ETHNOPHARMACOLOGICAL REVIEW OF NATURAL PRODUCTS IN CANCER PREVENTION AND THERAPY

ZEENAT AYOUB¹, ARCHANA MEHTA*, SIDDHARTHA KUMAR MISHRA²*

¹Department of Botany, ²Department of Zoology, Dr. Harisinh Gour Vishwavidyalaya (A Central University), Sagar (M.P.), India.

Email: mehtaarchana60@gmail.com; siddharthakm@yahoo.com

Received: 16 January 2018, Revised and Accepted: 28 February 2018

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 (phytochemicals) 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 to 3.8 times more in highly developed countries compared with those 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 synergistic 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 [VBL] 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 discovered by David Lane in 1979 (UK). Proteins are made, which function normally but opposite to that of oncogenesis 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, cells have the ability to commit suicide when something goes wrong. A number of SGs 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 fluoride 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

| 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        |
| Dignoxin      | 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’ 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 microtubule polymerization) | Microbe     |
| Tetracycline  | Antibiotic                     | Inhibition of protein synthesis by binding to the ribosome 30S subunit     | Microbe      |
| Manoolide     | Anti-inflammatory, analgesic    | Inhibition of phospholipase A2                                              | Marine organism |
| Spongistatin 1| Antifungal                     | Inhibition of tubulin polymerization                                        | Marine organism |

Table 1: Therapeutic drugs from natural sources

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 the 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 (TPP; 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 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...
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 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 2.5 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-κB 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 studies 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. Signaling 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 polymerase 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 the upregulation 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, caspase 3, caspase 9, Bax, and p-TEF 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 anticyclobacterial 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 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 kinetic activity assays, and by transmission electron microscopy, in vivo analysis on nude mice model was done. 16.7 and 188 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 factors, 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...
Curcuma longa has been recognized throughout the written history [83]. For centuries, this naturally occurring compound, known as curcumin, has been studied for its potential health benefits, especially in relation to its anti-inflammatory and anti-cancer properties [78]. Curcumin is derived from the ground rhizome of Curcuma longa and was proved genotoxic to the hepatic (HTC) cells after 24 h of treatment [81]. It has been revealed that curcumin inhibits the breast cancer cell proliferation through the function of Nrf2 to the Fen1 promoter. These records proposed that curcumin could inhibit the breast cancer cell proliferation as well as inhibition of proliferation, metastasis, and angiogenesis in colorectal cell lines [79].

Anticancer activity of rutin has 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 anti-angiogenic activity [90]. 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 µM 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 essay, which showed DNA damage significantly at highest concentration of 810 µM 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 immune suppression [82].

Curcumin (diferuloylmethane), a well-known flavonoid, 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 referred by its capability to adapt a number of 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 nociose 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 feni-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 Feni 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 expression in a Nrf2-dependent manner. Advanced analysis revealed that curcumin could inhibit the breast cancer cell proliferation through downregulation of Feni expression mediated by Nrf2 which might be a new method of tumor growth inhibition induced by curcumin in [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-benzopyran-5,10-dione is a constituent of phenolic compounds in certain fruits and nuts, such as strawberries, raisins, walnuts, mango kernel, longan seed, and pomegranate, and it was recognized that ellagic acid possesses many pharmacological activities including metal chelating, antibacterial, anti-fibrotic, anti-viral, anti-inflammatory, anti-cancer, and anti-inflammatory 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 5 phase, downregulating of cyclins A and B1 and upregulating of cyclin E, induction of apoptosis through intrinsic pathway (PAS-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-butane, 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 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-2,2-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 anti-tumor [104], immunosuppressive [105], anti-inflammatory, and antitumor [106]. Ergosterol peroxide reduced the growth of HL-60 cells and also induced apoptosis at the concentration of 25 µM 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-κB 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...
| Compounds          | Chemical structure          | Plant                        | Type of cancer                        | References |
|--------------------|-----------------------------|------------------------------|---------------------------------------|------------|
| Resveratrol        | ![Resveratrol Structure]    | *V. grandiflorum, V. vinifera* | Breast cancer CRC, ovarian cancer     | [111] [112] [113] |
| WA                 | ![WA Structure]             | *W. somnifera*               | Leukemia                              | [47] |
|                    |                             |                              | Breast cancer                         | [49] |
|                    |                             |                              | Pancreatic cancer                     | [50] |
|                    |                             |                              | Prostate cancer                       | [48] |
|                    |                             |                              | Colon cancer                          |          |
| Kaempferol         | ![Kaempferol Structure]     | *C. sinensis*                | Breast cancer                         | [57] |
|                    |                             | *C. spinosa*                 | Lung cancer                           | [58] |
|                    |                             | *(Capers)*                   | Prostate cancer                       | [59] |
|                    |                             | *C. sativus*                 | Kidney cancer                         | [60] |
|                    |                             | *(Saffron)*                  | Cervical cancer                       | [64] |
|                    |                             |                              | Stomach cancer                        | [63] |
| Dehydrocostus lactone | ![Dehydrocostus Structure] | *S. lappa*                   | Breast cancer                         | [63] |
|                    |                             | *A. lappa*                   | Lung cancer                           | [64] |
|                    |                             |                              | Leukemia                              | [67] |
|                    |                             |                              | Hepatocellular cancer                 | [66] |
|                    |                             |                              | Carcinoma                             | [70] |
|                    |                             |                              | Prostate cancer                       | [69] |
|                    |                             |                              | [60] |
| Quercetin          | ![Quercetin Structure]      | Capers, lovage, berries,     | OSCC                                  | [71] |
|                    |                             | citrus fruits, red onions,   | Prostate cancer                       | [74] |
|                    |                             | cherries, grapes, apples,    | Cervical cancer                       | [114] |
|                    |                             | broccoli, tea *(C. sinensis)*| Myeloid leukemia                      | [75,115] |
| Rutin              | ![Rutin Structure]          | *F. esculentum* (buckwheat), | Leukemia                              | [80] |
|                    |                             | *C. sinensis* (tea), and     | CRC                                   | [79] |
|                    |                             | *M. pumila* (apple) passion  | Hepatic cancer                        | [81] |
|                    |                             | flower                      |                                        |            |
| Curcumin           | ![Curcumin Structure]       | *C. longa*                   | Skin cancer                           | [91] |
|                    |                             |                              | Breast cancer                         | [92] |
|                    |                             |                              | Leukemia                              | [93] |
|                    |                             |                              | Lung cancer                           | [94] |
|                    |                             |                              | Hepatic cancer                        | [95] |

(Contd...)
such as cancer, cardiovascular disorders, HIV drug-induced lipid disorders, cold, flu, and prevention of tick bite, which appear to act effectively 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* (Annonaceae family) is commonly known as soursop, graviola, guanabana, paw-paw, and sirak. 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 leukemia 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 (EGGG) 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 in cancer cells which can be linked with the reduced production of MMP-2, MMP-9, and uPA. It has also been found that EGGG inhibits the growth of carcinoma of ovarian cell lines OVCA and HV, human colon, and rectal cancer cell lines HP-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 DMAA-induced skin tumorigenesis, and...
cytotoxocity [143], and also antitumor activity in murine lymphoma was reported approximately two decades back [144]. MAP30 (Momontica 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, bone-1 nasopharyngeal carcinoma, AGS gastric adeno carcinoma, and CL1-0 lung adeno carcinoma cells with IC50 value ranging from 0.25 to 0.35 mg/mL [146]. Besides, a cucurbitane-type triterpene screened from wild bitter gourd 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 antarcinogenic 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 p21 (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 is of western blot, Bcl-2 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 tropical and subtropical regions of the world [162]. In addition to cholesterol-lowering, anti-inflamatory, anti-diabetic, 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 CD4<sup>+</sup> and cylin D1 (cell cycle regulators), and expression of p53 was inhibited, in which p53 is an upstream controller of the CDK4-cylin D1 complex [166]. It provokes cell death in a number of animal and human cancer cells 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 4µg/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 an 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 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].

Oroxyllum 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 extract 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 demutagen 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 from the pyloric mucosa of the stomach of rats [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 32.5 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 menage 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.

ACKNOWLEDGEMENT

We acknowledge the financial supports received from the University Grants Commission (UGC - Government of India) and Department of Botany, Dr. Harisingsh Gour Vishwavidyalaya (a Central University), Sagar (M.P.), India.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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