Anticancer Agents Derived from Natural Products

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Abstract: Advances in the prevention and treatment of cancer require the continued development of novel and improved chemopreventive and chemotherapeutic agents. Throughout history, natural products have afforded a rich source of anticancer agents with diverse chemical structures and bioactivities. Recent technological and methodologic advances in structure elucidation, organic synthesis, and biological assay have resulted in the isolation and clinical evaluation of various novel anticancer agents. In this review, we will present the anticancer activities, mechanism of action, structure and activity relationships of six important anticancer agents from natural products, that is, taxol, betulinic acid, camptothecin, resveratrol, podophyllotoxin and curcumin.

Keywords: Anticancer agents, natural products, anticancer activity, mechanism of action, structure and activity relationship.

1. INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. It is caused by both external factors (tobacco, chemical, radiation, infectious organisms) and internal factors (hormones, inherited mutations, immune conditions, and mutations that occur from metabolism). Cancer is potentially one of the most preventable and curable life-threatening diseases. It is the second major cause of deaths after cardiovascular diseases. In 2007, an estimated 12.3 million people were diagnosed with cancer, and 7.9 million people died of cancer worldwide. By 2020, more than 16 million new cancer cases and 10 million deaths are expected [1].

Natural products and their derivatives have historically been a major source of new pharmaceuticals and have made enormous contributions to human health. Their role in the drug discovery process is especially pronounced in the areas of anticancer and infectious disease agents, where the fractions of the drugs derived from natural products amount to 60 and 75%, respectively [2]. A large number of plant, marine, and microbial sources have been tested as leads, and many compounds have survived the potential leads. Currently, more than 30 compounds of natural origin are in different phases of clinical study for the treatment of different types of cancer [3]. In this review, we will focus on six important anticancer leads, that is, taxol, betulinic acid, camptothecin, resveratrol, podophyllotoxin and curcumin. Emphasis will be placed on their anticancer activities, mechanism of action, structure and activity relationships.

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2. TAXOL

Taxol (generic name paclitaxel, Fig. **1a**), a complex polyoxygenated naturally occurring diterpenoid isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), is currently considered one of the most important anticancer agents [4]. Taxol possesses a molecular weight of 853.91, corresponding to the formula $C_{47}H_{51}NO_{14}$. It has a basic pentadecane, tetracyclic ring system and a N-benzoyl-β-phenylisoserine side chain attached at the C-13 hydroxyl as an ester linkage. Since its initial isolation in 1966 and subsequent structural determination in 1971 [5], a tremendous amount of research focusing on the science and applications of taxol has been performed [6]. The use of taxol was approved for the treatment of advanced ovarian cancer and metastatic breast cancer in 1992 and 1994 respectively. As taxol is a highly hydrophobic compound it is administered in solution with alcohol and purified Cremophor ® EL (polyoxyethylated castor oil) to aid delivery. Since taxol was originally isolated from a natural source having a limited supply, it is now derived semi-synthetically from the inactive taxane precursor, 10-deacetylbaccatin III, found in the needles of the European yew tree, Taxus baccata [7].

2.1. Anticancer Activity

Taxol was the first compound of the taxoid series approved for clinical trials in chemotherapy against various human tumors. It showed impressive activity for the treatment of different types of cancers such as breast, lung, head and neck, prostate, ovarian and cervical cancers and Kaposi's sarcoma. The unique action of taxol spurred the development of a second-generation semisynthetic taxane, docetaxel (Taxotere) [8], approved in 1996 for anthracycline-refractory advanced breast cancer and now also used in lung cancer regimens. Effective chemotherapy in combination with other anticancer agents such as cisplatin, carboplatin, or doxorubicin has also been reported [9].

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2.2. Mechanism of Action

Taxol exhibits a unique mechanism of antitumor activity. It binds to the β-subunit of the tubulin heterodimer, the key constituent protein of cellular microtubules. The binding of the drug accelerates the polymerization of tubulin, and stabilizes the resultant microtubules, thereby inhibiting their depolymerization. This inhibition of microtubule depolymerization results in the arrest of the cell division cycle mainly at the G2/M stage, leading to apoptosis through the cell-signaling cascade [6,9].

2.3. Structure and Activity Relationship of Taxol

A number of studies have been reported on the structure and activity relationship (SAR) of taxol [10-17]. A brief summary of its SAR is described as follows:

1 Most A-nor analogues were far more less active than palitaxel in both cytotoxicity and tubulin polymerization tests. 1-Deoxygenation caused slightly reduced activity [10].

2 The C-2-benzoyloxy is essential for activity. For acyl substitutions at C-2, *meta*-substituted compounds are more cytotoxic than paclitaxel. The *para*- and *ortho*-substituents usually have negative impact on activity. Di-substituted benzoyl analogues were generally less active than their mono-substituted counterparts [11].

3 The 4,5,20-oxetane ring is not essential for the interaction of paclitaxel analogues with microtubules when C-ring conformation is locked by cyclopropane, but the oxygen atom in D ring may participate in the stabilization of drug-tubulin complex [12-15]. Removal of the 4-acetyl group reduces the activity.

4 6α Substituents don't alter their *in vitro* and *in vivo* efficacies significantly. The derivatization of the C-7-hydroxyl or change of its stereochemistry has no significant effect on anticancer activity of the molecule. 7β-MeS and 7β-$MeOCH_2S$ analogues exhibited superior activity than paclitaxel [16].

5 Reduction of 9-ketone slightly increases the activity. The 10-acetate has better activity in the case of taxol but in some analogues 10-hydroxyls have better activity.

6 The importance of C-13 substituted phenylisoserine side chain to bioactivity of paclitaxel has been acknowledged for a long time. The C-2'-hydroxyl is crucial for anticancer activity. Replacement of 3'-Ph with other alkyl or alkenyl substitutions, especially 3'-isobutenyl and 3'-isobutyl groups, usually improves the activity of paclitaxel analogues [15]. Stereochemistry at C-2' and C-3' has a dramatic effect on activity. The (2'R,3'S) isomer is significantly less active than the natural (2'R,3'S) isomer, but the (2'S,3'S) and (2'R,3'R) isomers show comparable activity with the natural isomer [17].

The further SAR study would lead to the rational design of the next generation of taxoids with better specificity, lower toxicity as well as better pharmacokinetic properties.

3. BETULINIC ACID

Betulinic acid (3β-hydroxy-lup-20(29)-en-28-oic acid, BA, Fig. **1b**), is a naturally occurring pentacyclic triterpenoid isolated from many plant species including Betula alba. (Betulaceae) [18-20], Ziziphus spp. (Rhamnaceae) [21-23], Syzygium spp. (Myrtaceae) [24, 25], Diospyros spp. (Ebenaceae) [26-28] and Paeonia spp. (Paeoniaceae) [29-31]. Betulinic acid possesses a molecular formula of $C_{30}H_{48}O_3$ with an exact mass of 456.3603. It is a white crystalline solid that exhibits limited solubility in organic alcohols such as methanol, ethanol, chloroform, and ether. Betulinic acid has low solubility in water, petroleum ether, dimethyl formamide, dimethyl sulfoxide, and benzene. However, betulinic acid is highly soluble in pyridine and acetic acid [32].

3.1. Anticancer Activity

Extensive evidence indicates that betulinic acid possesses a broader spectrum of activity against a great number of cancer cell types [33]. Initially, BA was reported to be the growth inhibitor of human melanoma in athymic mice [34]. Fulda *et al.* demonstrated that BA induces apoptosis in neuroblastoma, medulloblastoma and Ewing's sarcoma cell lines [35], primary tumor cells cultured from medulloblastoma and glioblastoma [36], glioma cell lines [37], head and neck squamous cellular carcinoma cell lines [38], and haematological malignancies [39] were also sensitive to BA-induced cytotoxicity. Zuco *et al.* reported anti-proliferative capacity of BA *in vitro* in tumor cell lines originating from different tissues [40].

3.2. Mechanism of Action

The precise molecular target and mechanism of action remain elusive and are the focus of a number of ongoing research programs [41]. Accumulated experimental evidence indicates that betulinic acid triggers apoptosis through a mitochondrial-mediated pathway [42,43]. Chintharlapalli *et al.* reported the mechanism of betulinic acid–inhibited prostate cancer growth is due to activation of selective proteasome-dependent degradation of the transcription factors specificity protein 1 (Sp1), Sp3, and Sp4 [44]. Supplemental reports suggest that the generation of reactive oxygen species, inhibition of topoisomerase I, activation of the MAP kinase cascade, inhibition of angiogenesis, and modulation of pro-growth transcriptional activators and aminopeptidase N activity may play a role in betulinic acid-induced apoptosis. These potential mechanisms of action may enable betulinic acid to be effective in cells resistant to other chemotherapeutic agents [45].

3.3. Structure and Activity Relationship of Betulinic Acid

As betulinic acid is a promising anticancer agent, further studies have been performed to synthesize betulinic acid analogs in an effort to establish a meaningful structure activity relationship as well as to get more potent anticancer agents. A brief description of its SAR has been described herein [46]:

1 The C-1, C-2, C-3, C-4, C-20 and C-28 positions are the diversity centers in betulinic acid.

2 Three rings skeleton (A, B and C rings) had played an important role in eliciting anticancer activity. Expansion of ring A did not make a major difference in the cytotoxicity.

3 C-28 carboxylic acid was essential for the cytotoxicity. The halo substituent at C-2 position in betulinic acid improved the cytotoxicity.

4 The ester at C-3 position appeared to be a better substituent for enhancing the cytotoxicity.

4. CAMPTOTHECIN

Camptothecin (CPT, Fig. **1c**), a pentacyclic alkaloid, was first isolated from the Chinese ornamental tree Camptotheca acuminata, also known as the 'tree of joy' or 'tree of love'. It is a member of the quinolinoalkaloid group and has also been isolated from Ophiorrhiza pumila and Mapia foetida. It consists of a pentacyclic ring structure that includes a pyrrole (3,4β) quinoline moiety and one asymmetric centre within the a-hydroxy lactone ring with 20(S) configuration (ring E). The compound is a high melting substance, with a molecular weight of 348.111, corresponding to the formula $C_{20}H_{16}N_2O_4$. It gives an intense blue fluorescence under UV, and is optically active, +31.3 °C. The negligible water solubility of camptothecin, conferred by the unusually weak basicity of its quinoline nitrogen atom, greatly hampered its clinical development [47].

4.1. Anticancer Activity

CPT represents one of the most promising classes of anticancer drug. It shows anticancer activity mainly for solid tumors (e.g. colon, pancreatic cancer). Since CPT itself is highly toxic and insoluble, its derivatives, such as topotecan and irinotecan, have been developed. Indications of activity in ovarian and small-cell lung cancer in phase I trials led to further investigation of topotecan in these areas [48]. Irinotecan has also shown activity in colorectal cancer, upper gastrointestinal malignancies, non-small-cell lung cancer, small-cell lung cancer and other tumors [49].

4.2. Mechanism of Action

In 1985, topoisomerase I was found to be the target of camptothecin [50,51]. The DNA topoisomerases are nuclear enzymes that catalyze the relaxation of supercoiled chromosomal DNA during DNA replication. Topoisomerase I involves the transient single-strand cleavage of duplex DNA, followed by unwinding and relegation. Camptothecin reversibly induces single-strand breaks, thereby affecting the cell's capacity to replicate. The drug binds to and stabilizes the normally transient DNA-topoisomerase I cleavable complex. These stabilized breaks are fully reversible and nonlethal [52]. However, collision of the DNA replication fork with the ternary drug-enzyme-DNA complex produces an irreversible double-strand break [50,53]. Apoptotic cell death is then mediated by caspase activation. Inhibition of caspase activation shifts the cells from apoptosis to transient G1 arrest followed by cell necrosis [54]. Thus, the mechanisms of cell death need active DNA replication to be happening, resulting in cytotoxic effects from camptothecin that is S-phase-specific [55].

4.3. Structure and Activity Relationship of Camptothecin

The characteristic structural features of the camptothecins include a five-ring backbone (rings A-E) comprised of a quinoline subunit fused through two interposed rings to a terminal α-hydroxy-δ-lactone ring with a chiral center at position C-20. Attributed to the discovery of being a selective inhibitor against Topoisomerase I in the late 1980s [50], the family of CPT derivatives has been enlarged rapidly during the last two decades. Numerous studies exploring the SAR of CPT have provided novel insights and contributed to the clinical successes already realized. A brief description of its SAR are summarized here [18,56]:

1 The conjugation and planarity of the A, B, C and D rings are required for *in vitro* and *in vivo* activity of the CPTs. Modifications in rings A and B are well tolerated and give substantial increase of the activity than CPT in many cases. Substitution at the 7-, 9-, or 10-positions of most camptothecin derivatives enhances their antitumor activity, but at the 11- or 5-position usually leads to activity decrease [57, 58]. Compounds show little activity when ring B was saturated.

2 Modifications at the C and D rings of camptothecin led to complete loss of cytotoxicity. D-ring pyridone is required for antitumour activity.

3 α-Hydroxy lactone ring is necessary for activity. Modifications in the E-ring generally reduce or abolish this activity, however, further investigations demonstrated that many other E-ring modified CPT analogues, such as expanded seven-membered β-hydroxy lactone homocamptothecin (hCPT) [59], opened lactone form hydroxy-amide and ester-amide, opened lactone hydroxy-amide with conjugation of polyethylene glycol (PEG) through the C-17 hydroxyl as well as through C-21 carboxylic acid, were proved to have comparable or even better antitumor activity than CPT [60].

4 Oxygen at C-20 is essential for activity. Replacement of this oxygen with sulfur or nitrogen abolishes the activity of CPT.

5 Conformation at C-20 is crucial for better activity as the 20(S) isomer is 10- to 100-fold more active than 20(R). The naturally occurring 20*S*-isomer of camptothecin inhibits purified topoisomerase I 10-100 times more potently than the 20*R*-isomer [61].

5. RESVERATROL

Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene, RSV, Fig. **1d**), a naturally occurring polyphenol first isolated from the roots of white hellebore (Veratrum glandiflorum O. Loes), has been found to be produced by more than 70 plant species and classified as a phytoalexin. Resveratrol is an unsymmetrical and (*E*)-geometrical stilbene and possesses a molecular formula of $C_{20}H_{22}O_8$ with an exact mass of 390.40. It is a white fine powder soluble in ethanol. Due to its broad-spectrum health beneficial effects, such as anticancer, antioxidant, and cardioprotective functions, resveratrol is considered as the state-of-the-art nature's medicine [62].

5.1. Anticancer Activity

A large number of evidence suggests that RSV might be a promising molecule both in prevention and therapy of cancer. It can affect the processes underlying all three stages of carcinogenesis, involving tumor initiation, promotion and progression. A remarkable progress in dissecting the molecular mechanisms underlying anti-cancer properties of RSV has been achieved in the past decade [65]. As a potential anti-cancer agent, RSV has been shown to induce differentiation and apoptosis in a multitude of cancer cell lines, such as leukemia, hepatoma, neuroblastoma, prostate cancer, colon cancer, gastric cancer, pancreatic cancer, esophageal tumorigenesis, breast cancer cells and human melanoma cell (e.g., LU1205, WM9, WM35, WM793) [63,64]. The compound also significantly inhibits experimental tumorigenesis in a wide range of animal models. Resveratrol targets many components of intracellular signaling pathways including pro-inflammatory mediators, regulators of cell survival and apoptosis, and tumor angiogenic and metastatic switches by modulating a distinct set of upstream kinases, transcription factors and their regulators [65].

5.2. Mechanism of Action

Resveratrol modulates the expression or activities of a series of intracellular signaling molecules involved in carcinogen metabolism, cellular proliferation, cell cycle regulation and apoptosis. Kundu *et al.* [66] summarized the biochemical mechanisms responsible for chemopreventive and chemotherapeutic potential of resveratrol. Blocking the activation of various carcinogens and/or stimulating their detoxification, preventing oxidative damage of target cell DNA, reducing inflammatory responses and diminishing proliferation of cancer cells [66-68], the induction of apoptosis in various premalignant or cancerous cells, blockade of angiogenic and metastatic processes of tumor progression, and alleviation of chemotherapy resistance [67,69,70] are responsible for the chemopreventive and chemotherapeutic potential of this compound. Accumulating data from a wide range of *in vitro* and *in vivo* studies suggest that resveratrol has been shown to modulate signal transduction mediated by a distinct set of upstream kinases (e.g., MAP kinases [71], protein kinase C (PKC) [72], phosphatidylinositol-3-kinase/Akt (PI3K/Akt) [73] and transcription factors (e.g., nuclear factor-κB (NF-κB) [74,75], activated protein-1 (AP-1) [76,77], and signal transducer of activated transcription (STAT)-3 [75,78]. While numerous studies are coming up with multiple molecular targets of resveratrol to prevent cancer, it was proposed that resveratrol might follow the same pathway as does calorie restriction [66]. Despite substantial progress in the understanding of the molecular basis of anti-carcinogenic activities of resveratrol, there have been very few clinical studies commensurate with its preclinical findings.

5.3. Structure and Activity Relationship of Resveratrol

Regarding the biological activity of RSV and its analogues, several structural determinants could be revealed so far, such as number and position of hydroxyl and/or methoxyl groups, intramolecular hydrogen bonding, and stereoisomery. Both the antioxidant and apoptotic activities of the analogues containing 3,4-dihydroxyl groups were significantly higher than those of the trans-resveratrol and the other analogs in cultured HL-60 and Jurkat human leukemia cells [79]. Deletion of the hydroxyl group at position 4′ of RSV reduces its antioxidant activity and the ortho-dihydroxy structure enhanced its activity to inhibit LDL peroxidation and free radical trapping [80]. The observation that trans-stilbenes possessing a 4′-hydroxyl group and bearing ortho-diphenoxyl or para-diphenoxyl functionalities exert remarkably increased activity than RSV provides useful information for future anticancer drug design [81].

6. PODOPHYLLOTOXIN

Podophyllotoxin (Fig. **1e**), a bioactive lignan, was isolated from the roots of the North American *Podophyllum peltatum* Linnaeus, the Tibetan *P. emodi* Wall, or the Taiwanese species *Podophyllum pleinthum* [82]. Chemically, it is an aryltetralin lignan with a lactone ring. Since the bioactivity of podophyllotoxin curing venereal warts was found in the 1940s and its structure was elucidated in 1951, it has become an important pharmaceutical compound from which anti-cancer, anti-arthritis, and anti-wart compounds are derived [83]. Two of the semisynthetic derivatives of podophyllotoxin, that is, etoposide and teniposide, are currently used in frontline cancer chemotherapy against various cancers.

6.1. Anticancer Activity

Podophyllotoxin has been extensively used as a lead agent in the development of new anticancer drugs. Podophyllotoxin shows strong cytotoxic activity against various cancer cell lines. It is effective in the treatment of Wilms tumours, various genital tumours and in non- Hodgkin's and other lymphomas and lung cancer [84,85]. However, the high toxicity and severe gastrointestinal side effect of podophyllotoxin has limited its application as a drug in cancer chemotherapy. The biological activity of podophyllotoxin has led to extensive structural modification resulting in several more potent and less toxic anticancer agents. The podophyllotoxin derivatives etoposide, etopophos, and teniposide are currently used in the chemotherapy for a variety of malignancies including small cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma [86-88].

6.2. Mechanism of Action

Podophyllotoxin inhibits the assembly of tubulin into microtubules through interaction with protein at the colchicine binding site, preventing the formation of the spindle [89,90]. The compound blocks the catalytic activity of DNA topoisomerase II by stabilizing a cleavage enzyme-DNA complex in which the DNA is cleaved and covalently linked to the enzyme [91]. However, its semisynthetic derivatives showed different mechanisms of action. Etoposide and congeners induce a premitotic blockade in late S stage of the cell cycle because of the inhibition of DNA topoisomerase II (TopII), an enzyme required for the unwinding of DNA during replication. Etoposide binds to and stabilizes the DNA-protein complex preventing religation of the double-stranded breaks [89,90].

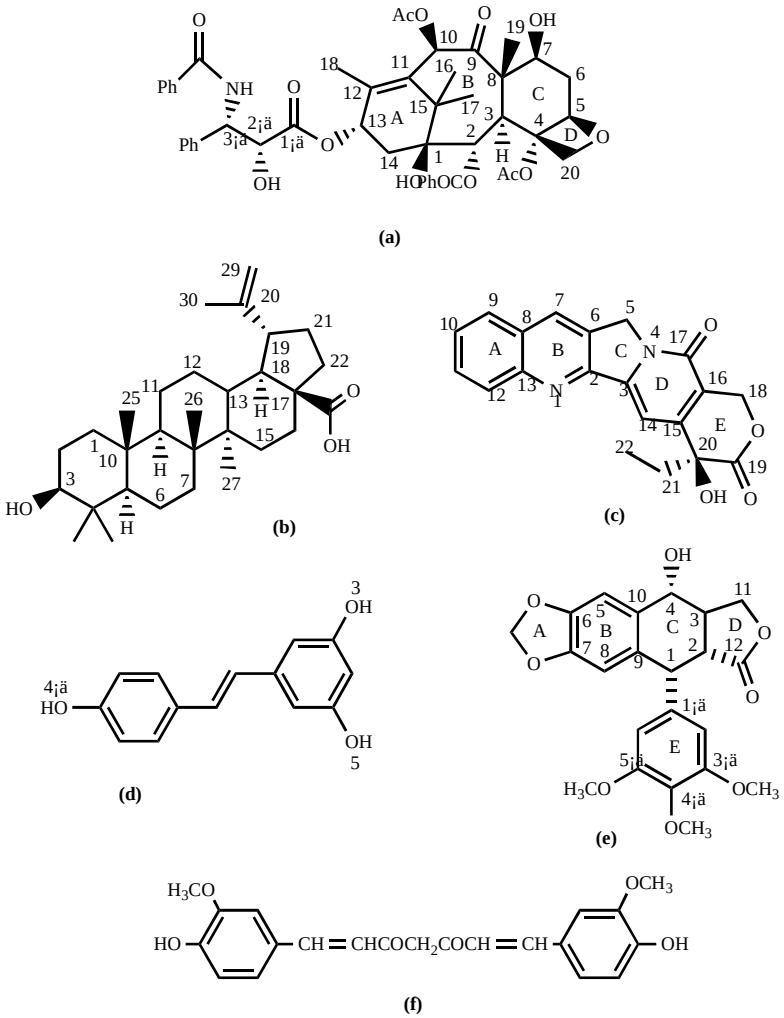

Fig. (1).

6.3. Structure and Activity Relationship of Podophyllotoxin

To improve topoisomerase-II inhibition and to overcome the problems of drug resistance, myelosuppression, and poor oral availability, extensive efforts have been made worldwide for the design and synthesis of new podophyllotoxin derivatives with potential antitumor activity. SAR studies on podophyllotoxin have revealed structural features critical for the topoisomerase-II inhibition includes 4′-demethylation, 4-epimerization, trans-lactone D ring with 2α, 3β configuration, and free rotation of ring E [90]. The comprehensive SAR of podophyllotoxin is described as follows:

1 The intact ring A is not essential for antimitotic activity [91]. Modification of the B ring resulted in a loss of activity [92].

2 The acylation of the hydroxyl group at C-9 did not influence on the cytotoxicity [93].

3 Modification of the C ring by aromatization or expansion gave compounds less potent than podophyllotoxin [94].

4 The 4β configuration is essential with various substituents at C-4 and the free 4′-OH group is crucial for cytotoxicity [95]. Modifications at the C-4 position are mostly acceptable and bulky groups at this position enhance both anticancer and topoisomerase activities.

5 The derivatives lacking a lactone ring are generally less potent as antitumor agents [96].

6 The free rotation of the E ring is necessary for antitumor activity. E ring oxygenation did not affect DNA cleavage [97].

7. CURCUMIN

Curcumin (Fig. **1f**) is a hydrophobic polyphenol derived from the rhizome of the herb Curcuma longa, commonly known as turmeric, which has been used as a healing agent for variety of illnesses for thousands of years in the Orient. Statistically from Pubmed, over 2600 papers with regard to various aspects of curcumin have been published over the last 5 decades. Chemically, it is a bis-α, β-unsaturated β-diketone (diferuloylmethane) that exhibits keto-enol tautomerism, having a predominant keto form in acidic and neutral solutions and a stable enol form in alkaline media. Curcumin is an orange–yellow crystalline powder practically insoluble in water and ether but soluble in ethanol, dimethyl-

sulfoxide, and acetone [98]. Curcumin has a melting point of 183 °C; its molecular formula is $C_{21}H_{20}O_6$ and molecular weight 368.37. Spectrophotometrically, the maximum absorption (λmax) of curcumin in methanol occurs at 430 nm and in acetone at 415– 420 nm [99].

7.1. Anticancer Activity

The exhaustive research and numerous investigations carried over the last few decades suggest that curcumin is one of the most promising and powerful chemopreventive and chemotherapeutic agents. Till now more than 800 reports have been published demonstrating the anticancer potential of curcumin. It has been shown to exhibit therapeutic potential against variety of different cancers including leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma [100]. Various clinical trials with curcumin, those that have been completed and those that are ongoing have been recently reviewed [98]. These trials have shown promise in patients with familial adenomatous polyposis, advanced pancreatic cancer, and multiple myeloma [101].

7.2. Mechanism of Action

Curcumin has been shown to suppress transformation, proliferation, and metastasis of tumors. Extensive research indicated that curcumin modulates several biochemical pathways and interact with numerous targets involved in carcinogenesis. Curcumin is a potent inhibitor of the activation of various transcription factors including NF-κB, AP-1, STAT proteins, peroxisome proliferator-activated receptor-γ (PPAR-γ), and β-catenin [102]. Curcumin has also been shown to downregulate the activity of multiple kinases (e.g., epidermal growth factor receptor (EGFR), extracellular receptor kinase (ERK), janus kinase (JAK), protein kinase C (PKC), autophosphorylation-activated protein kinase (AK), pp60c-src tyrosine kinase). Additionally, curcumin also appears to effectively regulate the activities of some enzymes that control tumor growth and proliferation (e.g., MMP (matrix metalloproteinase), iNOS (inducible nitric oxide oxidase), GST (glutathione S-transferase)), downregulate the expression of receptors (e.g., H2-R (histamine (2)-receptor), IL-8 R (interleukin 8-receptor)), suppresses the growth of several cytokines (e.g., TNF (tumor necrosis factor), IL (interleukin), MIP (macrophage inflammatory protein), and MCP (monocyte chemoattractant protein)), and inhibit the activation of growth factors (e.g., EGF (epidermal growth factor), NGF (nerve growth factor), HGF (hepatocyte growth factor), and PDGF (platelet-derived growth factor)) [100]. Curcumin's multitargeting ability may be the key to its therapeutic potential against cancer.

7.3. Structure and Activity Relationship of Curcumin

There are some reports of structure and activity relationship evaluation of curcumin analogues. These studies focused mainly on altering the aryl substitution, 1,3-diketone structure, and simplification of the dicinnamoylmethane pharmaco-phore [103]. The modification of curcumin to a diarylpentanoid and some types of the substitutions of a pair of alkoxy groups to the phenolic rings exhibit enhanced anticancer activity [104]. Structure-activity relationship analysis reveals that analogues with furan moiety have excellent inhibitory effect on thioredoxin reductase (TrxR) in an irreversible manner, indicating that the furan moiety may serve as a possible pharmacophore during the interaction of curcumin analogues with TrxR [105]. The water-soluble conjugates to poly-ethylene glycol molecules exhibited enhanced cytotoxicity as compared to that of the parent drug [106]. In a recent study, a series of curcumin analogues contained a pentadienone moiety were synthesized and exhibited potent anti-proliferative activity, which is 2-50 times more potent than curcumin [107].

CONCLUSIONS

The introduction of active agents derived from nature into the cancer prevention and treatment has changed the natural history of many types of human cancer. This review has described the mechanism of action and SAR studies of six anticancer agents obtained from plant kingdom. The huge structural diversity of natural compounds and their bioactivity potential have meant that many plant-derived products can serve as lead compounds for improvement of their therapeutic potential. Studies on mechanism of action of these anticancer agents not only reveal the molecular basis of their action, but also provide clues to the rational design of new analogues and even the molecules with different structures. The main problems with these agents include their low bioavailability due to the poor solubility in water, side effects and drug resistance. In forthcoming years, it is expected that the complementary of combinatorial chemistry, computational chemistry and bioinformatics and the advances of genomics, proteomics and pharmacogenetics will accelerate and benefit the R&D of new anticancer drugs from natural products.

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