconstituents were found to arrest cell cycle and to suppress growth of cancer cells (Tables 1, 2). A pure lectin (AMML) was isolated from *Astragalus mongholicus* roots and tested against the human cervical carcinoma cell line (HeLa), humanosteoblast-like cell line (MG63) and human leukemia cell line (K562) for antiproliferative and apoptotic effects. Interesting results were obtained in case of the HeLa cell line with 92 % inhibition of cell growth. It has been observed that AMML-treated HeLa cells showed typical features of apoptosis. The authors provided a first report that AMML treatment induced cell cycle arrest at S phase in HeLa cell (Yan et al. 2009).

Ren et al. (2006) studied rhodoxanthin from *Potamogeton crispus* L. for anticancer activity in HeLa cells. Rhodoxanthin inhibited growth of HeLa cells by arresting S phase of cell cycle. Rhodoxanthin treatment altered the mitochondria transmembrane potential and also increased intracellular Ca^{2+} ions which play a crucial role in inducing apoptosis in HeLa cells. Wu et al. (2009) evaluated *Physalis*

peruviana L. extracts for inducing anticancer effects in human lung cancer H661 cells. One of the extract named SCEPP-5 caused cell cycle arrest at S phase and regulated the expression of Bax and XIAP proteins. SCEPP-5 also affected p53 protein expression, induced cytochrome c release, caspase-3 activation and PARP cleavage which are known to play a role in apoptosis. Brohem et al. (2009) investigated 4-nerolidylcatechol (4-NC), a compound from *Potho-morphe umbellate* for apoptosis inducing potential in melanoma and dermal fibroblast cell lines. 4-NC inhibited growth of cells and induced apoptosis. It also caused G1 cell cycle arrest, suppressed invasiveness and decreased MMP-2 activity in melanoma cell lines. *Berberis lycium* Royle extracts and its alkaloids (berberine and palmatine) were evaluated for antiproliferative activity in p53-deficient HL-60 cells (Khan et al. 2010). Berberine and the BuOH extract found to be quite effective in inhibiting growth of HL-60 cells. Both samples, Berberine and the BuOH extract arrested the growth of cells in S-phase of cell cycle. They also modulated the expression of various proteins such as Chk2, Cdc25A and Cdc2 (CDK1). Cells treated with both samples showed downregulation of cyclin D1 gene expression and acetylation of α -tubulin. Experimental results suggested that berberine and its extract possessed potent antiproliferative and apoptotic inducing ability which can further be exploited in cancer chemoprevention.

The anti-cancer potential of Wuzhimaotao (*Ficus hirta* Vahl.) was investigated (Zeng et al. 2012) and it was observed that different extracts affected cell viability and morphology. HeLa cells treated with the extracts showed sub-G1 phase increase analysed by flow cytometry. These results suggested that Wuzhimaotao extracts could be used as an agent in development of anticancer drug against HeLa cells. Mechanistic studies were carried out to explore mechanism via which hexane extract fraction of *Tinospora cordifolia* induced apoptotic cell death in Ehrlich ascites tumor (EAT) in mice (Thippeswamy and Salimath 2007). Extract treatment activated caspase-3 and arrested G1 phase of cell cycle. Treatment with the extract also regulated the expression of proapoptotic (Bax increased) and anti-apoptotic genes (Bcl-2 decreased). The pericarp of *Pistacia atlantica sub kurdica* (Baneh) showed anticancer effects in human colon carcinoma HT29 cells. Exposure of cells to Baneh extract resulted in

lowering of cyclin A protein expression leading to S phase delay in cell cycle progression (Rezaei et al. 2012). Alkaloids Haemanthamine and Haemanthidine were evaluated for apoptosis inducing activity in p53-null Jurkat cells. Treatment of cells with both compounds caused the accumulation of cells at G1 and G2 phases of the cell cycle. They also upregulated the expression of p16 and Chk1 Ser345 phosphorylation (Havelek et al. 2014). Lin et al. (2013) reported that Capsaicin caused apoptosis and cell cycle arrest at G2/M phase in KB cancer cells. KB cells on treatment with Capsaicin showed activation of caspases 3 and 9 along with loss of mitochondrial membrane potential and PARP cleavage in the treated cells.

Conclusions

The studies carried out by the researchers all over the globe in the field of cancer chemoprevention have reiterated the use of natural plant products in traditional system of medicine as in Ayurveda against several diseases including cancer. Research has shown the potential of various phytoconstituents in combating cancer as besides targeting multiple cell signaling pathways, also show less side effects and are inexpensive in comparison to synthetic drugs. Further, studies are required to formulate formulations using natural products, based on their molecular targets for their effective use as chemotherapeutic and/or chemopreventive agents.

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Conflict of interest The authors declare that they have no conflict of interest.

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