

ETHNOPHARMACOLOGICAL REVIEW OF NATURAL PRODUCTS IN CANCER PREVENTION AND THERAPY

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ABSTRACT

The World Health Organization reports that approximately 80% population from developing countries are facing complications from synthetic drugs used in maintaining their primary health-care needs. The chemotherapeutic strategies are very striking and have earned serious concern as potential means of controlling the incidence of this dreadful disease. However, the major problem in cancer is the long lasting toxicity of the well reputable chemical drugs. Since ancient times, medicinal plants have attracted enormous attention, to fight against various diseases with their broad-spectrum biological and therapeutic properties. Although plants, phytochemicals and their analogues have been confirmed to be safe and effective, having strong anticancer properties. A number of pharmaceutical agents with diverse chemical structures of natural origin from plants have been discovered as anticancer agents such as vincristine, vinblastine, podophyllotoxin, camptothecin, taxol, resveratrol, withaferin A, quercetin, and curcumin. Further modifications of these phytochemicals led to the development of numerous outstanding molecules such as drugs like topotecan, irinotecan, taxotere, etoposide, and teniposide. In this in-depth review, we meticulously investigated the selected medicinal plants for their anticancer properties. In particular, novel compounds from plants have beneficial effects on human health. Our observations suggest the preventive and therapeutic use of phytochemicals in managing various human malignancies.

Keywords: Natural products, Anticancer drugs, Alkaloids, Podophyllotoxin, Camptothecin, Resveratrol, Curcumin, Quercetin etc., Cell cycle arrest, Apoptosis.

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INTRODUCTION

Over two decades ago, Hippocrates, the founder of medicine, described about 400 medicinal plants and advised "let food be your medicine and let medicine be your food [1]." Herbal plants continuously play a vital role in the health-care system throughout the world's population. In developing countries, folk medicines are essential part and have a long and everlasting history because of low cost, easy availability, tribal familiarity, and skilled/experienced all over the world [2]. Since ancient times, a huge number of modern drugs have been isolated from plants in whole, and its chemical compounds (photochemicals) are used as medicines in Asian and Greek countries [3]. Today's major scientific and technological processes in combinatorial chemistry and the remedies obtained from natural sources make an increased contribution to drug discovery. Some of the therapeutic drugs from natural sources are enlisted in Table 1, obtained from natural sources such as plants, microbes, and marine organisms with their therapeutic uses as well as modes of action [4-6].

CANCER

Cancer is a life-threatening, dreadful disease, growing health problem in developing as well as developed countries. It is regarded to be more of a developed world issue. All cancers except non-melanoma skin cancer are 1.8 times more in highly developed countries compared with less developed [7]. A recent report by the World Health Organization (WHO) 2014, about 6.2 million people were died due to cancer. It has also been expected that the number of annual cases of cancer enhances from 14 million in 2012 to 22 million within the next two millennia [8]. This disease is categorized by proliferation of cells abnormally, by which other cells/tissues are damaged which lies adjacent to these cells resulted in the destruction of them [9].

Several approaches of herbal drugs having the potency to improve immune cells of the body against cancer have been made. Thus, based

on the detailed reported and complex synergetic combinations of various phytochemicals with anticancer potential, a large number of herbal remedies have been designed to fight against cancer cells without damaging healthy cells of the body [10,11]. Plants have played a significant role as a source of valuable anticancer agents, and in one way or another, it is accepted that over 60% currently used anticancer agents are derived from natural sources, including plants, marine organisms, and microorganisms (Table 1) [12,13]. Because of the adverse or lethal side effects of chemotherapy, radiation therapy and due to the growing rate of mortality associated with cancer, new anticancer agents have been derived from nature. In the early 1950s, selection of medicinal plants as a source of anticancer agents was started, with the discovery and development of vinca alkaloids (vinblastine [VLB] and vincristine [VCR]) and the isolation of the cytotoxic podophyllotoxins [14].

CANCER-CAUSING GENES AND THEIR ACTION

Mainly four types of genes are involved in cell division. Most tumors have damaged copies of more than one of the genes as follows:

- i. Oncogenes (OG)
 Oncogenes have the potential to cause cancer. These genes play an important role in the cells to start dividing under normal conditions. Growth rate of cells increases on activation of such genes. Cancer develops when one of these genes get damaged, and it works like accelerator becoming jammed down the cell with all daughter cells and are permanently instructed to divide [15].
- ii. Tumor suppressor genes (TSG)
 It is also known as antioncogenes. These genes were codiscovered by David Lane in 1979(UK). Proteins are made, which function normally but opposite to that of ontogenesis with the help of TSG. One of the most important TSGs is p53 [15].
- iii. Suicide genes (SG)
 Suicide gene is a gene which causes a cell to kill itself through apoptosis. Apoptosis or cell suicide is treated to be a more complex

and extremely important process. To prevent harm to the neighboring cells usually, cells have the ability to commit suicide when something goes wrong. A number of SG are involved in cancer diseases. When the "SGs" get damaged, a faulty cell can protect dividing and become cancerous [15]. Cells usually have the ability to commit suicide whenever something goes wrong, to prevent damage to their neighbors. There are many different genes involved. If the "SGs" become damaged, then a faulty cell can keep dividing and become cancerous.

iv. DNA repair genes (DRG)

Since DNA is present in every cell of the body, which is continuously attacked from a variety of directions, cells contain different kinds of proteins whose work is to repair the damaged DNA [15].

PLANT-DERIVED ANTICANCER AGENTS IN CLINICAL USE

Anticancer drugs or anticancer agents can prevent or inhibit the maturation and proliferation of cancer cells. These agents travel to different parts of the body and devastate the cancerous cells. These drugs can also be used significantly in combination with radiotherapy, surgery, and immunotherapy in the united modality approach for many solid tumors particularly metastasis.

Vinca alkaloids

The vinca alkaloids are the first carriers to advance into clinical use against cancer in the form of bisindole alkaloids such as VLB and VCR (Fig. 1a) isolated from the rain forests of Madagascar periwinkle plant, *Catharanthus roseus* G. Don. (Apocynaceae) [14]. The mechanism of action of vinca alkaloids is that, as they interact with tubulin, mitotic spindle assembly disrupts. Particularly, when the vinca alkaloids specifically bind to β -tubulin, as a result they block the capability of α -tubulin to polymerize into microtubules. This directs to the killing of actively dividing cells by inhibiting progression during mitosis [16]. Recent studies show that vinorelbine (VRLB) and vindesine are the

two semi-synthetic analogs obtained from these agents (VLB and VCR). Primarily in combination with other cancer chemotherapeutic drugs, VLB and VCR are used for the treatment of various cancers, including lymphomas, leukemias, testicular cancer, breast and lung cancers, and Kaposi's sarcoma [14].

Another bifluorinated, semi-synthetic tubulin-targeted vinca alkaloid called vinflunine (Fig. 1b) is collected when the two fluorine atoms are introduced into VRLB molecule. It shows similar properties like other vinca alkaloids in mitotic-arresting and tubulin-interaction activities, but due to lesser neurotoxicity, microtubules involved in axonal transport show weak compatibility than those involved in mitosis. In *in vivo* preclinical studies, it has been identified that vinflunine is having marked and superior antitumoral activity than that of VLB against a large number of tumor models. In combination with other chemical drugs such as cisplatin, mitomycin C, doxorubicin, and 5-fluorouracil, vinflunine showed synergism [17].

Podophyllotoxin

Podophyllotoxin (Fig. 2a) is a renowned substance due to its precious anticancer activities and well-known use in chemotherapy, in pharmaceutical industry. The chief plant source of this compound is *Podophyllum emodi*, which is categorized as an endangered species due to over exploitation [18]. Besides, the second most frequently used source is *Podophyllum peltatum*, which produces only one-third part of the podophyllotoxin than that of *P. emodi* [19].

The main molecular mechanism of podophyllotoxin responsible for the anticancer activity is to prevent the assembly of tubulin into microtubules which induce apoptosis. Different *in vitro* experimental examinations showed the effect on microtubule assembly by the interaction of podophyllotoxin with tubulin. However, the fact was that podophyllotoxin hinders the formation of the mitotic spindle microtubules by preventing the polymerization of tubulin which induces

Table 1: Therapeutic drugs from natural sources

Drugs	Medicinal use	Mode of action	Source
Aspirin	Analgesic, inflammatory, antipyretic	Anti-inhibition of COX (cyclooxygenase)	Plant
Atropine	Pupil dilator	Antagonist of Ach (acetylcholine) at muscarinic receptors at post-ganglionic parasympathetic neuroeffector sites	Plant
Morphine	Analgesic	Opioid receptor agonist	Plant
Digoxin	For atrial fibrillation and CHF (congestive heart failure)	Inhibition of the Na ⁺ K ⁺ ATPase membrane pump	Plant
Taxol	Anticancer agent	Antimitotic agent (binds to and stabilizes microtubules)	Plant
Eugenol	Toothache	Reduces excitability of sensory nerves increases K ⁺ efflux and reduced Ca ₂ ⁺ influx	Plant
Quinine	Anti-malarial	Prophylaxis inhibition of protein synthesis in the malaria parasite	Plant
Caffeine	Stimulant	Adenosine receptor antagonist	Plant
Cyclosporine A	Immunosuppressant	Inhibition of clonal proliferation of T lymphocytes (through inhibition of microbe-lymphokine production)	Microbe
Tetracycline	Antibiotic	Inhibition of protein synthesis by binding to the ribosome 30S subunit	Microbe
Manoalide	Anti-inflammatory, analgesic	Inhibition of phospholipase A2	Marine organism
Spongistatin 1	Antifungal	Inhibition of tubulin polymerization	Marine organism

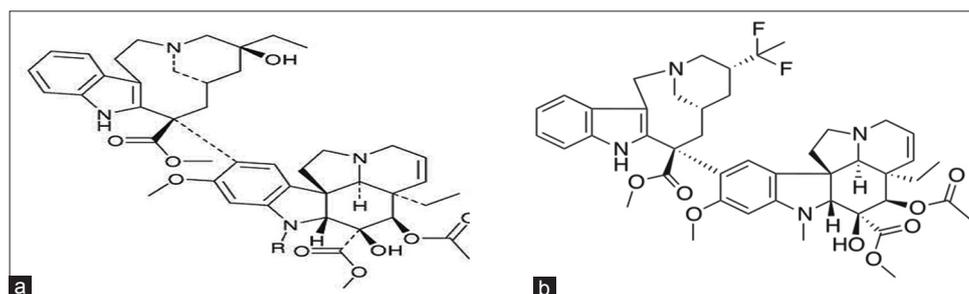


Fig. 1: (a) Vinblastine; R=CH₃, vincristine; R=CHO and (b) vinflunine

cell cycle arrest at mitosis. To mediate anticancer activity, dynamic equilibrium gets disturbed between the assembly and disassembly of microtubules due to the reversible binding of podophyllotoxin and tubulin, which eventually leads to mitotic arrest [20]. A number of lignans have been isolated which are closely related to podophyllotoxins, used as clinical trials, but due to lack of efficacy and unacceptable toxicity, they have to be avoided. After widespread research studies, the development of epipodophyllotoxins (an isomer of podophyllotoxin) such as etoposide (Fig. 2b) and teniposide (Fig. 2c) has been developed as clinically valuable agents and is used in the treatment of bronchial and lymphatic and testicular cancers [14].

In addition, a new podophyllotoxin derivative called podophyllotoxin acetate (PA) (Fig. 2d), which was formerly isolated from natural product library, used as a drug against cancer and also acts as a radiosensitizer [21]. In combination with TOP inhibitor like etoposide, PA boosts cell death and its chemosensitizing potential is measured to improve the effectiveness of cancer treatment. In other words, apoptosis is increased in non-small cell lung cancer cell lines such as NCI-H1299 (derived from the lymph node) and A549 (adenocarcinomic human alveolar basal epithelial cell) by the interaction of PA and TOP inhibitor (etoposide) in synergistic manner through the activation of p38 and caspases and inactivation of CREB-1 [22].

Camptothecin (CPT)

CPT (Fig. 3a), a quinoline alkaloid, is an effectual anticancer natural product, which has been first isolated from a Chinese plant *Camptotheca acuminata* belonging to the family Nyssaceae. Due to its broad as well as very powerful *in vitro* diversity, it was preferred as a model drug, against a broad range of solid tumors including small cell lung carcinoma, primary and metastatic colon carcinoma, and stomach, ovarian, breast, and pancreatic cancers [24].

On the other hand, CPT revealed ruthless and erratic side effects in clinical trials [25], but extensive studies led to the development of CPT derivatives in large numbers, and only topotecan (TPT; 9-dimethyl amino-10-hydroxy CPT) (Fig. 3b) and irinotecan (CPT-11; 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy camptothecin) (Fig. 3c)

received the Food and Drug Administration (FDA) approval for clinical use, in 1996, and were marketed by GlaxoSmithKline and Pharmacia (now Pfizer), respectively; at present, they are used for prescription of ovarian and colon cancers [26,27].

It is the drug's ability of CPT analogs to stabilize Top1-DNA cleavage complexes (Top1cc) at replication forks, thus leading to collision with DNA polymerase and irreversible DNA damage, which induce apoptosis that indicates the antitumor activity [28,29].

Taxanes

These are diterpenoid molecules and were first isolated from the plants of *Taxus* genus (Family - Taxaceae). Taxanes include the drugs such as paclitaxel (Fig. 4a), docetaxel (Fig. 4b), and cabazitaxel (Fig. 4c). Among them, the extraction of paclitaxel was done primarily from the bark of *Taxus brevifolia* [30]. From the past 30 years, such as paclitaxel, no other phytochemical has been discovered which attracted the concentration of community [31]. Clinically, it is used against many malignancies, while others, the semi synthetic analogs such as docetaxel and cabazitaxel are ideal for the curing of prostate cancer [32].

As the mitotic inhibitors, taxanes exert the antitumor activity by means of several modes of action first and principal mode, and they hinder spindle disassembly by the binding of beta- tubulin, thereby stabilizing the microtubule spindle, leading to the G2/M cell cycle arrest, in which apoptosis is induced, because microtubules are involved in numerous cellular processes such as mitosis, cellular transport, cell shape maintenance, and cell signalling [32,33].

Homoharringtonine (HHT)

HHT (Fig. 5) is isolated from the evergreen Chinese tree *Cephalotaxus harringtonia*, family Cephalotaxaceae, with clinical applications [34,35]. For several decades, this plant alkaloid has been considered as an antileukemic agent, mainly in China, and in 2012, ssHHT (omacetaxine mepesuccinate), a semi-synthetic form of HHT, has been used for curing of chronic myeloid leukemia after approval by the FDA [36]. It exerts its antileukemic activities by reducing protein synthesis and inducing cell death in a number of leukemia cell lines. This natural compound choked

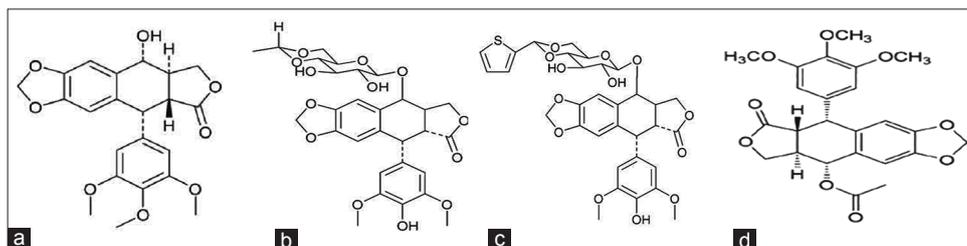


Fig. 2: (a) Podophyllotoxin, (b) etoposide, (c) teniposide and (d) podophyllotoxin acetate

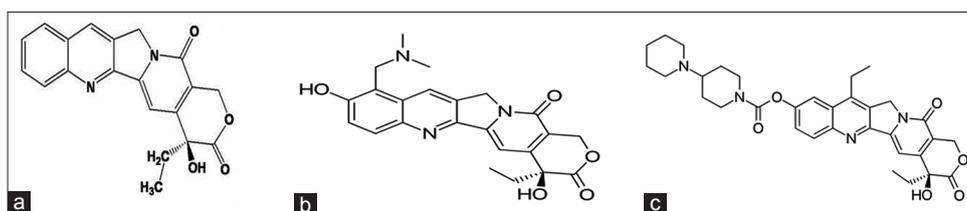


Fig. 3: (a) Camptothecin, (b) topotecan, (c) irinotecan

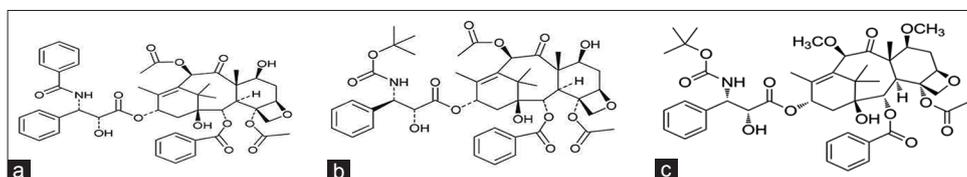


Fig. 4: (a) Paclitaxel, (b) docetaxel, (c) cabazitaxel

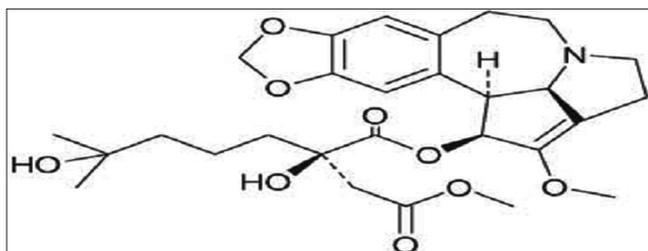


Fig. 5: Homoharringtonin

substrates from binding to the receptor site on the ribosome subunit, thus damages chain elongation, and hinders protein synthesis [37,38].

SOME OTHER MAJOR PLANT-BASED ANTICANCER AGENTS AND THEIR EFFECTS ON CANCER TYPES

Resveratrol

Resveratrol also known as 3, 4, 5'-trihydroxy-trans-stilbene is found as a natural polyphenol, in some plants being used as individual's nourishment [39], which is found in Grapes in major quantity [40]. Red wines also contain resveratrol in a significant amount [41]. From 1997, resveratrol was treated as a cancer chemopreventive mediator as it is being active in multiple steps of cancer such as initiation, promotion, and progression both *in vitro* and *in vivo*, and the development of cancer reduced through a number of complementary mechanisms such as inhibition of enzymatic activity in both forms of cyclooxygenase resulted in the reduction of cancer development [42]. It has also been reported that resveratrol could fight against tumor by apoptosis and cell cycle arrest. In tumor cell lines, the pro-apoptotic and anti-proliferative effects of resveratrol have been widely recognized by *in vitro* methods [43].

The effectiveness of this component has been extensively studied on colorectal cancer (CRC), as the treatment of 25 μM resveratrol causes 70% growth inhibition of CaCo-2 cells (the cell of heterogeneous human epithelial colorectal adenocarcinoma cells). Tumor incidence of mice reduced by giving high doses of resveratrol orally in drinking water and diet demonstration [44]. In a concentration- and time-dependent manner, resveratrol treatment of 100 μM also repressed the human pancreatic cancer cell line proliferation of PANC-1 and AsPC-1, and the fraction of sub-G0/G1 cells increased [45].

Withaferin A (WA)

WA is a first purified steroidal lactone, a highly oxygenated withanolide, isolated from the plant *Withania somnifera*, which is available as a dietary supplement in the US, and has been used for years in Indian Ayurvedic medicine. WA has been identified as antitumorigenic in various forms of cancer cells [46], including leukemia [47], prostate [48], breast [49], pancreatic [50], and ovarian [51]. A number of studies showed that WA exert a large number of activities such as it is one of the main biologically active withanolides, exerting a large variety of activities, including antitumor, radiosensitizing, anti-inflammatory, and cell death inducer and also showed antiangiogenic effects [46]. Many biological activities have been inclined by WA such as induction of apoptosis through NF- κ B and Akt inactivation [52], cell cycle arrest at G2/M phase [49], and reactive oxygen species generation [53].

Kaempferol

Kaempferol, also known as 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is regarded as a natural flavonoid, which is found in 80% of many edible plants such as kale, beans, tomato, grapes, broccoli, tea, cabbage, leek, endive, and strawberries [54,55]. Extensive studies reveal essential mechanisms related to anticancer effects of kaempferol in association with apoptosis, cell cycle, inflammation, angiogenesis, and reactive oxygen species [56a].

A number of *in vitro* and *in vivo* studied of kaempferol showed

antiproliferative and pro-apoptotic activities against different types of cancers such as breast cancer [57], lung cancer [58], prostate cancer [59], and kidney cancer [60]. It has been observed in one of the studies that kaempferol effectively reduces the proliferation of gastric cancer cells, through *in vivo* and *in vitro* mitochondrial pathways, apoptosis is induced. Cell cycle arrest was also seen at G2/M phase in which expression levels of regulating factors such as Cdk1, cyclin B1, and Cdc25C this phase also decreased by treating with kaempferol. Signalling pathway of ERK1/2 and PI3K/AKT was also reduced by kaempferol [61].

One of the studies on cervical cancer has examined that this compound suppresses the growth of HeLa cell (cervical cell) as compared to HFF cells (normal cells) on the basis of molecular mechanisms. Viability of cells was determined by MTT assay, and expression of telomerase genes and apoptosis was investigated by real-time polymeric chain reaction (PCR) after the cells were treated for 72 h with kaempferol (12–100 μM) and 5-FU (1–10 μM), as the positive control, resulted in decrease of cell viability on time and concentration-dependent manner. Kaempferol also induced cellular apoptosis of HeLa cells through the upregulation and downregulation of genes such as p53, p21, caspase3, caspase9, Bax, and PTEN and PI3K, AKT, and Bcl-2, respectively [62].

Dehydrocostus lactone

Dehydrocostus lactone is a therapeutic plant derived sesquiterpene, which has been extracted from *Saussurea lappa* [63] and *Aucklandia lappa* [64]. Dehydrocostus lactone has shown to possess antimycobacterial and antifungal activity [65], and it has been reported to induce apoptosis in different types of cancers such as lung cancer [66], breast cancer [67], and prostate cancer [68]. It has been studied that dehydrocostus lactone is used against hepatocellular cancer both by *in vitro* and *in vivo* methods, different *in vitro* methods are employed such as reverse transcriptase and PCR analysis, cell proliferation and clonogenic assay, caspase and apoptosis assay, immunoblot assay, and kinase activity assays, and by transmission electron microscopy, *in vivo* analysis on nude mice model was done. 16.7 and 18.8 μM were IC50 values, and these results proved that this compound showed anticancer activity. In addition, tumor volume significantly reduced to 50% in the animal studies after 45 days of treatment [69]. Furthermore, activation of NF-kappa B (a transcription factor) is inhibited by this compound by preventing tumor necrosis factor (TNF)-alpha (apoptosis inducing factor) induced degradation and phosphorylation of the inhibitory protein I-kappa B alpha in HL-60 human leukemia (HL) cells, and by enhancing the activities of caspase-3 and caspase-8, dehydrocostus lactone provides susceptibility of HL-60 cells to TNF-alpha in which apoptosis is induced [70].

Quercetin

Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one) is an aglyconic flavonoid found in a wide range of food products of humans, including capers, lovage, berries, citrus fruits, red onions, cherries, grapes, apples, cherries, broccoli, and tea (*Camellia sinensis*) [71]. It has been recognized to have a variety of valuable effects on human health including antiviral, cardiovascular, anticancer, and anti-inflammatory actions [72]. In addition to this, also derivatives of quercetin played an important role in human health, which include anti-allergic, antiviral, antiulcer effects, cardiovascular protection, anticancer activity, and anti-inflammatory properties [73]. It has been observed that the quercetin treatment decreased the colony-forming ability and cell viability and also inhibited the proliferation of SCC-25 cells through mitochondria-mediated apoptosis as well as through the cell cycle arrest at G1 phase in a dose-dependent manner. In the same manner, capabilities of invasion and migration of these cells also decreased by the treatment of quercetin. These results indicate that quercetin has great ability toward a new chemopreventive means and serves as additional remedial for oral squamous cell carcinoma [74].

It has been demonstrated that in a dose-dependent manner quercetin, repressed the viability of HeLa cervical cells by inducing mitochondrial

apoptosis through p53-dependent mechanism and also by cell cycle arrest at G2/M phase. This may result typical in mitochondrial membrane depolarization, nuclear morphology, modulation of cell cycle regulatory proteins and NF- κ B family members, upregulation of pro-apoptotic Bcl-2 family proteins, caspases and cytochrome-C, and Apaf-1, and downregulation of antiapoptotic Bcl-2 proteins and surviving [75].

Rutin

Rutin also called quercetin-3-rutinoside with chemical formula is 3,3',4',5,7 -pentahydroxyflavone-3-rhamnoglucoside and is a flavonol, which is found in large quantities in plants, such as *Fagopyrum esculentum* (buckwheat) [76], passion flower, apple, and tea, and it is a fundamental nutritional constituent of other food stuffs [77]. Rutin has numerous pharmacological properties, for example, anti-allergic, antioxidant, antiviral, anti-inflammatory, and anticarcinogenic [78]. Rutin is recognized to reduce the growth of cancer cell by apoptosis and/or by cell cycle arrest as well as inhibition of proliferation, metastasis, and angiogenesis in colorectal cell lines [79].

Anticancer activity of rutin has also been broadly studied in HL-60 cells, entrenched in a murine xenograft model which caused a major reduction in tumor size in the dose of 120 mg/kg, and this result suggests that rutin has a great antileukemic ability [80]. To find the toxicity of rutin and its defensive ability on hepatic cells, different essays have been used such as MTT assay, which showed toxicity at higher concentration of 810 μ M after 72 h of treatment where viability and proliferation of cells reduced, but it does not show any toxicity in different concentrations after 24 h of treatment, and the second is comet assay, which showed DNA damage significantly at highest concentration of 810 μ M of rutin and was proved genotoxic to the hepatic (HTC) cells after 24 h of treatment [81]. It has been revealed that rutin retards neoplasia with azoxymethane through immunosuppression [82].

Curcumin

Curcumin (diferuloylmethane), a well-known flavonoids, having chemical formula 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, has been isolated from the ground rhizome of the turmeric (*Curcuma longa*) [83]. For centuries, this naturally occurring phytochemical is used in a number of pharmaceutical applications [84]. Novel investigations divulge that curcumin and also the curcumin derivatives have diverse pharmacological activities including anti-inflammatory [85], antiviral [86], antimicrobial [87], free radical scavenging activity [88], and anticancer activity [89].

Its anticancer activity is refereed by its capability to adapt numerous pathways and target manifold genes, inflammatory cytokines, growth factors, transcription factors, adhesion molecules, enzymes, receptors, cell cycle proteins, and anti-apoptotic proteins which result in inhibition and apoptosis of migration and proliferation of cell [89]. Curcumin is found to be noxious to the cells which are cancerous and proved to be cytoprotective to healthy cells [90]. Predominantly, curcumin shows latent therapeutic and chemopreventive activities in a wide variety of cancers such as skin [91], breast [92], leukemia [93], lung [94], and hepatic [95]. It has been studied that curcumin inhibited fen1-dependent proliferation of breast (MCF-7) cancer cell in a dose-dependent manner using MTT assay, in which Nrf2 protein expression is extensively induced resulted in the downregulation of Fen1 gene expression in a Nrf2-dependent manner. Advanced analysis revealed that curcumin might guide to translocation of Nrf2 from the cytoplasm to the nucleus and Fen1 promoter activity decreased by decreasing the function of Nrf2 to the Fen1 promoter. These records proposed that curcumin could inhibit the breast cancer cell proliferation through downregulation of Fen1 expression mediated by Nrf2 which might be a new method of tumor growth inhibition induced by curcumin [92].

Curcumin also restrained the activation of Wnt/ β -catenin as well as Sonic Hedgehog pathways, which suggested that curcumin showed its interference consequences on lung cancer stem cells through the

inhibition of these pathways, which provides new insights of curcumin that it has therapeutic application in the elimination of lung CSC and of cancer [94].

Ellagic acid

Ellagic acid having chemical formula 2,3,7,8-tetrahydroxy[1]-benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione) is a constituent of phenolic compounds in certain fruits and nuts, for example, strawberries, raspberries, walnuts, mango kernel, longan seed, and pomegranate, and it was recognized that ellagic acid possesses many pharmacological activities including metal chelating, antibacterial, antifibrotic, antiviral, radical scavenging, antiatherogenic, antimutagenic, and anticancer activities [96-98]. It has been found that ellagic acid induces cell cycle arrest at G1 phase of cell cycle with successive apoptosis in cervical cancer cells by G1 cyclin-dependent kinase inhibitor p21WAF1/CIP1 activation [99]. It has also been observed that ellagic acid provoked the effects on colon adenocarcinoma cells (Caco-2 cells) by different ways such as cell-cycle arrest in S phase, downregulating of cyclins A and B1 and upregulating of cyclin E, induction of apoptosis through intrinsic pathway (FAS-independent and caspase 8-independent) via bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol, activation of initiator caspase 9 and effector caspase 3. Ellagic acid induced apoptosis in colon cancer cells through mitochondrial pathway without affecting the normal cells [100].

It has been observed that ellagic acid in higher doses is preventive against lung cancer, induced by tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, which was recognized to reduce the lung cytochrome P450 [101]. *In vitro* studies showed that ellagic acid also induced cell cycle arrest and apoptosis in human bladder (T24) cancer cells. To determine the cell viability, caspase-3 activity, apoptosis, and gene expression, different tests such as caspase-3 activity, polymerase chain reaction, and flow cytometric assay were performed. Results indicate that ellagic acid extensively decreased the viable cells, induced cell cycle arrest at G0/G1 phase, and apoptosis. Ellagic acid is also caused cell cycle arrest at G0/G1 phase of T24 cells, by increased p53 and p21 and reduced the CDK2 gene expression, and also the activity of caspase-3 is promoted to different time periods, which may lead to apoptosis induction [102].

Ergosterol peroxide

Ergosterol peroxide with chemical formula 5,8-epidioxy-22E-ergosta-6,22-dien-3-ol is isolated from the plant *Naematoloma fasciculare* in higher concentrations [103]. Ergosterol peroxide has a number of pharmacological activities such as antiviral [104], immunosuppressive [105], anti-inflammatory, and antitumor [106]. Ergosterol peroxide reduced the growth of HL60 cells and also induced apoptosis at the concentration of 25 μ M after an incubation period of 24 h [107].

It has been suggested that ergosterol peroxide from Chaga mushroom (*Inonotus obliquus*) downregulated β -catenin signalling and resulted in reduced transcription of cMyc, cyclin D1, and CDK-8, which exerted pro-apoptotic and antiproliferative activities in CRC cells. This compound suppressed CRC cell lines proliferation and inhibited colitis-associated colon cancer in AOM/DSS-treated mice efficiently [108]. Aqueous extract of Chaga mushroom has been reported to prevent intestinal inflammation and CRC chemical-induced mice models by regulating NF- κ B and Wnt/ β -catenin signalling [109,110]. These observations indicate that Chaga mushroom extract contains ergosterol peroxide as a great role in preventing CRC (Table 2).

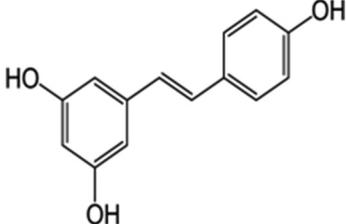
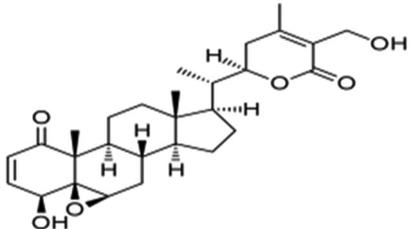
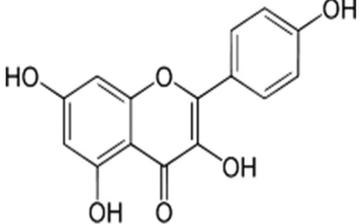
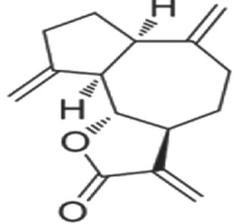
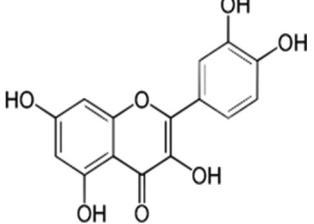
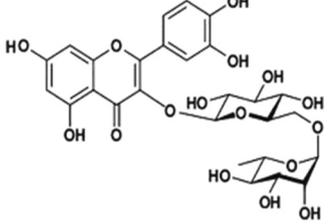
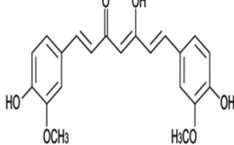
SOME PLANTS WITH ANTICANCER ACTIVITY

A wide range of herbal plants with therapeutic values is being used against cancer, and some important areas are as follows:

Allium sativum

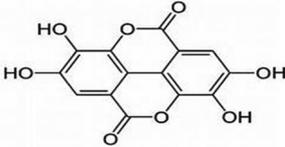
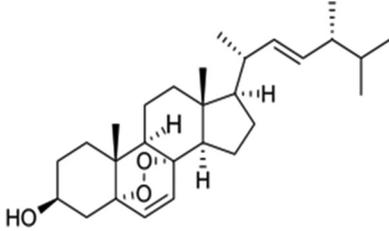
A. sativum, the medicinal prosperity of Allium vegetables, especially garlic (*A. sativum*), has been recognized throughout the written history [118]. It has been used for curing of a number of diseases

Table 2: Some plant-based anticancer agents and their effects on cancer type

Compounds	Chemical structure	Plant	Type of cancer	References
Resveratrol		<i>V. grandiflorum</i> , <i>V. vinifera</i>	Breast cancer CRC ovarian cancer	[111] [112] [113]
WA		<i>W. somnifera</i>	Leukemia Breast cancer Pancreatic cancer Prostate cancer Colon cancer	[47] [49] [50] [48]
Kaempferol		<i>C. sinensis</i> <i>C. spinosa</i> (Capers) <i>C. sativus</i> (Saffron)	Breast cancer Lung cancer Prostate cancer Kidney cancer Cervical cancer Stomach cancer	[57] [58] [59] [60] [64] [63]
Dehydrocostus lactone		<i>S. lappa</i> <i>A. lappa</i>	Breast cancer Lung cancer Leukemia Hepatocellular Carcinoma Prostate cancer	[63] [64] [67] [66] [70] [69] [68]
Quercetin		Capers, lovage, berries, citrus fruits, red onions, cherries, grapes, apples, broccoli, tea (<i>C. sinensis</i>)	OSCC Prostate cancer Cervical cancer Myeloid leukemia	[71] [74] [114] [75,115]
Rutin		<i>F. esculentum</i> (buckwheat), <i>C. sinensis</i> (tea), and <i>M. pumila</i> (apple) passion flower	Leukemia CRC Hepatic cancer	[80] [79] [81]
Curcumin		<i>C. longa</i>	Skin cancer Breast cancer Leukemia Lung cancer Hepatic cancer	[91] [92] [93] [94] [95]

(Contd...)

Table 2: (Continued)

Compounds	Chemical structure	Plant	Type of cancer	References
Ellagic acid		Cloudberry, raspberry, rose hip, strawberry	Cervical cancer Colon cancer Lung cancer Bladder cancer	[116] [99] [100] [101] [102]
Erogsterol Peroxide		<i>N. fasciculare</i>	Leukemia Prostate cancer Colorectal cancer (CRC)	[103] [107] [117] [108]

CRC: Colorectal cancer, *V. grandiflorum*: *Veratrum grandiflorum*, *V. vinifera*: *Vitis vinifera*, *C. sinensis*: *Camellia sinensis*, *C. spinosa*: *Capparis spinosa*, *S. lappa*: *Saussurea lappa*, *A. lappa*: *Aucklandia lappa*, *C. sinensis*: *Camellia sinensis*, OSSC: Oral squamous cell carcinoma, *F. esculentum*: *Fagopyrum esculentum*, *M. pumila*: *Malus pumila*, *C. longa*: *Curcuma longa*, *N. fasciculare*: *Naematoloma fasciculare*, *W. somnifera*: *Withania somnifera*, *C. sativus*: *Crocus sativus*

such as cancer, cardiovascular disorders, HIV drug-induced lipid disorders, cold, flu, and prevention of tick bite, which appear to act efficiently against erythro-leukemic disorders as well as breast and prostate cancer cells [119,120]. The anticancer activity of garlic is due to the presence of a number compounds, and among them, two major groups have been identified as effective against cancer, one group contains lipid-soluble allyl sulfur compounds which include diallyl disulfide and diallyl trisulfide, and the other group contains water-soluble γ -glutamyl S-allylcysteine (SAC) compounds such as SAC and S-allyl mercaptocysteine [121]. Several mechanisms of garlic and their organosulfur compounds explained the preventive measures of cancer, and these include free radical scavenging property, inhibition of mutagenesis, modulation of enzyme activities, reduction of DNA adduct formation, and effects on cell proliferation and tumor growth [122].

It has also been reported that WEHI-164 tumor cells were injected in a pre-clinical BALB/c mice model and then divided into six groups. The boiled garlic extracts at 20 mg/kg/0.2 mL were given to the treatment group. After 3 weeks, the results showed that the tumor size of garlic extract-treated groups was reduced significantly as compared to the control group [123].

***Annona muricata* L**

A. muricata L. (Annonaceae family) is commonly known as soursop, graviola, guanabana, paw-paw, and sirsak. Previously, it has been demonstrated that the leaves of *A. muricata* showed significant cytotoxicity against several cancer cell lines without disturbing the normal cells [124,125]. The constituents isolated from *A. muricata* leaves are *Annonaceous acetogenins*, alkaloids, and essential oils. Among them, *A. acetogenins* are powerfully understood to be dependable for the promising anticancer effect [126]. Recently, *in vitro* methods determine the mechanism of action of ethyl acetate extract of *A. muricata* leaves against colon cancer cells (HT-29 and HCT-116) and lung cancer cells (A549) by the induction of apoptosis in these cell lines through the mitochondrial-mediated pathway. This shows antiproliferative effect, associated with cell cycle arrest in the G₁ phase [127]. Due to the remarkable antiproliferative effect, *A. muricata* was expressed as "the cancer killer [125]."

It has also been recommended that ethanolic extract of *A. muricata* leaves has apoptosis-inducing potential against myelogenous leukemic K562 cells. This was confirmed by TUNEL assay [128]. Recent studies by *in vitro* and *in vivo* methods of the water extract of *A. muricata* leaves were performed against the benign prostatic hyperplasia (BPH-1) cell line and rat's prostates, and it showed the repressive effect on BPH-1 cells with an upregulation of Bax and a downregulation of Bcl-2 at the mRNA level having IC₅₀ value of 1.36 mg/mL after 72 h associated.

The size of the rats' prostates was decreased, after 60 days of treatment with the extract in the concentration of 30 and 300 mg/mL doses, which was indicated to appear through induction of apoptosis [129].

Not only *in vitro* but also *in vivo* investigations are limited to anticancer examination of *A. muricata*. A reported case study of 66-year-old woman having metastatic breast cancer resulted in the stabilization of this disease by the consumption of the leaves boiled in water and Xeloda [130].

C. sinensis

C. sinensis (L.), family Theaceae, is commonly known as "Tea" which is most accomplished drink in the world. Chinese tea is produced from the leaves and leaf buds of this plant species. Instead, many teas such as green tea, white tea, black tea, and oolong tea are also collected from this plant, but they are processed in different ways according to their oxidation levels [131]. It has been reported that teas contain nearly 4000 bioactive compounds, one-third of which is contributed by polyphenols [132], which are mostly flavonoids [133]. Among polyphenols, catechins such as (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), (-)-epigallocatechin (EGC), and (-)-EGC gallate (EGCG) are thought to be responsible for health benefits that have conventionally been recognized to tea particularly green tea. (-)-EGCG of green tea is most effective catechin and obtained in higher concentration as compared to black tea [134,135]. It has been confirmed that green tea has the efficiency to cure skin cancer caused by ultraviolet radiation [136].

Catechins from green tea have reputed anticancer properties in the tumor cell proliferation inhibition, and also, they help in the devastation of leukemia cells [137]. Epidemiologically, it has been shown that EGCG, a potent polyphenol in green tea, has been seen to play a crucial role on invasion inhibition and migration of human oral and colon cancer cells which can be linked with the reduced production of MMP-2, MMP-9, and uPA. It has also been found that EGCG inhibits the growth of carcinoma of ovarian cell lines OVCA and HEY, human colon, and rectal cancer cell lines HT-29 and HCA-7 [138,139].

Momordica charantia

This plant is from family Cucurbitaceae, popularly known as bitter gourd, bitter apple, bitter melon, Karela, balsam pear, and wild cucumber. In stern and Southern Asia, it is an essential market vegetable [140] and is extensively cultivated in Asia, Africa, and South America [141]. It has been reported that the crude extracts of fruit and leaf of *M. charantia* have antitumor capability on some tumors, which include prostate cancer [142], melanoma and DMBA-induced skin tumorigenesis, and

cytogenicity [143], and also antitumor activity in murine lymphoma was reported approximately two decades back [144]. MAP30 (Momordica protein of 30 kDa) is one of various ribosome-inactivating proteins (RIPs) from *M. charantia* showed anti-tumor activity, and its effectiveness has been tested in estrogen-independent and highly metastatic human breast tumor MDA-MB-231 cells, resulted in the inhibition of *in vitro* expression of the HER2 gene plus inhibition of tumor cell proliferation [145].

Particularly, the extract of *M. charantia* using methanol as solvent revealed cytotoxic consequence against a variety of cancer cell lines such as HCT-116 colorectal, Hone-1 nasopharyngeal carcinoma, AGS gastric adenocarcinoma, and CL1-0 lung adenocarcinoma cells with IC50 value ranging from 0.25 to 0.35 mg/mL [146]. Besides, a cucurbitane-type triterpene screened from wild bitter melon provoked apoptotic death in breast cancer cells through the activation of peroxisome proliferator-activated receptor γ [147].

W. somnifera

A shrub of Solanaceae family regarded as one of the important members of generally regarded as safe plants found all over in India [148], having anticarcinogenic properties [149]. It has been suggested that this plant is used as an alternative long-term remedy to avoid the spread of cancer cells, after the analysis of root extracts against vimentin pro-metastatic protein, and thus, this plant is used to create motility inhibition of cells of breast tumors in different formulations [150].

Formerly, the extract from the roots of *W. somnifera* was used to treat many ailments such as rheumatism, arthritis, and hypertension in traditional Indian medicine [148], but presently, in the United States, the same extract is used as a dietary enhancement and has received universal attention due to its pharmacological actions [151]. Essential phytochemicals of *W. somnifera* are withanolides, withaferin, and derivatives [152]. WA, a steroidal lactone, isolated from the extracts of this plant showed significant antitumor efficiency *in vivo* [151]. It has been proved that even in small concentrations, the root extracts of *W. somnifera* can inhibit the breast cancer metastasis with nominal adverse effects in rats [150]. Similarly, it has also been described that *W. somnifera* was used against prostate tumors by the metabolic inactivation of CDC2 catastrophe followed by cell death, by acting as a phase G2/M cell cycle of tumor cells [153].

The study reveals that the active component of aqueous leaf extract such as triethylene glycol shows accountable anticancer activity by the activation of p53 and pRB (tumor suppressor protein) by preparing the hydroalcoholic leaf extract to evaluate the cytotoxicity against breast cancer, lung cancer, and ovary cancer [154], this suggests that the leaf extracts are more effective for breast cancer compared to lung and ovary cancer, and this hydroalcoholic leaf extract contains polyphenolic compound which is more effective against cancer cells.

C. sativus

C. sativus L. (saffron) is an important member of family Iridaceae, which among the various spices has been created an interest, because in addition to flavoring means, it has been used in a large number of properties including antimutagenic, free radical scavenging, and immunomodulating effects, after a number of pharmacological experiments [155]. By the ancient Chinese, Arabian, and Indian cultures, saffron is used as an herbal remedy for a variety of disorders including cancer [156]. Saffron is rich in carotenoids, which include two major natural carotenoids, crocin and crocetin, which are responsible for its color. After the pre-clinical evidences, it has been revealed that the dietary intake of saffron and its ingredients affects antitumor property through *in vitro* and *in vivo* methods [157]. It has the potential to induce apoptotic and cytotoxic effects in A549 (lung cancer cells), and following saffron administration, cell proliferation reduced by giving it in a time- and dose-dependent way [158].

It has been investigated that the antiproliferative activities of extracts obtained from saffron and its chemical constituent "crocin" against

5 different malignant and also non-malignant prostate cancer cell lines, by which all these cells were incubated for 48 h in different concentrations of saffron extract and crocin. It has been observed that both saffron extract and crocin reduced proliferation of these malignant cell lines having IC50 values for saffron extract ranging between 0.4 and 4 mg/mL, and for crocin, it may range from 0.26 to 0.95 mM/mL, in a time- and concentration-dependent way, but there is no change in non-malignant cells. By the presence of the most of the apoptotic cells, flow cytometry analysis revealed that majority of cells were arrested at G0/G1 phase. It has been studied that after the analysis of western blot, Bcl-expression was strikingly downregulated, while Bax was upregulated. These findings suggest that both saffron extract and crocin inhibit cell proliferation, inducing apoptosis, and arrest cell cycle progression and act as a chemotherapeutic as well as chemopreventive agent for prostate cancer management [159].

It has also been reported by other researchers that the saffron extract and crocin extensively repressed the growth of CRC cells, while normal cells were not affected [160]. To find the effect of crocetin on cancer cells of breast, the MDA-MB-231 cells which are highly persistent were used, and their viability and persistence were measured with the WST-1 assay and a reconstituted basement membrane, respectively. Results show that invasiveness of MDA-MB-231 cell inhibited through crocetin through down regulation of MMP expression [161]. Recent studies showed that crocetin has major potential as an antitumor agent in cell cultures and animal model systems by inducing apoptosis, enhancing anti-oxidative system, affecting the growth of cancer cells (by inhibiting nucleic acid synthesis), and hindering growth factor signaling pathways [156].

C. longa

C. longa L. a perennial herb, from the family Zingiberaceae, measures up to 1m height having a short stem, which is being widely cultivated in Asian countries, mostly in India and China and is distributed throughout tropical and subtropical regions of the world [162]. In addition to cholesterol-lowering, anti-inflammatory, antidiabetic, and antioxidant properties, curcumin has said to have anticancer activity in both *in vitro* and *in vivo* models. Clinical studies on humans showed that curcumin is safe and effective. It has been confirmed by the FDA that this compound curcumin is generally recognized as safe [163,164].

It has been studied that these methods (*in vitro* and *in vivo*) designate that curcumin avoids carcinogenesis by disturbing two main processes such as tumor growth and angiogenesis [165]. It has been confirmed that administration of curcumin extensively reduces the levels of CDK4 and cyclin D1 (cell cycle regulators), and expression of p53 was inhibited, in which p53 is an upstream controller of the CDK4-cyclin D1 complex [166]. It provokes cell death in a number of animal and human cell lines including melanoma, leukemia, and carcinoma of ovaries, lungs, liver, colon and breast [167]. Cell growth of Chinese Hamster Ovary cell is inhibited by the extracts obtained from *C. longa* at a concentration of 0.4 mg/mL, and in the same concentration, it was proved to be cytotoxic against Dalton's lymphoma cells and lymphocytes. The cytotoxic effect was seen at room temperature (30°C) within half an hour. Curcumin, the active constituent of *C. longa* also showed cytotoxic effects against Dalton's lymphoma cells and lymphocytes at a concentration of 4 μ g/mL. Initial trials signified that *C. longa* extract and curcumin diminished the growth of animal tumours [168].

Achyranthes aspera

A. aspera L., from the family Amaranthaceae, is a small herb with a number of medicinal properties, against dysentery, rheumatism, bronchitis, malarial fever, renal and cardiac dropsy, asthma, hypertension, cough and diabetes mellitus, found throughout India [169]. In addition to this, Indian Ayurvedic medical practitioners have used this herb, especially the leaves and roots as a therapeutic agents for cancer therapy [170]. This plant alone or in amalgamation has played a very crucial role to cure pancreatic cancer as well as tumors of other organ sites. Undependable reports indicate that the plant extract recovered the

whole general welfare in cancer patients, especially those suffering from cancer of pancreas, when the extract is administered orally. It has been demonstrated that the leaf extract of this plant obtained using methanol as solvent system showed cellular specificity, and time- and dose-dependent cytotoxicity to the cancer cells of humans *in vitro* without harming the normal cells [171].

It has been reported that the alkaloid, non-alkaloid, and saponin fractions obtained from methanolic extract showed cancer prevention induced by the carcinogen 12-O-tetradecanoylphorbol-13-acetate (at a concentration of 100 µg) on the Epstein-Barr virus early antigen in Raji cells. The non-alkaloid fractions having polar compounds showed the most significant inhibitory activity *in vitro* [172].

Oroxylum indicum

O. indicum (also called Sonapatha) from the family Bignoniaceae is found to be an important herb in Ayurvedic medicine, in which all of its parts showed indigenous medicinal properties [173]. Using various *in vivo* and *in vitro* models, studies have proved a number of anticancer probabilities of *O. indicum*. It has been reported that the extraction of *O. indicum* with ethanol in the concentration of 0.05% showed antiproliferative and cytotoxic effects against Hep 2 cell lines [174].

It has been reported that the methanolic fruit extract of this plant also caused *in vitro* proliferation of HL-60 cell lines and the most important and active chemical constituent baicalein (a flavonoid) isolated from this extract, provoked apoptosis of tumor cells in advanced doses, and showed more cytotoxicity against HL-60 cell lines. After treating with baicalein, the cell viability was quantified using trypan blue staining after 24 h, and the results indicate that this compound caused 50% inhibition of HL-60 cell lines at 25–30 µM concentration [175].

Some researchers reported that the extract obtained from this plant using the same solvent system powerfully reduced the Trp-P-1 mutagenicity in an Ames test. It happened due to the presence of baicalein (3.95±0.43%, dry weight) in the methanolic extract having the IC50 value of 2.78±0.15 µM and it acted as desmutagen as it repressed the Trp-P-2 N-hydroxylation [176]. It has been found genotypic and showed cell proliferative activity after the administration of a crude extract of *O. indicum* in the concentration of 0.25–2 g/kg of body weight of the pyloric mucosa of the stomach of rat [177]. In addition, the extract obtained from *O. indicum* using ethanol as solvent showed strong toxicity on many tumor cell lines such as B-16, HL-60, CEM, and HCT-8 having IC50 values 17.2, 14.2, 19.6, and 32.51 g/mL, respectively [178].

Recently, it has been confirmed that *O. indicum* extracts such as methanolic and aqueous extracts revealed extensive cytotoxicity in certain cell lines having restrained levels of DNA protection from oxidative stress [179].

CONCLUSION

The American Cancer Society defines cancer as a group of diseases that are characterized by the uncontrolled growth and spread of abnormal cells. Normal cells divide rapidly to supply the new growth necessary to replace injured cells and then return to normal rate of division. Cancer cells divide haphazardly and accumulate into a non-structured mass or tumor. The tumor becomes invasive when they spread beyond their point of origin, and even after spreading, they continue to behave like cancer at the original site. All our cells share a majority of functions and are similar in structure. Cancers can be classified by function and location of the cells from which they originate. The cancer can be classified as per their derivation, like carcinomas, which are derived from epithelial tissues, leukemias which originate from white blood cells, and myeloma which is the cancer of white blood cells that are responsible for the manufacture of antibodies.

According to the WHO, approximately 80% population from developing countries are facing complications from synthetic drugs. There are various methods for treatment of cancer. Surgery is typical and first

choice and is done when cancer is localized meaning it has not spread. The next method is chemotherapy which is used depending on the type and stage of cancer. The chemotherapeutic strategies are very striking and have earned serious concern as potential means of controlling the incidence of this dreadful disease. Chemotherapy especially treats cancer by injecting strong medicine to a patient and allowing the drugs to travel throughout the body. The treatment is given in cycles. The side effects include vomiting, hair loss, infections, and fatigue. Radiation also treats localized cancer. It destroys cancer cells, so they do not multiply. It is used alone or in addition to chemotherapy. More than one half people undergo radiation.

Although a great advancement has been made in treatment and control of cancer progression. A number of undesired side effects sometimes occur during chemotherapy. Since ancient times, medicinal plants have attracted enormous attention to fight against various diseases due to their broad-spectrum biological and therapeutic properties. The use of medicinal plant products to manage or arrest the carcinogenic provides an alternative to use the conventional allopathic medicine for treatment of the disease. Many herbs with diverse chemical structures of natural origin from plants have been discovered as anticancer agents, such as VCR, VLB, podophyllotoxin, CPT, taxol, resveratrol, WA, quercetin, and curcumin. These plant-derived products have shown promise anticancer therapies. There are evidences that these plant products have shown relatively low side effects, and more research on plants and plant-derived chemicals may result in the discovery of potent anticancer agents. We aim to investigate the selected medicinal plants for their anticancer properties. In particular, novel compounds from plants have beneficial effects on human health.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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