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Plant-derived anticancer agents: A green anticancer approach

Javed Iqbal[1], Banzeer Ahsan Abbasi[1], Tariq Mahmood[1*], Sobia Kanwal[2], Barkat Ali[1], Sayed Afzal Shah[1], Ali Talha Khalil[3,4,5]

[1]*Department of Plant Sciences, Quaid-i-Azam University Islamabad, 45320, Pakistan*

[2]*Department of Zoology, University of Gujrat, Sub Campus Rawalpindi, Pakistan*

[3]*Department of Eastern Medicine and Surgery, Qarshi University, Lahore, Pakistan*

[4]*UNESCO UNISA Africa chair in nanoscience and nanotechnology, South Africa*

[5]*Nanosciences African Network (NANOAFNET), South Africa*

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ABSTRACT

Cancer is a frightful disease and represents one of the biggest health-care issues for the human race and demands a proactive strategy for cure. Plants are reservoirs for novel chemical entities and provide a promising line for research on cancer. Hitherto, being effective, chemotherapy is accompanied by certain unbearable side effects. Nevertheless, plants and plant derived products is a revolutionizing field as these are Simple, safer, eco-friendly, low-cost, fast, and less toxic as compared with conventional treatment methods. Phytochemicals are selective in their functions and acts specifically on tumor cells without affecting normal cells. Carcinogenesis is complex phenomena that involves many signaling cascades. Phytochemicals are considered suitable candidates for anticancer drug development due to their pleiotropic actions on target events with multiple manners. The research is in progress for developing potential candidates (those can block or slow down the growth of cancer cells without any side effects) from these phytochemicals. Many phytochemicals and their derived analogs have been identified as potential candidates for anticancer therapy. Effort has been made through this comprehensive review to highlight the recent developments and milestones achieved in cancer therapies using phytomolecules with their mechanism of action on nuclear and cellular factors. Furthermore, drugs for cancer treatment and their limitations have also been discussed.

1. Cancer: a global menace

Cancer is a severe metabolic syndrome and is one of the leading cause of death regardless of developments in the tools of disease diagnosis, treatment and prevention measures [1–3]. Cancer is one of the principal causes of mortality and morbidity around the globe and the number of cases are constantly increasing estimated to be 21 million by 2030 [4,5]. It is estimated that in 2017, the United States alone will have approximately 1 688 780 new cancer diagnoses cases and 600 920 cancer deaths [6]. This uncontrolled proliferation of a normal cell which produces genetic instabilities and alterations accumulates within cells and tissues which transforms normal cell into a malignant cell. These genetic instabilities include mutations in DNA repair genes (*p21, p22, p27, p51, p53* and tool box for DNA), tumor suppressor genes (*p53, NF1, NF2, RB* and biological breaks), oncogenes [*MYC*, *RAF*, *Bcl-2*, *RAS* (biological accelerators)] and genes involve in cell growth metabolism. Both external factors (radiations, smoking, tobacco, pollutants in drinking water, food, air, chemicals, certain metals and infectious agents) and internal factors (genetic mutations, body immune system and hormonal disorders) can cause cancer [7]. There are several types of cancer in human being; among these the lung cancer is reported the top listed in male followed by breast cancer in female [8,9]. Detailed information about several forms of cancer is given in Table 1. It is a major public health burden in both developing and developed countries being treated by medicinal plants as a whole or by their phytochemicals very frequently [10,11].

Previously, around 10.9 million new cancer cases, 24.6 million persons living with cancer, 6.7 million deaths reported

*Corresponding author: Tariq Mahmood, Department of Plant Sciences, Quaid-i-Azam University Islamabad, 45320, Pakistan.
Tel: +92-5190643050
E-mail: tmahmood.qau@gmail.com (T. Mahmood).

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around the world each year [12]. Based on World Health Organization data, above 14.1 million new cancer cases and 8.2 million deaths were mentioned globally in the year 2012 and over 70% new cancer cases has been estimated during the next twenty years [13–15]. Nearly, 80% of the world's population depend on traditional medicines and more than 60% of clinically approved anticancer drugs are derivatives of these medicinal plant [16,17]. According to literature survey, there are many anticancer drugs clinically approved and are recommended for the cancer treatment [18,19].

Among these different forms of cancer, lung cancer is reported the most in male followed by breast cancer in female. The information is gathered from the cancer stat facts (https://seer.cancer.gov/statfacts/more.html) and cancer statistics (2017) by Siegel.

2. Drugs for cancer treatment and their limitations

A large number of efforts have been made to minimize the harmful side effects of drugs during the process of cancer therapy like preventing the side effects on the nearby cells and tissues, increasing drug accumulation and efficacy in the lesion, developing novel drug delivery and targeting systems [20]. There are so many other methods for the treatment of cancer like they involve surgery of tumor, radiotherapy, immunotherapy, chemotherapy, cancer vaccinations, photodynamic therapy, stem cell transformation or combination thereof often accompanied by severe side effects. Such side effects include limited bioavailability, toxicity, nonspecificity, fast clearance and restriction in metastasis [21,22]. Treatment methods depend upon the cancer type, stage and location. Chemotherapeutic agents involve cytostatic and cytotoxic drugs which have shown promising results alone or in combination with other cancer therapies. These chemotherapeutic agents involve topoisomerase inhibitors [*e.g.* irinotecan (side effects include: neutropenia, sensory neuropathy, and diarrhoea) and doxorubicin (side effects include cardiotoxicity), alkylating agents *e.g.* oxaliplatin, melphalan, carboplatin, cisplatin and cyclophosphamide (side effects include: nephrotoxicity, gastrointestinal toxicity, cardiovascular toxicity, pulmonary and hematologictoxicity), microtubules acting agent *e.g.* vincristine, vinblastine, docetaxel and paclitaxel *etc.*] [18,23]. The above mentioned drugs are highly effective against a wide range of cancers, but these drugs are also having some limitations (side effects, expensive, very complex, not eco-friendly and toxic). There are cells in our body which multiply rapidly under normal physiological conditions like hair follicle cells, bone marrow cells and digestive tract cells *etc*., These present anticancer drugs also target these rapidly dividing normal cells which is a big challenge thus, harmful side effects arise. Due to these side effects there is decreased blood production, GIT inflammation, hair loss, immunosuppression, heart diseases and nervous disorders may arise. Another limitation is that these cancer cells resist to these drugs as they go through mutations. *e.g.*, Drug resistant genes (*ABCA4* and *ABCA12*) were over-expressed in human MCF-7 breast cancer cells respectively when docetaxel was applied. However, when phytochemical curcumin was applied in association with docetaxel down regulation of drug resistance genes was observed [24]. Thus, treating cancer cells by employing mono-target chemical agent is not an effective method. Therefore, based on extensive research findings, phytochemicals and their derived analogues possess most promising option for the better and less toxic cancer treatment [19].

Table 1
Organ based different forms of cancers and estimated new cancer cases and deaths by 2017.

S.No.	Cancer type	Estimated new cases in 2017	Estimated deaths in 2017
1	Bladder cancer	79 030	16 870
2	Lung cancer	222 500	155 870
3	Larynx cancer	13 360	3 660
4	Non-Hodgkin lymphoma	72 240	20 140
5	Oral cavity cancer	49 670	9 700
6	Liver cancer	40 710	28 920
7	Cervical cancer	12 820	4 210
8	Kidney cancer	63 990	14 400
9	Ovary cancer	22 440	14 080
10	Endometrial cancer	61 380	19 920
11	Colon and rectum cancer	135 430	50 260
12	Anal cancer	8 200	1 100
13	Brain & nervous system cancer	23 800	16 700
14	Testis cancer	8 850	410
15	Melanoma (Skin)	87 110	9 730
16	Testis cancer	8 850	410
17	Leukemia	62 130	25 500
18	Stomach cancer	28 000	10 960
19	Prostate cancer	161 360	26 730
20	Bone and joint	3 260	1 550
21	Breast cancer	252 710	40 610
22	Oral cavity & pharynx	49 670	9 700
23	Thyroid cancer	56 870	2 010
24	Pancreas cancer	53 670	43 090
25	Small intestine	10 190	1 390
26	Hodgkin lymphoma	8 260	1 070
27	Esophagus cancer	16 940	15 690
28	Myeloma	30 280	12 590

3. Current cancer therapy via phytochemicals: a novel approach

Medicinal plants serve as nature's gift to humans to help them pursue better health. Plants and their bioactive compounds are in medicinal practices since ancient times. Several medicinal plant species and their phytochemicals inhibit the progression and development of cancer [24]. It has been researched that plant kingdom comprised of approximately 250 000 plant species and only around 10% have been studied for treatment of different diseases. Phytochemicals and their derived analogues are present in different parts of the plant, *e.g.,* flower, flower stigmas, pericarp, sprouts, fruits, seeds, roots, rhizomes, stem, leaf, embryo, bark and perform several pharmacological functions. Several plant products such as alkaloids, flavonoids, lignans, saponins, terpenes, taxanes, vitamins, minerals, glycosides, gums, oils, biomolecules and other primary and secondary metabolites play significant roles in either inhibiting cancer cell activating proteins, enzymes and signaling pathways [Cdc2, CDK2 and CDK4 kinases, topoisomerase enzyme, cycloxigenase and COX-2 (Cycloxigenase), Bcl-2, cytokines, PI3K, Akt, MAPK/ERK, MMP, TNK, mechanistic target of rapamycin (mTOR) (detailed information in Figure 1)] or by activating DNA repair mechanism (*p21, p27, p51, p53* genes and their protein products), Bax, Bid, Bak proteins, stimulating the formation of protective enzymes (Caspase-3, 7, 8, 9, 10, 12), inducing antioxidant action (antioxidant enzymes

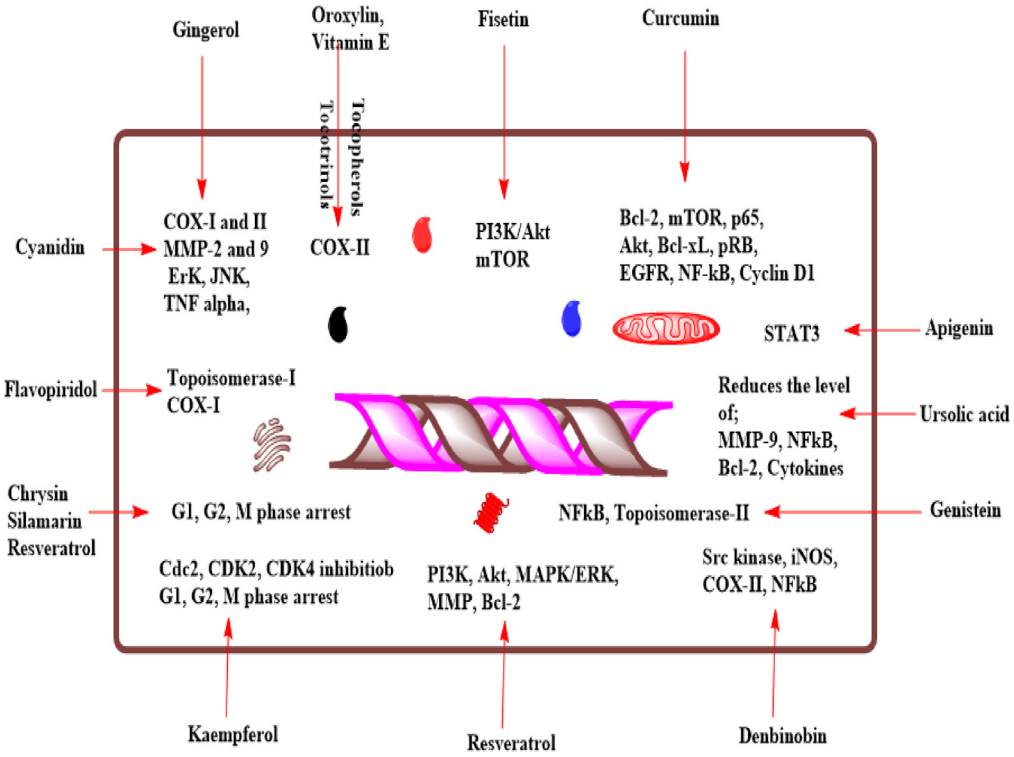

Figure 1. Impact of anticancer phytochemicals after activating expression of various genes, proteins, enzymes and signaling cascades in order to block cancer initiation and progression.

e.g. GSH, GST and GPxn), thus showing strong anticancer effects in terms of their efficacy on the above mentioned proteins, enzymes and signaling pathways (detailed information in Figure 2) [15,25]. Detailed information about these medicinal plants, family, part used and specific type of anticancer phytochemical and their mechanism of action against particular type of cancer is given in Table 2. Furthermore, the generalized model of carcinogenesis, anti-cancer mechanism of body and natural phytochemicals against cancer is discussed (Figure 3). Literature for 2010–2017 was thoroughly reviewed from ISI web of knowledge. The results are given in Figure 4.

3.1. Vinca alkaloids

Vinca alkaloids (VA) are a versatile group of phytochemicals isolated from *Catharanthus roseus* (*C. roseus*) (Apocynaceae) and are employed in the theraphy of several type of cancer namely, breast, liver, leukemia, testes lung cancer. The four main VA in use are, vinorelbine, vindesine, vincristine and vinblastine [158]. The vinca alkaloids (vincristine and vinblastine) bind a specific site termed as tubulin heterodimers (vinca-binding site) disrupting the functions of microtubules or by arresting cell cycle at metaphase [159]. Currently, semi-synthetic derivatives of vinca alkaloids are vinorelbine, vindesine, vinfosiltine and vinovelbine which have been introduced in the market. These derivatives are used alone or in combination with other phytochemicals agents to fight against large number of cancers [160]. According to a scientific report, almost 64 cultivars of *C. roseus* were screened for vinca alkaloids where Cooler Rose Hot reported the highest level of serpentine alkaloids. In the near past, endophytic fungi cultured and isolated from *C. roseus* has been discovered as an alternative method for the production of the different vinca alkaloids [161].

3.2. Taxanes

Taxanes represent promising anticancer agents that act by binding to microtubules and has key role in cell division [161]. First-generation taxanes (*e.g.* docetaxel and paclitaxel) are strong anticancer agents in terms of their efficacy on its different molecular targets. Paclitaxel (taxol) was first extracted from the bark and leaf of *Taxus baccata* (*T. baccata)* and *T. canadensis*, *Corylus avellana* and is used to cure a wide range of cancers including ovarian, breast and lung cancer. Binding of paclitaxel with β-tubulin in the lumen of microtubules leads to decrease in microtubule dynamics and halt cell cycle at M phase while docetaxel, a semi synthetic derivative from *T. baccata* is primarily used in breast, pancreas, prostate and lung cancers therapies [161,162]. The primary mechanism of taxanes is to induce microtubule stabilization, apoptotic cell death and mitotic arrest [163]. Analogs of paclitaxel which are currently undergoing clinical trials include larotaxel, milataxel, ortataxel and tesetaxel. Larotaxel is used as alone or together with other therapies for urethral bladder, pancreatic, lung and breast cancer [164]. Furthermore, out of 2069 cancer clinical trials documented by the National Cancer Institute as of July 2004, 248 are taxane-derived drugs, containing 134 with paclitaxel, 105 with docetaxel and 10 with miscellaneous taxanes are used either alone or together with other anticancer agents [97]. Taxanes (paclitaxel, docetaxel) and its nuclear and cellular targets are given in Figure 2.

3.3. Campothecin derivatives

Campothecin (family of topoisomerase I poisons) is another class of plant derived clinically-active chemotherapeutic agents possesses strong anticancer potential inhibiting topoisomerase I

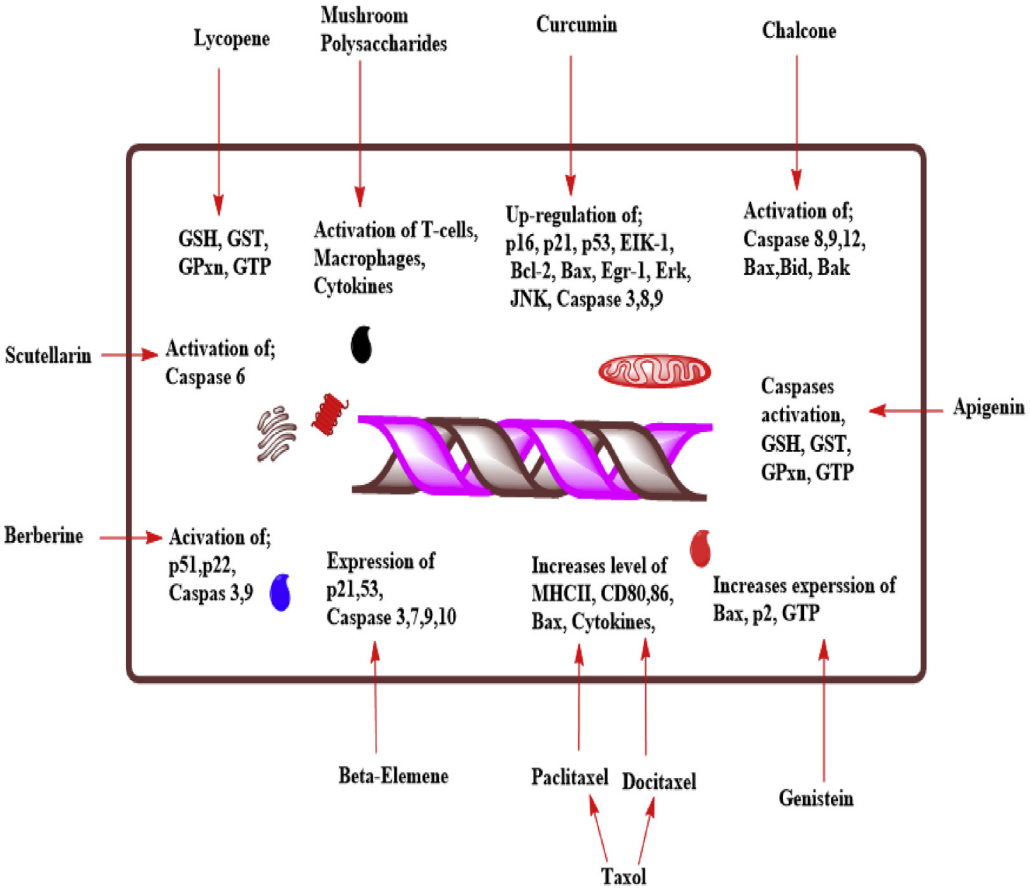

Figure 2. Impact of anticancer phytochemicals after inhibiting expression of various genes, proteins, enzymes and signaling cascades in order to block cancer initiation and progression.

in a large number of cancers [165]. It was first isolated from *Camptotheca acuminata* (Nyssaceae). The isolate of *Camptotheca acuminata* has been the only agent out of 1 000 different plant extracts screened out for anticancer activity which have shown efficacy and the active constituents isolated has been identified as camptothecin. Extensive research is performed by several research organizations for effective camptothecin derivatives like topotecan (hycamtin) and irinotecan, where irinotecan is used to treat colorectal cancer while topotecan is used to treat ovarian and lung cancer [166].

3.4. Cephalotaxus

Cephalotaxus alkaloids are also a multipurpose group of phytochemicals that are used against wide range of cancer including A-549 lung cancer, HeLa, SGC-7901 gastric cancer cell lines. They function by inhibiting protein synthesis and targeting the molecular events in synthesis of protein such as initiation of protein synthesis, release of nascent peptide, polyribosome degradation but do not have any effect on elongation of new peptide chain [167]. Harringtonine and isoharringtonine cephalotaxus alkaloids are anticancer agents isolated from *Cephalotaxus harringtonia*. Anticancer agent like homoharringtonine has been researched to treat large number of cancers including chronic and acute myelogenous leukemia [168]. In China, harringtonine in combination with homoharringtonine are successfully used for the treatment of chronic myelogenous leukemias, acute myelogenous leukemia [16]. The homoharringtonine also been approved by FDA for the treatment of chronic myelogenous leukemia in different countries around the world such as China, Japan, Pakistan, USA and Germany [169].

3.5. Colchicine

Colchicine is a natural bioactive compound isolated from *Colchicum autumnale* (Colchicaceae) and has been researched to treat several diseases like crystal arthritis, cirrhosis, gout *etc.* It binds permanently to tubulin, stabilizes microtubule formation, arrest cell cycle at different phases and induces apoptosis [170]. Unluckily, colchicine's action is not very specific and targets rapidly dividing normal cells and arrest their cell cycle. Therefore, semisynthetic derivatives (colchicinamide, deacetylcolchicine) of colchicine have been developed which are less toxic and are used for the treatment of variety of cancers including colorectal (HCT-116), chronic granulocytic leukemia, melanoma, central nervous system and breast cancers [50,161]. Colchicine shows toxicities and therefore is not recommended for the treatment of cancer disease. In recent years, *Gloriosa superba* in tropical regions reported to be vital source of colchicine [161].

3.6. Ellipticine

Ellipticine (topoisomerasellinhibitor) along with elliptine (now isoreserpiline) is also naturally occurring anticancer compound extracted from the stem, bark, leaf and root of *Bleekeria vitensis* and *Ochrosia elliptica*. These alkaloids are also found in *Aspidosperma*, *Ochrosia*, and several Apocynaceae members. The most significant DNA-damaging mechanisms of ellipticine

Table 2
List of some important medicinal plants and their phytochemicals against specific type of cancer.

Plant name	Family	Part used	Phytochemicals	Specific cancer suppressed	Literature cited
Peganum harmala	Zygophyllaceae	Roots	Harmine	Breast cancer (Both *in vitro* and *in vivo*)	[26]
Curcuma longa	Zingiberaceae	Rhizomes	Curcumin, ascorbic acid	Leukemia, glioblastoma and colon cancer (*In vitro*)	[27]
Allium wallichii	Amaryllidaceae	Whole plant	Steroids, terpenoids, flavonoids, reducing sugars and glycosides	Prostate cancer, breast cancer, cervical cancer (*In vitro*)	[28]
Artemisia annua	Asteraceae	Whole plant	Artemisinin	Liver, breast and pancreatic cancer (Both *in vitro* and *in vivo*)	[29]
Debregeasia saeneb	Urticaceae	Stem	Tannins	Internal tumors (*In vitro*)	[25]
Camelia sinesis	Theaceae	Leaves	Epicatechingallate, picatechin, epigallocatechin	Lung, bladder, skin, prostate and breast cancer (Both *in vitro* and *in vivo*)	[30]
Paeonia suffruticosa	Paeoniaceae	Seed	Polysaccharides (HBSS, CHSS, DASS, and CASS)	Prostate, colon, human breast, and cervical cancer (*In vitro*)	[3]
Ocimum sanctum	Lamiaceae	Leaves	Eugenol, orientin, vicenin	Breast, liver and fibrosarcoma cancer (*In vitro*)	[31]
Ginkgo biloba	Ginkgoaceae	Leaves	Ginkgetin, ginkgolide A & B	Hepatocarcinoma, ovary, prostate, colon and liver cancer	[32]
Camellia sinensis	Theaceae	Leaves	Theabrownin	Lung cancer (*In vivo*)	[33]
Ziziphus mauritiana	Rhamnaceae	Leaves, bark, fruit	α-linolenic acid, Methyl stearate	Leukemia, human cervical and liver cancer (*In vitro*)	[34]
Solanum nigrum	Solanaceae	Leaves	Solamargine, solasonine	Breast, liver, lung and skin cancer (*In vitro*)	[35]
Vigna unguiculata	Fabaceae	Seeds	Black-eyed-pea trypsin/ Chymotrypsin inhibitor	Human breast cancer (*In vitro*)	[36]
Ziziphus spina-christi	Rhamnaceae	Flowers, leaves	Doxorubicin, spinanine-A, rutnine, quercetin	Lung cancer and breast cancer (*In vivo*)	[37]
Glycyrrhiza glabra	Leguminosae	Roots	Licochalcone-A, licoagrochalcone	Prostate, breast, lung, stomach and kidney cancer (*In vivo*)	[38]
Herba epimedii	Berberidaceae	Leaves	Icariin, icaritin, icariside II	Prostate, lung, kidney and gastric cancer (Both *in vitro* and *in vivo*)	[39]
Elusine coracana	Poaceae	Seeds	Ragi bifunctional inhibitor	Myeloid leukemia cell and K562 cell line (Both *in vitro* and *in vivo*)	[40]
Psoralea corylifolia	Leguminosae	Seeds	Psoralidin	Stomach and prostate cancer	[41]
Peltophorum dubium	Fabaceae	Seeds	Peltophorum dubium trypsin inhibitor	Rat lymphoma cells, human leukemia cells	[42]
Vicia faba	Fabaceae	Seeds	Field bean protease inhibitors	Skin cancer (Both *in vitro* and *in vivo*)	[42]
Xanthium strumarium	Asteraceae	Fruit	Xanthatin	Lymphocytic leukemia and liver cancer (*In vitro*)	[43]
Nigella sativa	Ranunculaceae	Seeds	Thymoquinone	Colon, prostate, breast and pancreas cancer	[44]
Ocimum sanctum	Lamiaceae	Leaves	Eugenol, orientin, vicenin	Breast, liver and fibrosarcoma	[31]
Moringa oleifera	Moringaceae	Flowers, leaves	Moringa oleifera protease inhibitor (MoPI)	Abdominal cancer (Both *in vitro* and *in vivo*)	[40]
Glycine max	Fabaceae	Seeds	Bowman-Birk inhibitors	Colorectal, prostate and colon cancer (Both *in vitro* and *in vivo*)	[40]
Bauhinia variegata	Fabaceae	Flower	Kaempferol galactoside	Breast, lung and liver cancer (*In vivo*)	[44]
Withania somnifera	Solanaceae	Roots	Withaferin A, D	Breast, cervix, prostate and colon cancer (*In vivo*)	[45]
Aegle marmelos	Rutaceae	Bark, root	Lupeol	Lymphoma, melanoma, leukemia and breast cancer (*In vitro*)	[46]
Zingiber officinale	Zingiberaceae	Ginger	Gingerol	Ovary, cervix, colon, liver and urinary caner (*In vitro* and *in vivo*)	[47]
Sylibum marianum	Asteraceae	Flower, leaves	Silibinin	Lung, liver, skin, colon and prostate cancer (Both *in vitro* and *in vivo*)	[48]

(*continued on next page*)

Table 2 (*continued*)

Plant name	Family	Part used	Phytochemicals	Specific cancer suppressed	Literature cited
Capsicum annuum	Solanaceae	Pepper	Luteolin	Colorectal cancer (Both *in vitro* and *in vivo*)	[49]
Colchicum autumnale	Colchicaceae	Leaves	Colchicine	Hodgkin's lymphoma, chronic granulocytic leukemia (Both *in vitro* and *in vivo*)	[50]
Aegle marmelos	Rutaceae	Stem bark	Skimmianine	Liver cancer (Both *in vitro* and *in vivo*)	[51]
Boswellia serrata	Burseraceae	Gum	Boswellic acid	Prostate cancer (*In vitro*)	[52]
Sylibum marianum	Asteraceae	Leaves, flowers	Silymarin	Colorectal cancer and colon cancer (Both *in vitro* and *in vivo*)	[53]
Curcuma longa	Zingiberaceae	Dried rhizome	Curcumin	Colon adenocarcinoma (*In vitro*)	[54]
Alstonia scholaris	Apocynacea	Root bark	O-methylmacralstonine, talcarpine,villalstonine, pleiocarpamine	Lung cancer (Both *in vitro* and *in vivo*)	[55]
Podophyllum peltatum	Podophyllaceae	Leaves	Podophyllotoxin	Non-small cell lung carcinoma (Both *in vitro* and *in vivo*)	[56]
Andrographis paniculata	Acanthaceae	Whole plant	Andrographolide	Colon cancer (Both *in vitro* and *in vivo*)	[49]
Ziziphus jujuba	Rhamnaceae	Fruits, seeds, leaves	Linoleic acids, triterpenoids	Breast cancer, human Jurkat leukemia T cells (Both *in vitro* and *in vivo*)	[57]
Podophyllum hexandrum	Berberidaceae	Leaves	Podophyllotoxin	Breast, ovary, lung, liver, bladder and testis cancer (*In vitro*)	[58]
Betula utilis	Betulaceae	Bark	Betulinic acid	Melanomas (*In vitro*)	[59]
Panax ginseng	Araliaceae	Roots	Panaxadiol	Human colon cancer (Both *in vitro* and *in vivo*)	[60]
Panax pseudoginseng	Araliaceae	Roots	Panaxadiol	Human colon cancer (Both *in vitro* and *in vivo*)	[60]
Gossypium hirsutum	Malvaceae	Cotton	Gossypol	Mice xenograft (HT-29) and colorectal cancer (Both *in vitro* and *in vivo*)	[61]
Passiflora caerulea	Passifloraceae	Flower	Chrysin	Colorectal cancer (*in vitro*)	[62]
Plumbago zeylanica	Plumbaginaceae	Leaves	Plumbagin	Liver, fibrosarcoma, leukemia and breast cancer (*In vitro*)	[63]
Capsicum annuum	Solanaceae	Pepper	Luteolin	Colorectal cancer (Both *in vitro* and *in vivo*)	[49]
Zingiber officinale	Zingiberaceae	Rhizomes	6-Shogaol	Ovary cancer (*In vitro*)	[64]
Curcuma longa	Zingiberaceae	Root, rhizome	Curcumin	Breast, lung, colon, prostate esophagus, liver and skin cancer (*In vitro*)	[65]
Oldenlandia diffusa	Rubiaceae	Stem bark, leaves, fruit peel	Ursolic acid	Lungs, ovary, uterus, stomach, liver, colon, rectum and brain cancer (Both *in vitro* and *in vivo*)	[66]
Zingiber officinale	Zingiberaceae	Ginger	6-Shogaol	Ovary cancer (*in vitro*)	[64]
Zingiber officinale	Zingiberaceae	Root	Gingerol	Colon, breast and ovarian cancer (Both *in vitro* and *in vivo*)	[47]
Broussonetia papyrifera	Moraceae	Fruits, leaf, bark	2S-abyssinone Ilverubulin	Glioblastoma and brain cancer (*In vitro*)	[67]
Glycyrrhiza uralensis	Fabaceae	Roots	Isoliquiritigenin	Human lung cancer (*In vitro*)	[68]
Boerrhavia diffusa	Nyctaginaceae	Roots	Punarnavine	Malignant melanoma cancer (*In vitro*)	[69]
Vitis vinifera	Vitaceae	Seeds extract	Procyanidins	Human colon cancer (*In vitro*)	[70]
Polygonum cuspidatum	Polygonaceae	Whole plant	Resveratrol	Colorectal, skin and liver cancer (*In vitro*)	[71]
Morinda citrifolia	Rubiaceae	Roots	Damnacanthal	Lung cancer, sarcomas (*In vitro*)	[72]
Biophytum sensitivum	Oxalidaceae	Fruits and berries	Alcoholic extract	Dalton's lymphoma ascites, Ehrlich ascites carcinoma (*In vitro*)	[73]
Gossypium hirsutum	Malvaceae	Whole plant	Gossypol	Breast, stomach, liver, prostate and bladder cancer (*In vitro*)	[74]
Aloe vera	Asphodelaceae	Leaves	Alexin B, emodin	Leukemia, stomach cancer (*In vivo*)	[75]
Vaccinium macrocarpon	Ericaceae	Fruit	Hydroxycinnamoyl ursolic acid	Cervical, prostate cancer (*In vitro*)	[76]
Annona crassiflora	Annonaceae	Leaves	Caffeic acid, sinapic acid, rutin	Glioma, renal, ovary cancer (*In vitro*)	[77]

Table 2 (*continued*)

Plant name	Family	Part used	Phytochemicals	Specific cancer suppressed	Literature cited
Annona coriacea	Annonaceae	Seeds	Ferulic and sinapic acid	Glioma, lymphoid melanoma, lung, renal and ovary cancer	[77]
Argemone gracilenta	Papaveraceae	Whole plant	Argemonine and berberine	B-cell lymphoma, leukemia (*In vitro*)	[78]
Psoralea corylifolia	Leguminosae	Seeds	Bavachanin, corylfolinin, psoralen	Lung, osteosarcoma, fibrosarcoma and liver cancer (*In vitro*)	[79]
Moringa oliefera	Moringaceae	Leaves	Niazinine A	Blood cancer (*In vitro*)	[80]
Amoora rohituka	Meliaceae	Stem bark	Amooranin	Lymphocytic leukemia (*In vitro*)	[81]
Conyza Canadensis	Asteraceae	Roots	Conyzapyranone A and B	Epidermoid carcinoma (*In vitro*)	[82]
Ziziphus rugosa	Rhamnaceae	Pericarp and seed	Betulinic acid	Cytotoxicity against human melanoma cells (*In vivo*)	[83]
Panax ginseng	Araliaceae	Leaves	Panaxadiol, panaxatriol	Breast, ovary, lung, prostate and colon cancer (*In vitro*)	[84]
C. roseus	Apocynaceae	Leaves	Vinblastine, Vincristine	Breast, ovary, cervix, lung, rectum and testis cancer (*In vitro*)	[85]
Centella asiatica	Apiaceae	Leaves	Asiatic acid	Melanoma, glioblastoma, breast (*In vivo*)	[86]
Viscum album	Santalaceae	Sprouts	Viscumin, digallic acid	Breast, cervix, ovary, stomach, colon, kidney, lung cancer (Both *in vitro* and *in vivo*)	[87]
Leea indica	Vitaceae	Leaves	Gallic acid	Ehrlich ascites carcinoma (*In vitro* and *in vivo*)	[88]
Liriodendron tulipifera	Magnoliaceae	Stem	Costunolide, tulipinolide, liriodenine, germacranolide	KB (Oral cancer), HT29 cell line (Both *in vitro* and *in vivo*)	[89]
Viscum album	Santalaceae	Fruits	Viscumin, digallic acid	Breast, ovary, lung, kidney, bladder and testis cancer (*In vitro*)	[87]
Cicer arietinum	Fabaceae	Seeds	Bowman-Birk-type protease	Breast and prostate cancer (*In vitro*)	[90]
Crocus sativus	Liliaceae	Dry stigmas	Crocetin	Hippocampal cell death and lung cancer (*In vivo*)	[91]
Centella asiatica	Apiaceae	Leaves	Asiatic acid	Melanoma, glioblastoma and breast cancer (*In vivo*)	[92]
Tylophora indica	Asclepiadaceae	Leaves	Tylophorine	Breast cancer (*In vivo*)	[93]
Dioscorea colletti	Dioscoreales	Rhizomes	Dioscin	Liver and human gastric cancer (*In vitro*)	[94]
Croton macrobotrys	Euphorbiaceae	Leaves	Corydine, salutaridine	Leukemia and lung cancer (*In vitro*)	[95]
Clausena lansium	Rutaceae	Seeds	Clausenalansamid A and B	Gastric, liver cancer (*In vitro*)	[96]
Bleekeria vitensis	Apocynaceae	Leaf	Elliptinium	Myelogenous leukemia and breast cancer (*In vivo*)	[97]
Combretum caffrum	Combretaeae	Bark, kernal and fruit	Combretastatins	Colon, and leukemia and lung cancer (*In vivo*)	[97]
Solanum lycopersicum	Solanaceae	Fruit	Lycopene	Prostate and colon cancer (*In vivo*)	[98]
Plumbago zeylanica	Plumbaginacea	Roots	Plumbagin	Blood and skin cancer (*In vitro*)	[99]
Crocus sativus	Iridaceae	Flower stigmas	Crocin, picrocrocin, crocetin, and safranal	Sarcoma and oral cancer (Both *in vitro* and *in vivo*)	[100]
Actaea racemosa	Ranunculaceae	Rhizomes, roots	Actein	Liver and breast cancer (*In vivo*)	[101]
Peristrophe bicalyculata	Acanthaceae	Aerial parts	β-Caryophyllene, α-zingiberene	Breast cancer (*In vitro*)	[102]
Cannabis sativa	Cannabinaceae	Leaf	Cannabinoid	Lung, pancreas, breast, prostate and colorectal cancer (Both *in vitro* and *in vivo*)	[103]
Sylibum marianum	Asteraceae	Flower, leaves	Silymarin	Colorectal cancer (Both *in vitro* and *in vivo*)	[104]
Enterolobium contortisiliquum	Fabaceae	Seeds	Enterolobium contortisiliquum trypsin inhibitor	Gastric and breast cancer (Both *in vitro* and *in vivo*)	[105]
Linum usitatissimum	Linaceae	Leaves, flowers	Cynogenetic glycosides	Breast cancer (*In vitro*)	[106]
Calvatia caelata	Agaricaceae	Fruiting bodies	Laccases (Enzymes)	Liver, breast cancer (*In vitro*)	[107]
Tylophora indica	Combretaeae	Bark, Kernel fruit	Tylophorine	Breast cancer (*In vivo*)	[97]
Allium sativum	Amaryllidaceae	Buds, leaves	Allylmercaptocysteine, allicin	Lymphoma, cervix cancer (*In vivo*)	[108]

(*continued on next page*)

Table 2 (*continued*)

Plant name	Family	Part used	Phytochemicals	Specific cancer suppressed	Literature cited
Hibiscus mutabilis	Malvaceae	Pepper	Lectin	Liver, breast cancer (*In vitro*)	[109]
Plumbago zeylanica	Plumbaginaceae	Roots	Plumbagin	Blood cancer, skin cancers (*In vitro*)	[99]
Saffron crocus	Iridaceae	Dry stigmas	Saffron	Liver, lung cancer and pancreatic cancer (*In vitro*)	[110]
Taxus brevifolia	Taxaceae	Bark	nab-Paclitaxel	Ovarian and breast cancer (Both *in vitro* and *in vivo*)	[23]
Vitis vinifera	Vitaceae	Fruit	Cyanidin	Colon cancer (*In vivo*)	[111]
Actaea racemosa	Ranunculaceae	Rhizomes and roots	Actein	Liver and breast cancer (*In vivo*)	[101]
Pyrus malus	Rosaceae	Bark, fruit	Quercetin, procyanidin	Colon cancer (Both *in vitro* and *in vivo*)	[112]
Betula Sp.	Betulaceae	Leaves	Betulinic acid	Human melanoma xenografts and leukemia (*In vitro*)	[113]
Tabernaemontana divaricata	Apocynaceae	Leaves	Cononitarine B, Conophylline	Liver, lung, breast and colon cancer (*In vitro*)	[114]
Smilax chinensis	Liliaceae	Rhizomes	Tannin, saponins and flavonoid	Sarcoma-180 and ascites sarcoma (Both *in vitro* and *in vivo*)	[112]
Allium sativum	Liliaceae	Whole plant	Allin	Carcinoma of human (mammary) gland (Both *in vitro* and *in vivo*)	[115]
Aloe vera	Liliaceae	Whole plant	Aloesin, emodin	Anti-angiogenic activity (*In vitro*)	[116]
Curcuma longa	Zinziberaceae	Roots	Curcumin	Stomach cancer (*In vitro*)	[117]
Emblica officinalis	Euphorbiaceae		Polyphenols, tannins	Lymphoma and melanoma (*In vitro*)	[118]
Momordica charantia	Cucurbitaceae	Leaves, Roots	Charantin, cucurbitane-type triterpene	Colon cancer and breast cancer (*In vitro*)	[119]
Stevia rebaudiana	Asteraceae	Leaves	Labdane sclareol properties	Anti-tumorous and cytotoxic (*In vitro*)	[120]
Camellia sinensis	Theaceae	Leaves	Epigallocatechin gallate	Brain, prostate, cervical and bladder cancer (*In vivo*)	[121]
Nelumbo nucifera	Nelumbonaceae	Embryos	Neferine	Liver cancer (*In vitro*)	[122]
Ocimum sanctum	Lamiaceae	Leaves	Caryophyllene, camphor	Ssarcoma-180 solid tumor (*In vitro*)	[11]
Calvatia caelata	Agaricaceae	Fruiting bodies	Calcaelin	Breast and spleen cancer cells (*In vivo*)	[123]
Pleurotus sajor-caju	Agaricaceae	Fruiting bodies	Ribonucleases	Leukemia and liver cancer (*in vivo*)	[124]
Lentinus edodes	Marasmiaceae	Fruiting bodies	Lentinan	Sarcoma-180 in mice (*In vivo*)	[124]
Schizophyllum commune	Schizophyllaceae	Fruiting bodies	Schizophyllan	Head and neck cancer (*In vivo*)	[125]
Matricaria chamomilla	Asteraceae	Whole plant	Apigenin	Colorectal cancer (*in vivo*)	[126]
Fagopyrum sculentum	Polygonaceae	Seeds	Buckwheat inhibitor-1 protein	T-acute lymphoblastic leukemia (T-ALL) cells (*in vitro*)	[127]
Glycine max	Fabaceae	Seeds	Soybean trypsin inhibitor	Human ovarian cancer (*in vivo*)	[128]
Ipomoea batata	Convolvulaceae	Roots	Trypsin inhibitor protein	Promyelocytic leukemia cells (*In vitro* and *in vivo*)	[129]
Lavatera cashmeriana	Malvaceae	Seeds	Lavatera cashmeriana protease inhibitors (LC-pi I, II,III)	Leukemia, lung, colon cancer (*In vitro*)	[130]
Lens culinaris	Fabaceae	Seeds	Lentil (Lens culinaris trypsin inhibitor)	Human colon cancer (Both *in vitro* and *in vivo*)	[131]
Medicago scutellata	Fabaceae	Seeds	Medicago scutellata trypsin inhibitor	Human breast and cervical cancer (*In vitro*)	[132]
Phaseolus acutifolius	Fabaceae	Seeds	Tepary bean protease inhibitor	Leukemia L1210 and lymphoma MBL2 (*In vitro*)	[133]
Pisum sativum	Fabaceae	Pea	Protease inhibitors, rTI1B, rTI2B	Human colorectal and colon cancer (*In vitro*)	[134]
Phaseolus vulgaris	Fabaceae	Seeds	Tepary bean protease inhibitor	Leukemia L1210 and lymphoma MBL2 (*In vitro*)	[133]
Coccinia grandis	Cucurbitaceae	Leaves	(CG) protease inhibitors	Colon cancer (*In vitro*)	[135]
Ginkgo biloba	Ginkgoaceae	Leaves	EGb and bilobalide	Colon cancer (*In vivo*)	[136]
Curcuma zedoaria	Zingiberaceae	Whole plant	Curcumin	Colorectal cancer and B-16 melanoma cells (*In vitro*)	[137]
Clematis manshrica	Ranunculaceae	Flower, Leaves	1,4-benzoquinone,5-*o*-ethyl- embelin, 15-carbon isoprenoid	Liver cancer and blood cancer (*In vivo*)	[138]

Table 2 (*continued*)

Plant name	Family	Part used	Phytochemicals	Specific cancer suppressed	Literature cited
Vitex agnus- castu	Verbenaceae	Fruit	Vitex or luteolin	Human uterine, ovarian, cervical and breast cancer (*In vitro*)	[139]
Withania somnifera	Solanaceae	Root stem and leaves	Adriamycin and 5-fluorouracil	Human cervical cancer cell (*In vitro*)	[140]
Aristolochia fontanesii	Aristolochiaceae	Roots	Aqueous extract	Breast cancer (*In vitro*)	[141]
Centella asiatica	Apiaceae	Whole plant	Asiatic acid, Tamoxifen	Breast cancer (*In vitro*)	[142]
Carissa spinarum	Apocynaceae	Fruit	Alkaloids, saponins, tannins, flavonoids	Nasopharyngeal carcinoma (*In vitro*)	[143]
Asclepias curassavica	Asclepiadaceae	Aerial pats	Asclepin, cardenolides	Liver cancer (*In vitro*)	[144]
Annona squamosa	Annonaceae	Seed	Bullatacin	Liver cancer (*In vitro*)	[145]
Bryophyllum pinnatum	Crassulaceae	Leaves	Bryophyllin A	Cervical cancer (*In vitro*)	[146]
Butea monosperma	Fabaceae	Flower	Butrin, (7,3′,4′-trihydroxyflavanone-7,3′-diglucoside)	Liver cancer (*In vitro* and *in vivo*)	[147]
Vitex negundo	Lamiaceae	Fruit	Chrysoplenetin	Human pancreatic cancer (*In vitro*)	[148]
Moringa oleifera	Moringaceae	Seed	Pterygospermin 4-(4′-*O*-acetyl-α-L-rhamnopyranosyloxy), benzylisothiocyanate,4-benzylisothiocyanate	Lung, neuroblastima and colon cancer (*In vitro*)	[149]
Syzygium cumini	Myrtaceae	Fruit	Kaempferol-7-*O*-methylether, γ-sitosterol	Leukemia (*In vitro*)	[150]
Argemone mexicana	Papaveraceae	Leaves	Pancorine, (þ)-argenaxine, (þ)-higenamine,angoline	Gall bladder and breast cancer (*In vivo*)	[151]
Citrus limon	Rutaceae	Fruits	5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone	Human colon cancer (*In vitro*)	[152]
Taxus wallichiana	Taxaceae	Stem bark	Diterpenoid 2-deacetoxytaxinine	Breast and kidney cancer (Both *in vitro* and *in vivo*)	[153]
Berberis vulgaris	Berberidaceae	Roots stem and bark	Berberine	Breast, liver, colon cancers (*In vitro*)	[154]
C. roseus	Apocynaceae	Bark, leaves	Vindesine	Leukemias, testicular, breast and lung cancer (*In vitro*)	[113]
C. roseus	Apocynaceae	Bark, leaves	Vincristine	Lymphocytic leukemia (*In vivo*)	[113]
C. roseus	Apocynaceae	Bark, leaves	Vinblastine	Lymphocytic leukemia (*In vivo*)	[113]
T. baccata	Taxaceae	Bark, leaves	Cabazitaxel	Prostate cancer (*In vivo*)	[154]
Colchicum autumnale	Colchicaceae	Leaves	Colchicine	Multiple solid tumors (*In vitro* and *in vivo*)	[155]
T. baccata	Taxaceae	Bark, leaves	Larotaxel	Breast, bladder and pancreatic cancer (*In vivo*)	[156]
Taxus brevifolia	Taxaceae	Bark	Paclitaxel	Breast and ovarian cancer (*In vivo*)	[113]
Berberis vulgaris	Berberidaceae	Root, stem bark	Berberine, cannabisin	Breast, prostate and liver cancer (*In vivo*)	[157]

were considered to be topoisomerase II inhibition and intercalation with DNA in order to avoid proliferation [171]. Ellipticine and their derivatives *e.g.* N-2-(diethylaminoethyl)–9–hydroxyellipticinium chloride, 2-N-methyl 9-hydroxyellipticine are efficient anticancer compounds and are used to cure ependymoblastoma, leukemia, myeloma, melanoma, breast and colon cancer [172,173]. Ellipticine also perform their functions by inhibiting p53 protein phosphorylation and inhibit CDK2 kinase in human lung and colon cancer. A derivative of ellipticine (elliptinium) is also in clinical trials in France to check out its anticancer potential against breast cancer [174].

3.7. Berberine

Berberine is a strong anticancer compound in terms of its efficacy and clinical trials isolated from the root and rhizome of *Tinospora cordifolia*, *Berberis vulgaris*, *Berberis aquifolium* and *Rhizoma coptidis* [175]. Berberine has been used for the treat of variety of cancers namely; breast, prostate and colorectal cancer [176]. Berberine induces apoptosis and cell cycle arrest at G_2/M phase in breast, colorectal and liver cancer, inhibit anti-apoptotic proteins c-IAP1and Bcl-2, activate pro-apoptotic proteins (p21, p53, caspase-3 and caspase-9) [177]. The molecular targets of berberine are illustrated in Figure 2.

3.8. Combretastatins

The combretastatins is a class of anti-angiogenic agents isolated from *Combretum caffrum* (Combretaeae) and specifically suppresses tumor angiogenesis. For this purpose, National Cancer Institute has collaborated with botanical Research Institute of South Africa and developed novel anticancer agent combretastatins and many derivatives. Combretastatinn of family Stilbenes act against tumor and causes tumor necrosis due to

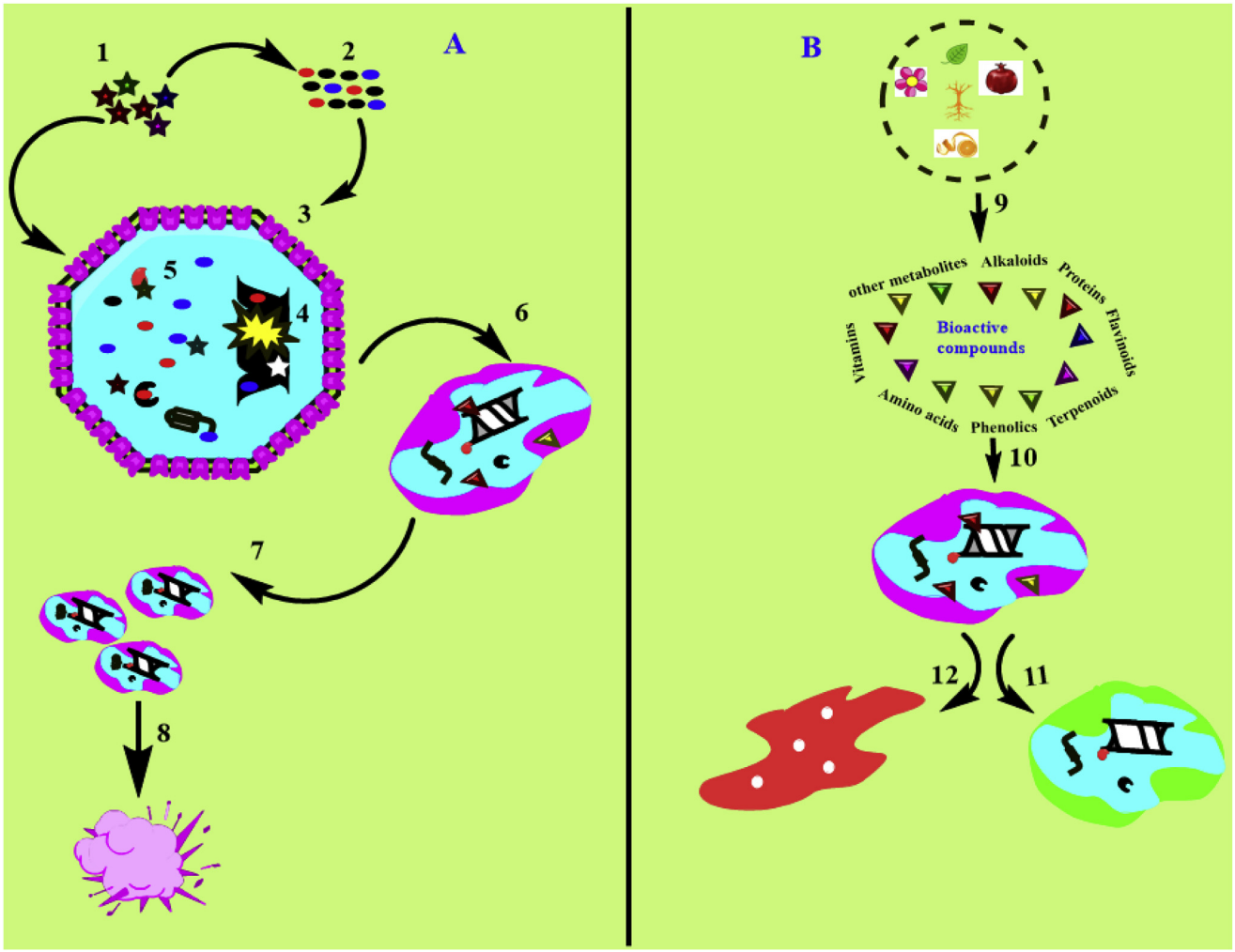

Figure 3. Schematic representation of carcinogenesis model.
(A) In step 1, 2 and 3 various carcinogen and reactive oxygen species ROS entering the cell. Step 4: the entered carcinogen causes genetic mutations that leads to cancer initiation. Step 5: interference of carcinogen and ROS with cellular proteins, enzymes and growth factors. The attack of carcinogen and ROS on DNA, proteins and enzymes of a normal cell. Step 6: transformation of normal cell into cancerous cell. Step 7: Proliferation of cancer cell. Step 8: Tumour cell. (B) Step 9: Different bioactive compounds isolated from different plant materials. Step 10: Application of bioactive compounds on cancerous cell. Step 11: Either cell become normal after phytochemical therapy. Step 12: Or phytochemicals causes apoptosis in cancerous cell.

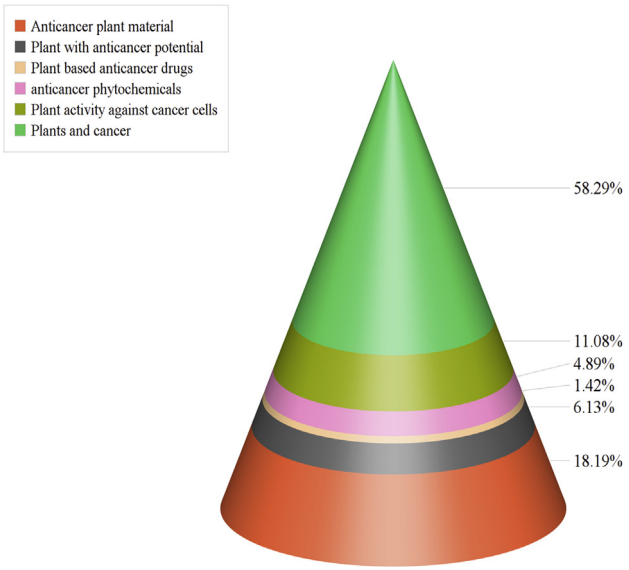

Figure 4. Literature published during 2010–2017 on anticancer phytochemicals.
Search results of different keywords used related to plant phytochemicals and cancer (2010–2017).

its antiangiogenic property. Combretastatins (A-4 CA4) is a water soluble analog and is effective against leukemia, lung cancer and colon cancers [97]. The different parts of Indian medicinal plant *Terminalia bellerica* (Combretaceae) fruit, kernel and bark are used in isolation of active combretastatins compounds with strong anticancer properties [16,97]. This agent is presently under research to cure medullary thyroid and anaplastic thyroid cancer [178].

3.9. Triterpenoid acids

Triterpenoid acids are also naturally occurring phytomolecules with anticancer properties. Moreover, these potent anticancer agents have shown strong anticancer results in both *in-vitro* and *in-vivo* against leukemia, pancreatic and breast cancer. Other anticancer agents like, CDDO (2-cyano-3, 12-dioxoolean1, 9-dien-28-oic acid) and its methyl ester are active against ovarian cancer [113]. Betulinic acid is another triterpenoid isolated from *Ziziphus mauritiana*, *Ziziphusrugosa* and *Ziziphus oenoplia* and *Betula* Sp. (Betulaceae) and is cytotoxic against a wide range of cancer including human melanoma [179].

3.10. Capsaicin

Capsaicin is also a natural phytochemical isolated from red pepper and exert strong anticancer, antimutagenic, anti-metastatic, anti-angiogenic and chemopreventive functions in pancreatic, prostatic, liver, skin, leukemia, lung, bladder, colon, and endothelial cells [180,181]. Capsaicin regulate different molecular targets in breast cancer like, caspase-3, reactive oxygen species (ROS), Rac1, and HER-2 *etc*. [182]. Capsaicin is more potent by inducing apoptosis in the presence of *p53* gene product (p53 known as the 'Grandfather of the genome' in terms of care) [183]. Capsaicin produced apoptosis in breast cancer (H-Ras, MCF10A cells) by inducing ROS and Rac1 signaling pathways. These ROS and Rac1 pathways are specifically induced by proteins like, p38, c-Jun N-terminal protein kinase-1 [184].

3.11. Flavones/Flavonoids

Flavonoids are also plant-specific secondary metabolites with around 8 000 diverse compounds largely distributed in fruits, grains, tea, vegetables, soybean and play a vital role for the treatment of large number of cancer [110]. Freeze-dried berries rich in anthocyanins have been studied for anti-cancer potential against oral lesions [185], familial adenomatous polyposis [186], and esophageal dysplastic lesions [187]. Flavopiridol is a plant-derived semisynthetic flavone that inhibit cyclin-dependent kinase with anticancer activity against esophageal and gastric cancers [188]. To date, meta-analyses have primarily focused on the functions of dietary flavonoids including inhibition of DNA topoisomerase I, and cycloxigenase and are used against breast [189], lung [190], stomach and colorectal cancer [191]. Flavopiridol and its mechanism of action on different enzymes are given in Figure 1.

3.12. Cyanidin glycosides

Cyanidin is an organic compound isolated from apples, grapes, plums, blackberry, raspberry, red berries, cranberry, red onion and red cabbage with multiple biological functions as for *e.g.*, antioxidant, radical scavenging effects, inhibit cell groth and division through *COX-2* and *iNOS* gene expression in colon cancer cells [192]. Cyanidin-3-orutinoside, cyanidin-3-*O*-glucoside and freeze-dried black raspberries selectively inhibit cell growth and induced apoptosis in a highly tumorigenic rat esophagus RE-149 DHD cell line [192]. Cyanidin glycosides from red berries perform functions of anticancer via many mechanisms. It stops the synthesis of COX-2 enzyme in colon cancer, induces apoptosis in prostate cancer, stops MMP-9 expression in bladder and lung cancer [193]. Stops the Erk phosphorylation and MMP-2 and MMP-9 in fibrosarcoma cells, suppresses expressions of Jun N-terminal kinases (JNK), MMP-9 and Erk enzymes in gastric cancer (stomach cancer) [194]. Cyanidin and its nuclear and cellular targets are summarized in Figure 1.

3.13. Saffron (Crocetin)

Crocus sativus L. commonly known as Saffron, rich in potent anticancer compound carotenoids, crocin, crocetin and safranal [67]. Saffron is marked as a promising agent for a novel anticancer drug against human lung, liver, skin, pancreatic, colorectal and breast cancer by regulating different nuclear and cellular factors, inhibiting iNOS, COX-2 enzymes, reduced serum level IL-β, TNF-α, cyclin B, cyclinA and cdk2, upregulate Bax/Bcl-2 ratio, regulate of caspase-3, 8 and 9 expression, down-regulate MMP-2, MMP-9 expression, induces apoptosis, targets microtubules and inhibit invasion and metastasis [91,195].

3.14. Epigallocatechin gallate

The main polyphenolic constituent of green tea called epigallocatechin possess the ability to restore genes expression of tumor suppression such as retinoid X receptor alpha, results in breast cancer inhibition by binding to many high affinity target proteins such as, 70 kDa zeta-associated protein (Zap-70) [196]. Molecular docking studies confirmed that both PI3K and mTOR signaling pathways binds well to the PI3K kinase domain active site displaying ATP-competitive activity in MDA-MB-231 and cervical cancer [197], brain cancer [198] and bladder cancer [199].

3.15. Gingerol

Gingerol is also a group of bioactive compound isolated from the fresh rhizome of *Zingiber officinale* containing [6]-gingerol, [8]-gingerol and [10]-gingerol with marked anticancer properties in colon, pancreas, ovarian and breast cancers. It down-regulates the expression of iNOS and TNF-alpha through suppressing NF-κB nuclear translocation and IκBα phosphorylation [200,201]. Oyagbemi *et al.* summarized the mechanisms of action of gingerol onK562 cells, MOLT4 cells with high reactive oxygen species, induced apoptosis in leukemia cells by mitochondrial pathway [201]. [10]-gingerol has strong anticancer potential than that of [6]-gingerol and [8]-gingerol and have shown promising results for the treatment of MDA-MB-231 and MDA-MB-468 breast cancer. The inhibitory effect of [10]-gingerol on MDA-MB-231 cells was related with the reduction of number of cell divisions, cell cycle arrest, induces apoptosis and releases proapoptotic mitochondrial cytochrome c [202]. Gingerol mechanism of action on different molecular targets is given in Figure 1.

3.16. Lycopene

Lycopene is a bright red pigment with anticancer potential isolated from tomatoes, watermelons, red papayas and red carrots and plays significant role in targeting PI3K/Akt signaling pathway in pancreatic and stomach cancer by down-regulating Erk and Bcl-2 proteins [165]. It up-regulates anti-oxidant enzymes (GSH, GST and GPxn) and removes oxidative damage caused by the carcinogens in breast, endometrial, prostate and colon cancer [203]. HT-29 colorectal cancer cells and animal models have shown that lycopene has also effect on cell proliferation and progression by interacting with various cellular signaling pathways like, NF-κB and JNK [204]. Lycopene also inhibited invasion, metastasis and proliferation in human SW480 colorectal cancer cells by restraining NF-κB and JNK activation, causes inflammation and suppresses the expression of COX-2, iNOS IL-1β, IL-6, and TNF-α [205]. Lycopene and its different nuclear and cellular targets are given in Figure 2.

3.17. Vitamin D from mushroom

Mushrooms exposed to light like vertebrates serve a better source for vitamin D after exposure to ultraviolet B light. Light

exposed mushrooms vitamin D has been involved in therapy of wide range of cancer including colon cancer [206], breast cancer [207] pancreatic_ENREF_105 and ovarian cancer by targeting different proteins, enzymes and signaling pathways, prevents carcinogenesis, metastasis and induces apoptosis [208].

3.18. Polysaccharides from mushrooms

Biologically active polysaccharides have been detected in fruiting bodies and mycelial mass of Macromycetes. Mushroom polysaccharides prevent carcinogenesis and display immune cell-mediated anticancer potentials [209]. Polysaccharides with antitumor functions like glucans, lentinan, tegafur, tegafur in combination with lentinan, and schizophyllan have been used for the treatment of lung, breast, and gastric cancers, enhance cellular immunity in the tumor cell, induce apoptosis, prevent invasion and metastasis, act as a macrophage activator, T-cell adjuvant, induce gene expression of cytokines and increase patient's survival with head and neck cancers [210]. Mushrooms polysaccharides and its molecular targets are given in Figure 2.

3.19. Dietary fibers from mushrooms

Mushrooms dietary fibers are also used as strong anticancer agents against different kind of cancers targeting different molecular pathways. Mushroom cell walls contain high molecular weight materials which cannot be digested and absorbed by human intestine, but can absorb carcinogenic substances (heavy metals and free radicals *etc.*), chitin, homo- and hetero-polysaccharides and in this way these high molecular weight materials have been proven as strong anticancer agent against a variety of cancers [211].

3.20. Proteins from mushroom

Mushroom proteins are one of the most extensively studied bioactive substances of mushrooms with their pharmaceutical potential and protein engineering. Many potent anticancer agents such as lectins, bolesatine, hemolysins, phallolysin, nebrodeolysin, laccases, calcaelin and ribonucleases have been isolated from different species of mushrooms (*e.g.*, *Polyporus adusta* and *Ganoderma carpense*, *Pleurotus ostreatus*, *Pleurotus eryngii*, *Pleurotus nebrodensis*, *Amanita phalloides* and *Calvatia caelata etc.*) and are used to treat a variety of cancers including lung cancer [212,213]. *Ganoderma lucidum* extracts can significantly inhibited the release of MMP-2, MMP-9, IL-6 and IL-8 in triple negative breast cancer cells [214]. In the past several chemical compounds extracted from mushroom possessed anticancer properties such as polysaccharopeptide significantly increased the ratio of $CD4^+/CD8^+/CD14^+/CD16$, T lymphocytes, increase the quantity and percentage of the B lymphocytes and CVP, induce apoptosis and cell cycle arrest [215].

3.21. Vitamin E from plant oil

Vitamin E has been reported as anti-tumor agent and represents a group of compounds consisting of both tocotrienols and tocopherols. It is fat-soluble anti-oxidant present in sunflower oil, germ oil, safflower oils and wheat. It has been researched that both tocopherols and tocotrienols exhibit antitumor properties like proapoptotic, anti-proliferative effects in both either *in-vitro* and *in-vivo* studies [216].

3.22. Fisetin

Fisetin is an active flavone found in various plant species such as strawberries, apple, grape and onion. It has been examined for its potential anticancer consequences; these are anti-migration and anti-proliferation, apoptosis effects on human colon cancer [111,217]. Fisetin is also used to treat human lung cancer by displaying dual inhibition of PI3K/Akt signaling pathways [218]. Moreover, it has anticancer effects in a wide range of cancer cells. For instance, fisetin found to induce apoptosis through inhibition of MAPK signaling network in human lung cancer and reactive oxygen species production in human oral cancer. It also induces apoptosis in human renal carcinoma caki cells via p53-mediated up-regulation of DR5 expression [219]. The mechanisms of action of fisetin on different signaling pathways are given in Figure 1.

3.23. Resveratrol

Resveratrol is also a naturally occurring polyphenol and has been identified in mulberries, peanuts, grapes, bilberries and blueberries. Resveratrol play substantial role in curing a wide range of cancers including breast, colorectal, liver, pancreatic, prostate cancer and lung carcinoma by up-regulating p53 and Bcl-2 associated X proteins and down-regulating MMPs, NF-κB, AP-1, Bcl-2, cyclins, cyclin dependent kinases, cytokines, and COX-2 proteins [220,221]. Resveratrol is known to inhibit angiogenesis, suppressing VEGF protein action by reducing MAP kinase phosphorylation [222]. The mechanism of action of resveratrol on different nuclear and cellular factors are given in Figure 1.

3.24. Anticancer compounds from algae

More than 50% of the marine blue-green algae are largely used for the isolation of anticancer compounds which are effective in either inducing apoptosis or triggering signaling pathways through activation of protein kinase-c enzymes, NF-κB, MAPK kinases, p53, cytokines release and ROS production. The cell extracts of *Calothrix* [Calothrixin A (I) and B (II), *Lyngbya majuscule* (Curacin-A)] are strong antiproliferative agents with inhibitory role in colon, renal and breast cancers [97]. Similarly, cryptophycin 1 isolated from a species of Nostoc (GSV 224) revealed strong cytotoxicity against human solid tumors. The compounds isolated from edible seaweed like *Padina boergeseni*, *Ulva reticulata*, *Gracilaria foliifera*, *Palmaria palmate*, *Acanthaphora spicifera*, *Sargassum thunbergii*, *Ascophyllum nodosum* and *Eclonia cava* have also shown marked anticancer activities and are used to treat kidney cancer, ammary adenocarcinoma, colon adenocarcinoma, human nasopharyngeal and colorectal cancer [223,224]. Cyanobacterium (*e.g. Spirulina platensis*) is effective against different types of human cancers (liver, lung, stomach and breast cancer via the production of valuable products (phycobiliproteins including c-phycocyanin, phycocyanobilin, allophycocyanin) [225].

3.25. Apigenin

Apigenin (APG) is a naturally occurring flavonoid identified in the different fruits and vegetables such as celery, chamomile and parsley with features including low toxicity and non-mutagenic, induces apoptosis and targets leptin/leptin receptor pathway in

lung cancer. Apigenin also activates caspase dependent extrinsic apoptosis pathway, inhibit signal transducer and activator of transcription 3 (STAT3) signaling pathways [226,227]. APG is also used to treat MDA-MB-453 breast cancer through inhibiting STAT3 signaling pathway by expression levels of caspase-3, caspase-8, induces extrinsic apoptosis, blocking the phosphorylation of JAK2 and STAT3 pathways [226]. Detailed information about apigenin regulating different protein, enzymes and signaling pathway are given in Figure 1 and 2.

3.26. Curcumin

Curcumin is also a lead phytochemical extracted from *Curcuma longa* with inhibitory property over the growth of human glioblastoma cells by modulating several nuclear and cellular factors, upregulates the expressions of different genes and their products [*p16, p21* and *p53* (These genes are also called as 'Grandfather of the genome' in terms of care for the cell], Bcl-2 associated X protein (Bax protein), EIK-1 (ETS oncogenic family), extracellular signal regulated kinase (Erk enzyme), early growth response protein 1, c-Jun N-terminal kinase, and caspase enzymes (Caspase-3, 8, 9) and decreases the level of Bcl-2, mTOR, p65, protein kinase B (Akt), retinoblastoma protein (pRB), NF-κB, and cyclin D1 proteins [54]. Detailed information about curcumin and its mechanism of action on different proteins and signaling cascades are summarized in Figures 1 and 2.

3.27. β-elemene

β-elemene a sesquiterpene, is a lso a promising anticancer agent with a wide range of its effect against drug-resistant tumors and has been isolated from *Curcuma wenyujin* [228]. β-elemene is major component of traditional Chinese medicine and inhibit different forms of cancer, induces apoptosis and cell death, inhibit the expression of VEGF, downregulates Akt phosphorylation and CD34 expression, suppressing PI3K/Akt/mTOR, MAPK and pathway, attenuating angiogenesis and upregulates the E3 ubiquitin ligases, Cbl-b and c-Cbl in human gastric cancer [229,230]. β-elemene molecular targets are given in Figure 2.

3.28. Chalcone

Chalcone is also a naturally occurring anticancer flavonoid in fruits and vegetables. It is responsible for activation of different caspases (caspase-8, 9, 12 enzymes), upregulate the of pro-apoptotic proteins expression (Bid, Bax, and Bak proteins), decreases anti-apoptotic *Bcl-2* gene expression and have been used for the treatment of the treatment of colon, lung, breast, liver and prostate cancer [231]. Chalcone targeted different nuclear and cellular factors (Bax, Bid, and Bak, Bcl-2 proteins, caspase-8, 9, 12 enzymes are illustrated in Figure 2.

3.29. Sesquiterpene lactones

Sesquiterpene lactones constitute large and diverse group of bioactive compounds isolated from several plant families (*e.g. Asteraceae*) exhibiting cancer cell cytotoxicity and antineoplastic efficacy and are used for the treatment of a large number of cancer like, prostrate, liver, lung, breast esophageal cancer [232]. Sesquiterpene lactone *e.g* deoxyelephantopin and isodeoxyelephantopin are components of *Elephantopus carolinianus* and *Elephantopus scaber* and have been shown to induce apoptosis via multiple mechanisms, comprised induces ROS, mitochondrial dysfunction, modulate Bcl-2 family protein, arrest cell cycle, inhibit NF-κB, and STAT3 activation [233].

3.30. Chrysin

Chrysin [5,7-dihydroxyflavone], is an effective anticancer compound showed less side effects and distributed in propolis, honey and blue passion flower, chamomile and possess strong antitumor effects on different cancer cell lines (DU145 and PC-3) [234,235]. This flavone has also induced apoptosis in SW480 colorectal cancer, arrest cell cycle at G_2/M phase, results in DNA cleavage and apoptosis, increasing ROS production and lipid peroxidation, suppressed the abundance of S6, AKT, PI3K, P90RSK and P70S6K, proteins, stimulate MAPK and ERK1/2 and P38 proteins in the prostate cancer cells [161,236]. Chrysin and its mechanism of action on different targets are given in Figure 1.

3.31. Scutellarin glycoside

Scutellarin is a promising anticancer agent isolated from medicinal plant species, *Scutellaria barbata* and *Scutellariaaltissima* and exhibits anti-tumor functions on different cancers for example, human colon cancer, liver cancer, and prostate cancer [237]. Scutellarin suppressed cancer cell proliferation, induces cell cycle arrest at G_2/M phase, upregulating caspase-3, 9, and Bax/Bcl-2 ratio in prostate cancer [238]. Scutellarin also induced apoptosis in liver carcinoma (HepG2 cells) via STAT3 signaling cascade and caspase-3 enzyme activation [177]. In addition, this chemical agent also induces apoptosis in human colorectal cancer, inhibiting cell growth and induces apoptosis by regulating the *p53* gene product [239]. The molecular targets of scutellarin are given in Figure 2.

3.32. Oroxylin flavone

Oroxylin A is a potential flavone isolated from the *Scutellariae radix* down-regulate the expression of *COX-2* and *iNOS* genes, block NF-κB, inhibit the activation of LPS-induced NF-κB by blocking IκB degradation [240]. Oroxylin A in combination with 5-FU is also used to treat colorectal cancer, exhibiting double action with COX-2 inhibition and increased ROS generation. Thus, oroxylin combination therapy could be a promising tool in order to reduce 5-FU doses and subsequent *in-vivo* side effects [241]. Oroxylin and its molecular targets are illustrated in Figure 2.

3.33. Kaempferol

Kaempferol is also a naturally occurring anticancer agent isolated from propolis, black tea, grapefruit, broccoli. Kaempferol possess significant antitumor potential on a large number of cancer cells *e.g.* colorectal cancer and HT-29 cancer cells by activating the expression of caspase-3 enzyme, *p53* gene and its products [242,243], arrest cell cycle at G_1 and G_2/M phase by inhibiting the activity of different enzymes (CDK2, Cdc2 and CDK4) [244]. Kaempferol and its nuclear and cellular targets are illustrated in Figure 1.

3.34. Genistein

Genistein is potent antitumor agent isolated from soybeans, lentils, beans and chickpeas. This isoflavone possessed pro-apoptotic function against colorectal cancer [245]. Genistein perform numerous functions as for example, up-regulate the expression of pro-apoptotic proteins (Bax and p21), inhibiting NF-κβ and topoisomerase II enzymes [246,247], upregulate antioxidant enzyme expression such as glutathione peroxidase [248]. Genistein and its action on different protein, enzyme and signaling pathways are given in Figures 1 and 2.

3.35. Silymarin

Silymarin is also naturally occurring flavolignan extracted from *Sylibum marianum*. This flavolignans mixture contained silydianin, silychrystin, silibinin (silybin A and B), and isosilybin (A and B), [249]. Silymarin induces cell cycle arrest and apoptosis by acting on cyclin dependent kinases and has been used together with paclitaxel and doxorubicin to treat colorectal cancer [250].

3.36. Ursolic acid

The ursolic acid is triterpene is the main constituent in herbal species likewise rosemary and basil plants. This antioxidant compound play significant role in the modulation of cellular redox status of normal cells and exerts pro-oxidative action on tumor cells. It exhibits pro-apoptotic effects on colorectal cancer (HCT116 cell line) by reducing the level of pro-inflammatory NF-κB cytokine, survival effectors Bcl-2 and pro-metastatic MMP-9 matrix metalloprotease [251]. Ursolic acid and molecular mechanism of action on different nuclear and cellular targets are given in Figure 1.

3.37. Ginsenosides

Ginsenosides constitue a class of active compounds responsible for pharmacological activities obtained from ginseng root. Preclinical and clinical researches demonstrated that ginsenosides have cancer preventing activities to various tumors, including liver, breast, gastric, ovarian, melanoma and colon cancer [252]. The six major ginsenosides (Rb1, Rb2, Rc, Rd, Re, and Rg1) constitute around 80% of the total ginsenosides in ginseng root and various minor ginsenosides [Rg3(S), Rh2(S), F2, compound K (C-K), Rg2(S), Rh1(S), F1, protopanaxatriol and gypenoside XVII] possess anti-invasion and anti-migration properties, induces apoptosis and cell cycle arrest [253]. Panaxadiol is a strong anticancer agent isolated from *Panax ginseng* and *Panax pseudoginseng* and has potent anti-cancer activity in different cancer cell lines and signaling pathways [254]. The same results were found with protopanaxadiol metabolite that significantly enhanced 5-FU effects on HCT116 cells by arresting cell cycle at G_1 phase and induces apoptosis [60]. One other member ginsenoside Rg3, is able to block NF-κB expression in HCT116 cell line leading to apoptosis [255]. Furthermore, ginsenoside-Rg5 is used to treat human cervical cancer by inducing apoptosis and cause DNA damage [256].

3.38. Celastrol

Celastrol is also a strong anticancer compound in terms of its efficacy isolated from the bark of *Tripterygium wilfordii* and inhibits heat shock protein, blocking its interaction with Cdc37, apoptosis induction via caspase-3 enzyme in ovary (OVCAR-8), colon (SW620), lung 95-D and prostate cancer [257]. Celastrol also induces apoptosis and inhibit the expression of oncoprotein in acute myelogenous leukemia1-ETO/C-KIT [8,21] [258]. It is also used to treat lung cancer cells through Hsp90 client protein degradation and caspases-dependent pathways [259]. Data from different cancers reports such as breast, lung, colon, prostate, esopharyngeal, glioblastoma, liver, skin, myeloma, pancreas, liver, leukemia, and gastric cancer) and animal models have suggested that celastrol induces apoptosis and cell cycle arrest, autophagy by the activation of ROS/c-JNK signaling pathway, inhibit angiogenesis and exhibit anti-invasive effect, upregulate death receptors in breast and colon cancer, activate Fas/Fas ligand pathway in lung cancer and inhibit PI3K/Akt/mTOR pathway in triple negative breast cancer [260].

3.39. Gossypol

Gossypol is also a natural phytochemical found in cotton seeds (Gossypium) and *Thespesia populnea*, displays potential anti-cancer activities, has completed phase II clinical trials for treatment of human breast and prostate cancer. Its antitumor properties have been studied in a variety of tumors (lymphoid, hematologic and solid tumors). Gossypol suppresses cell proliferation, induces autophagy and apoptosis in colorectal cancer, HT-29, HCT116 and RKO cancer cell lines [61].

3.40. Polysaccharides from plants

Plant polysaccharides are also promising anticancer agents and have long been used as theraphy for variety of cancers *e.g.* liver (HepG2 cells), lung (A549) cells, HL-60 cells, H157 cells, ovarian cancer, and human lymphatic endothelial cells [58]. Polysaccharides as anticancers agents haven been reported variously from medicinal plants [261]. Recently, researchers are shifting their research direction from microbe's polysaccharides to plant polysaccharides as they are non-toxic [262]. Many *in-vitro* and *in-vivo* studies indicated that these polysaccharides inhibit tumor cell proliferation by inducing cell cycle arrest and apoptosis in different type of cancers [66,263]. There are numerous reports on the role of polysaccharides in inducing cell cycle arrest and apoptosis, regulate different signaling cascades and cell cycle genes and inhibit cancer cell proliferation in a wide range of cancer cell lines (HepG2 cells, A549 cells, human lymphatic endothelial cells and ovarian cancer [239,264–266].

3.41. Isothiocyanates

Isothiocyanates is a potent phytochemical occurs in vegetables belongs to family Crusiferae such as watercress and broccoli and are used for the treatment of different cancer namely, colorectal cancer, cervical cancer, lung cancer, prostate cancer, and human T-Leukemia cells without causing any toxic side effects [267]. These natural isothiocyanates can induce apoptosis and ROS-mediated mechanism, arresting cell cycle at G_2/M phase, downregulate activated signaling cascades and modulate epigenetic changes, inhibit cell proliferation, progression and invasion-metastasis in colorectal and prostate cancer [268]. Sulforaphane, a

dietary isothiocyanate possess anticancer property in cervical cancer cells via inducing G_2/M arrest, downregulate cyclinB1 and up-regulate GADD45β proteins [269].

3.42. Genipin

Genipin is a natural phytochemical isolated from *Gardenia jasminoides* and is used to treat breast cancer [270]. In breast cancer, genipin regulates different protein and enzymes as for examples, caspase-3, Bax, Bcl-2, JNK, p38, MAPK. Genipin has anti-proliferative activity in MDA-MB-231 breast cancer cells by down-regulating Bcl-2 expression and up-regulating Bax and caspase-3, pro-apoptotic signaling cascades such as JNK and p38 MAPK [271].

3.43. Denbinobin

Denbinobin is another multifunctional phytochemical isolated from the stem of *Ephemerantha lonchophylla* and *Dendrobium moniliforme* with potent anti-cancer, anti-angiogenesis and apoptosis-inducing properties [272]. This compound inhibits metastasis by inhibiting Src kinase activity, decreases iNOS and COX-2 activity in concentration-dependent manner by suppressing NF-κB activation in human breast cancer cells [273].

4. Different strategies for the development of anticancer phytochemicals

The potential of medicinal plants as therapeutic agents depends upon the quality and quantity of active phytochemicals in them, which vary with latitude, longitude, altitude, age, climate and season from species to species. Pharmacological functions and their level vary with plant parts. These bioactive phytomolecules can also be used in anticancer therapeutics but they still demand further research. The purification of active phytomolecules may involve various strategies such as combinatorial chemistry, isolation assays, and bioassay-guided fractionation. Bioassay guided fractionation with various analytical techniques could be used to separate various bioactive compounds from the mixture of compounds. The process begins with the natural extracts test (from dry/wet plant material) with confirmed biological activity. Then, suitable matrices are used for the fractionation of active extracts, tested for bioactivity and various analytical techniques such as TLC, HPLC, FTIR, Mass spectroscopy and NMR *etc.* must be used for the separation of active fractions. For polarity order rise different solvents should to use. Superdex, Sephadex, Silica or any other suitable matrix can be used for fractionation. There are so many dyeing agents used for the detection of natural compounds in medicinal plants *e.g.* Vanillinesulfuric acid. These procedures

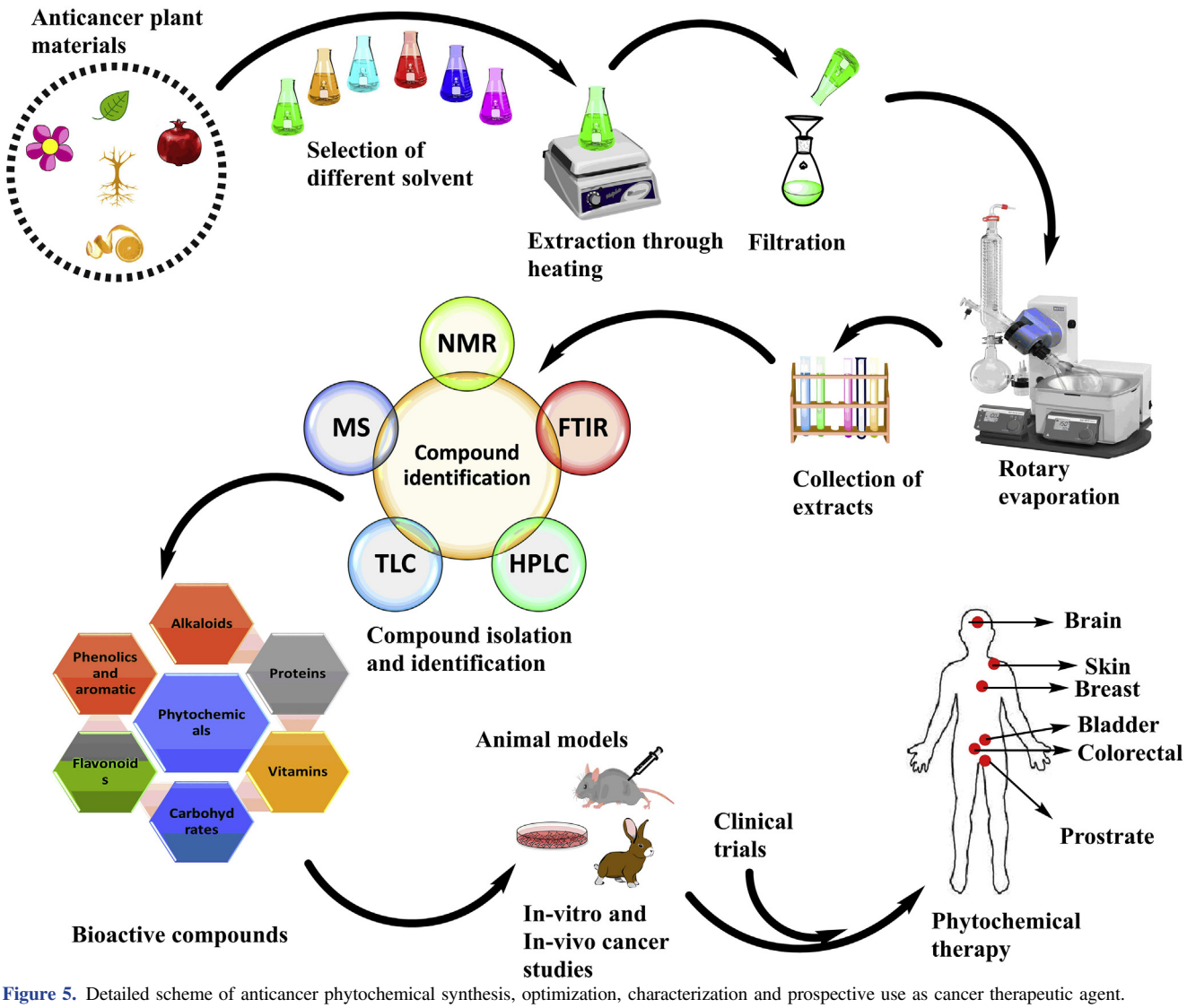

Figure 5. Detailed scheme of anticancer phytochemical synthesis, optimization, characterization and prospective use as cancer therapeutic agent.

could be change however purity, quality and quantity of the bioactive compounds should be high as much as possible and this can be achieved by using high quality of solvents, matrices and careful handling. After purification of these phytomolecules they must be examined for *in-vitro* or *in-vivo* anticancer effects. If a better anticancer property is achieved by the molecule then other aspects like pharmacokinetics, pharmacodynamics, immunogenicity, metabolic fate, biosafety and side effects, drug interactions, dose concentration *etc.* must be researched for future drug designing. Detailed scheme of bioactive compound synthesis, optimization, characterization, testing, and potential application as a cancer therapeutic agent is shown in Figure 5.

5. Conclusions and future prospects

It has been evident from the present review that phytochemicals serve as promising and effective research area with bright future. The growing incidence of cancer and high cost, various limitations in the conventional therapy including high cost, and high toxicity of present anticancer drugs has faced a severe challenge to all the researchers to design and develop an alternative, eco-friendly, biocompatible and cost-effective strategy in a greener way. Under this scenario, phytomolecules are expected to revolutionize cancer treatment in the next decade. High biodegradability and biocompatibility have increased the efficacy of these phytomolecules in cancer therapy. This comprehensive review paper provides information on medicinal plants and their bioactive compounds with potential to cure different types of cancer. Potential anticancer phytochemicals described in this comprehensive review article should be further researched in clinical trials (Curcumin, epigallocatechin, isothiocyanates, gossypol, sulforaphane, garcinol, *etc.*) on different models for their effectiveness and toxicological documentation. Furthermore, extensive research work should be carried out on these phytochemicals to evaluate their possible applications, toxicological and particular genotoxic profile against a wide range of cancer in both either *in-vitro* or *in-vivo*.

Conflict of interest statement

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.apjtb.2017.10.016.

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