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REVIEW ARTICLE

Anticancer Alkaloids from Trees: Development into Drugs

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ABSTRACT

Trees have made an enormous phytochemical contribution in anticancer drugs' development more than any other life form. The contributions include alkaloids that are biosynthesized in various ways and yield. Lead alkaloids isolated from the trees are taxol and camptothecins that currently have annual sales in billion dollars. Other important alkaloids isolated from these life forms include rohitukine, harringtonine, acronycine, thalicarpine, usambarensine, ellipticine, and matrines. Studies on their mechanism of action and target on the DNA and protein of cancerous cells aided the development of potent hemisynthesized congeners. The molecules and their congeners passed/are passing a long period of historical development before approved as antineoplastic drugs for cancer chemotherapy. Some of them did not find the application as anticancer drugs due to ineffectiveness in clinical trials; others are generating research interest in the antineoplastic activity at the present and have reached clinical trial stages. Potentials in antineoplastic molecules from trees are high and are hoped to be commensurate with cancer types afflicting human society in the future.

Key words: Alkaloids, camptothecin, cancer, natural products, taxol, trees

INTRODUCTION

Cancer is among diseases afflicting human society with estimated 14.1 million cases and 8.2 million deaths around the world,[1] with more than half recorded in less-developed nations and a projected increase to 19.3 million cases per year is expected.[2] Screening of plant kingdom for natural products with anticancer properties contributed to the discovery of anticancer alkaloids and recent progress in cancer chemotherapy through drugs development.[3-5] The alkaloids are secondary metabolites that are biosynthesized by the plants for a defensive role, and in many cases, no biological function is attributed to the molecules.[6] Over 10,000 are known from over 300 plant families, among which 10–25% are higher plants.[5,7-10] Studies on structure-activity-relations, hemisynthesis of congeners, and total synthesis aided their modification into anticancer drugs with enhanced solubility, efficiency, or stability in the human body.[11,12] The alkaloids and their congeners target DNA replication or protein synthesis in the mechanism of action on tumor cells, resulting in apoptosis of the neoplastic cells.[13-16] Their yield quantity depends on species and tissue of the tree; in some trees, their yield quantity is greatest in leaves, fruits, or seeds while in others, root or bark; however, in most cases, the yield is low leading to over-exploitation of natural population for the molecules.[17-20] Research on their use in cancer therapy improved therapeutic efficacy, knowledge evolution in pharmacognosy, and future development of natural product-based drug discovery approach.[21] Among difficulties in developing anticancer drugs are time need for discovery, development, and commercialization that can take from few years to as many as 40 years.[22-25] The improvements made in cancer chemotherapy in the present century are the results of more contributions from alkaloids isolated from trees than any other life form and have led to prolonged survival of patients inflicted with cancer of various kinds. The screening and identification of many anticancer alkaloids from tree species, modern technology, and advancement in instrumentation techniques made the achievements possible.[24,25] Lead alkaloids isolated from trees that show anticancer properties and developed drugs or drugs in stages of development are Taxol® and Camptothecin® discovered in the 1960s. Their isolation and structural elucidation revolutionized modern cancer research, established new principles for the development of other bioactive compounds from natural sources, and improved lives of cancer patients.[26] This article discusses the evolution of select anticancer alkaloids isolated from trees into antineoplastic drugs, their mechanism(s) of action, role, and recent advances.

Taxol

Taxol renamed Paclitaxel® and sold under the trademark Taxol® is the most successful anticancer agent developed from trees. The alkaloid – natural product taxol [Figure 1a], was isolated for the first time from the bark of *Taxus brevifolia* and characterized as part of the National Cancer Institute (NCI) screening program at Research Triangle Institute (RTI).[4] Together with other baccatins, the natural product taxol is isolated at low level from needles, seeds, and bark of *T. brevifolia*, in addition to other *Taxus species*, few gymnosperms, angiosperms, and several endophytes, as reviewed.[27] The yield quantity varies with genotype, tissue, season, and environmental factors,[17,18,28] endophytes and culture condition,[29] storage condition and extraction technique used.[30,31] The poor solubility and limited supply hampered

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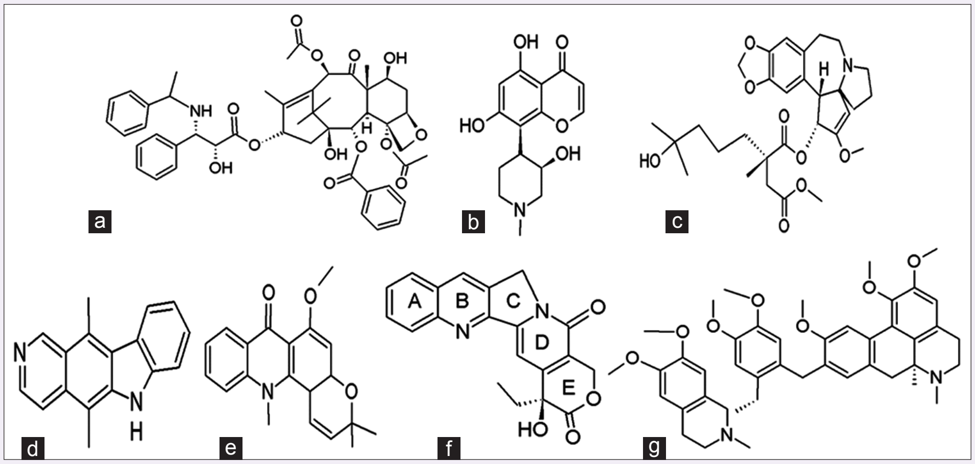

Figure 1: Chemical structures of some anticancer alkaloids isolated from trees: (a) taxol, (b) rohitukine, (c) homoharringtonine, (d) ellipticine, (e) acronycin, (f) camptothecin, (g) thalicarpine

its development into a useful drug for cancer chemotherapy. However, it passed clinical trial stages in the 1980s before approved by the United States Food and Drug Administration (FDA) for the treatment of refractory ovarian cancer.[32] The drug taxol was later approved for treatment of patients with advanced Kaposis sarcomas, breast, colon cancers and solid tumor types besides lung, bladder, prostate melanoma, esophageal, and neck cancers with an estimated annual sales above $1 billion.[32-34] Mechanism of action of the drug in tumorous cells involves stabilization of cellular microtubules through binding β-tubulin subunit, leading to interference with their normal breakdown during cell division with resultant stabilization of the polymer through protection from disassembly.[14,35] The cells show defects in mitotic spindle assembly, chromosome segregation, and cell division and are unable to achieve metaphase spindle configuration, resulting in blockage in the progress of mitotic division and prolonged activation of the mitotic checkpoint. Because of this effect, apoptosis or reversion to G-phase of the cell cycle without cell division gets triggered.[36,37] The spindle inhibition role is attributed to suppress of microtubules dynamic and occurs at lower concentrations than those needed to block mitosis. At higher therapeutic concentrations, suppression of microtubules detachment from centrosome occurs.[38,39] Due to small taxol yield from the natural sources, needing tons of trees to be fell to obtain milligram and motivated to generate new chemical understandings; several laboratories attempted a total synthesis of the molecule.[40,41] The discovery of 10-deacetylbaccatin III from needles of *Taxus* species in greater yield quantity provided a renewable source for semisynthesis and assured continuous supply without threat to the population of the *Taxus* species.[42-44] Successful synthesis and semisynthesis lead to exploration of structural activity relation (SAR) and generation of congeners. The generated congeners produced significant quantities for medical testing or therapeutic use; however, due to cost, the route is regarded unsuitable to meet demand.[45] Extensive research is carried out to find ways to mitigate side effects of taxol drugs in cancer patients through alteration of administration; solvent is used for dilution of the antineoplastic agent and safe delivery into the body of patients. Several strategies are also used to create new taxol formulations including the use of albumin nanoparticles, development of congeners, prodrugs, among others. The DHA-paclitaxel, PG-paclitaxel, as well as tumor-activated taxol prodrugs, are undergoing continued testing and under way to be introduced into widespread clinical use. In the last decade, nine taxanes underwent clinical trials; nab-paclitaxel, abraxane, and cabazitaxol are recent taxanes approved by the FDA. An update on new taxane congeners and formulations was recently reviewed.[46] The importance of taxol can be appreciated considering out of 269 cancer clinical trials recorded by the NCI in the year 2004, 248 involved taxanes-derived drugs. Among them, 134 with paclitaxel, 105 with docetaxel, and 10 with miscellaneous taxanes as single agents or in combined with other anticancer agents.[47] Much lives-saving cancer statistics could be cited and most notable is the treatment of ovarian cancer, in which survival rate of patients increased since the introduction of taxol in the treatment regimen.[47] Nowadays, the supply of taxol for the production of the drugs is met by semisynthesis from a precursor, fermentation technology of microbes, and using plant cell culture. Taxol is then extracted from latter, purified by chromatography and isolated by crystallization. Advances in new technologies and refined techniques of extraction from natural sources are facilitating continuous supply to meet demand.

Camptothecin

Camptothecin is monoterpene pentacyclic quinoline alkaloid discovered from leaves extracts of *Camptotheca acuminata* during screening of natural products for anticancer drugs development at RTI in an extensive screening program of the NCI on anticancer agents.[47] The alkaloid is produced in Nothapodytes nimmoniana at higher yield quantity than other plant natural sources [Table 1]. Besides plant sources, camptothecin is produced by many endophytes isolated from camptothecin-producing host plants as well as when the endophytes were grown in culture media.[48] Camptothecin and congeners are S-phase-specific drugs that show spectrum activity on neoplastic cells. The tumor cells need prolonged exposure to camptothecin concentration exceeding least threshold to exert an effect.[49-51] During bioactivity testing of camptothecin, it showed a remarkable prolongation of mice with L1210 leukemia cells,[47] Walker WM tumor,[49-53] and P388 leukemia.[53] The success encouraged preliminary and clinical trials with a resultant remarkable anticancer activity. However, side effects of low solubility and high adverse drug reaction halted further studies.[49] During phase I trials, primarily in gastrointestinal tumors, the partial response for a short duration with unpredictable side effects of diarrhea, vomiting, severe hemorrhagic cystitis, and myelosuppression was shown.[54,55] In clinical trials carried out in the USA, very poor response in patients was recorded;[56] however, in China, effective response in intestinal, gastric, bladder carcinoma and head and neck cancers was observed.[57] Following

Table 1: Plant sources of camptothecin

Source species	Family	Reference
N. nimmoniana (J. Grah) Mabb.	Icacinaceae	[171]
*C. acuminat*a Decne.	Nyssaceae	[3,172]
Ervatamia heyneana (Wall) T. Cooke	Apocynaceae	[173]
Merrilliodendron megacarpam (Hmsl.) Sleum	Icacinaceae	[174]
Mostuca brunonis Didr.	Loganiaceae	[175]
C. lowreyana	Nyssaceae	[172, 176]
P. klaineana Pierre ex Exxel amd Mendonca	Icacinaceae	[176]
P. volubilis	Icacinaceae	[177]
C. grandiflora	Apocynaceae	[178]
S. kleinii	Icacinaceae	[177]
O. mungos Linn.	Rubiaceae	[179]
O. pumila Champ.	Rubiaceae	[180]
O. liukiuensis	Rubiaceae	[181,182]
O. kuroiwai	Rubiaceae	[181]
O. rugosa var. *decumbens, var*. prostate	Rubiaceae	[183]
O. rugosa var. prostate	Rubiaceae	[184]
O. communis	Rubiaceae	[185, 186]
O. tomentosa	Rubiaceae	[185]
O. japonicas	Rubiaceae	[186]
O. shendurunii	Rubiaceae	[187]
O. grandiflora	Rubiaceae	[187]
O. oriantha	Rubiaceae	[187]
O. trichocarpon	Rubiaceae	[187]
O. pectinata	Rubiaceae	[187]
O. filistipula	Rubiaceae	[188]
G. comosa	Stemonuraceae	[177]
G. coriacea	Stemonuraceae	[177]
G. polymorpha	Stemonuraceae	[177]
G. tetrandra	Stemonuraceae	[177]
I. cirrhosa	Icacinaceae	[177]
I. hookeriana	Icacinaceae	[177]
M. dentata	Icacinaceae	[177]
M. kleinii	Icacinaceae	[177]
N. herpeticum	Icacinaceae	[177]
A. dimidiata	Icacinaceae	[177]
C. andamanicus (Kurz) R.A.Howard	Icacinaceae	[177]
D. binectariferum	Meliaceae	[189]

D. binectariferum=Dysoxylum binectariferum, C. andamanicus=Codiocarpus andamanicus, A. dimidiata=Apodytes dimidiata, N. herpeticum=Natsiatum herpeticum, M. kleinii=Myrceugenia kleinii, M. dentata=Miquelia dentata, I. hookeriana=Iodes hookeriana, I. cirrhosa=Iodes cirrhosa, G. comosa=Gomphandra comosa, G. polymorpha=Gomphandra polymorpha, G. tetrandra=Gomphandra tetrandra, O. filistipula=Ophiorrhiza filistipula, O. barberi=Ophiorrhiza barberi, O. communis=Ophiorrhiza communis, O. tomentosa=Ophiorrhiza tomentosa, O. japonica=Ophiorrhiza japonica, O. shendurunii=Ophiorrhiza shendurunii, O. grandiflora=Ophiorrhiza grandiflora, O. oriantha=Ophiorrhiza oriantha, O. pectinata=Ophiorrhiza pectinata, O. rugosa=Ophiorrhiza rugosa, O. kuroiwai=Ophiorrhiza kuroiwai, O. liukiuensis=Ophiorrhiza liukiuensis, O.pumila=Ophiorrhiza pumila, O.mungos=Ophiorrhiza mungos, S.kleinii=Sarcostigma kleinii, C. grandiflora=Chonemorpha grandiflora, P. volubilis=Plukenetia volubilis, P. klaineana=Pyrenacantha klaineana, C. acuminata=Camptotheca acuminata, N. nimmoniana=Nothapodytes nimmoniana

these trials, research on antitumor activity of camptothecin slowed due to the poor solubility and unpredictable cytotoxicity, but discovery of the unique mechanism of tumor inhibition of cells in the mid-1980s revived interest in possibility to use the molecule and developed congeners to treat cancer patients.[15,49] The mechanism of action in camptothecin involves binding topoisomerase I–DNA covalent complex, resulting in the formation of a ternary complex that gets stabilized and DNA prevented from religation during replication. The effect causes damage in DNA and apoptosis of the cancer cells due to the conversion of single-strand break into double-strand break resultant from the collision of the replication fork at cleavable complex.[15] The 20 (S)-hydroxyl, pyridine moiety of D-ring, lactone moiety of E-ring in the chemical structure [Figure 1f] and planarity of 5-membered ring are structural features important for the antitumor activity.[58] When A and B rings in the chemical structure were modified [Figure 1f], potent and soluble congeners resulted.[49,54] Irinotecan and topotecan are the first water-soluble congeners approved by the US FDA for the treatment of metastatic colorectal, ovarian, and primary colon cancers. The two congeners marketed by Pharmacia and GlaxoSmithKline in the USA had a combined annual sales near $1 billion in 2003.[26] In July 2004, from 2069 cancer clinical trials recorded by the NCI, 94 involved camptothecin-derived drugs. Among these numbers, 64 are with irinotecan, 26 with topotecan, and 4 with other miscellaneous congeners either as single agents or in combined with other anticancer agents.[47] Following the successful development of the congeners and growing understanding of the SAR of camptothecin, development of another generation of the congeners started and currently, many are in different phases of clinical trials. Congeners such as 9-amino camptothecin, 9-nitro camptothecin, and belotecan are investigated for use alone or in combined therapies as late-stage treatment and show a differential response in patients with dose. Studies on causes and effects for optimization of proper applicable uniform therapeutic dosage, mechanism of resistance and sensitivity to the congeners across patients are promising. Preclinical studies indicated that proper sequencing with drugs that modulate cell cycle checkpoints could enhance the anticancer activity of camptothecins. Enhancement in therapeutic effectiveness of the drugs through combination with other anticancer drugs and treatment modalities such as radiation and biological agents is the focus of attention in clinical research.[59] Considering increasing knowledge on SAR of camptothecin, development of congeners with improved pharmacodynamics, pharmacokinetics, and clinical pharmacology with less adverse effect than the current ones approved for cancer chemotherapy is hoped in near future. Pharmacokinetic profile of irinotecan and severe adverse effects are not yet understood in clinical practice.

Rohitukine

Rohitukine is a chromone alkaloid first isolated from leaves and stems of Amoora rohituka,[60] later in *Dysoxylum binectariferum*,[61] *Schumanniophyton magnificum*, and *Schumanniophyton problematicum*[62,63] and from isolated endophytes.[64,65] Rohitukine N-oxide and N-demethylrohitukine-3'-acetate were isolated from the stem bark of *S. magnificum*[66,67] and endophytes isolated from *D. binectariferum*.[65] Rohitukine showed many bioactivities including anti-inflammatory and immunomodulatory effects,[61] inhibition of *in vitro* adipogenesis, and arrest of mitotic clonal expansion with dyslipidemia *in vivo*.[68,69] The alkaloid showed anti-fertility activity and efforts are made to enhance anti-implantation activity through structural modification[70] but showed toxicity at a moderate level against human HL-60 promyelocytic leukemia and HCT-166 colon cancer cells.[67] The distinctive chemical structure of rohitukine [Figure 1b] presents a framework for derivatization and chemical synthesis of new novel molecules.[61] Flavopiridol and P-276-00 are two rohitukine congeners currently evaluated in the advanced phase II clinical trials for potential antitumor therapy.[71] The congeners inhibited proliferation of several human tumor cells *in vitro* and *in vivo* through inhibition of many cyclin-dependent kinases (CDKs) via interference with their phosphorylation, hamper of activation, as well as blockage of cell cycle progression at G1 and G2 stages.[72] Flavopiridol is an approved potent orphan drug for treatment of chronic lymphocytic leukemia[73,74] and a pan-CDK inhibitor that arrests the cell cycle in G1/S or G2/M phase.[72] It shows effective action against most cancer cell lines and tumorous growth suppression in animals.[75-78] The congener blocks

HIV-1 Tat transactivation,[79] viral replication via inhibition of P-TEFb kinase activity.[80] In preclinical trials, flavopiridol showed inhibited proliferation of several human tumor cells in the *in vitro* and *in vivo*, leading to successful phase I trial.[81-83] Phase II along with phase III trials against many classes of cancers as a single agent showed discouraging results but in a combinatorial regimen with other agents, particularly with paclitaxel and cis-platinum showed encouraging results.[84,85] P-276-00 is another congener and promising anticancer drug in phase II clinical trial, for an advanced form of refractory neoplasm and multiple myelomas.[86,87] In the *in vitro* and *in vivo* trial studies, the congener inhibited transcription in multiple myelomas by inhibiting transcription of positive regulatory Cdk9-T[88] and growth of Mantle Cell Lymphoma cell lines through apoptosis induction in time- and dose-dependent way with potent cytotoxicity against nodal and blastic variant cells due to the accumulation of the cells in G1-S phase in the cell lines.[89] It showed toxicity profile with antitumor activities and potential to inhibit the HIF-1 pathway but did not show enhanced cytotoxicity in prostate cancer cells. However, it arrested them in G2/M phase of the cell cycle.[90] P-276-00 inhibited tubular formation of human umbilical vein endothelial cells[91] migration of prostate cancer cells in the *in vitro* with significant *in vivo* efficacy in PC-3 xenograft model[92] and is likely anti-angiogenic in chemotherapy of prostate cancer.[93,94] Although the biosynthetic pathway of rohitukine is yet to be elucidated, several semisynthetic congeners are in advanced stages of the clinical trial against cancer cells and in humans. Prospecting for a new source of the alkaloid from plants and endophytes will offer an alternative source of utility.

Harringtonine

Harringtonine and cephalotaxine were isolated for the first time from *Cephalotaxus harringtonia* and other members of the genus.[94,95] The chemical structure of harringtonine [Figure 1c] was determined,[96] and anti-leukemic effect of esters (harringtonine, homoharringtonine, isoharringtonine, deoxyharringtonine) on mouse P-388 and L-1210 cell lines established.[97] The esters of harringtonine differ in structural side chain methylene group, and homoharringtonine is most active of the series while members lacking the methylene group are inactive.[98] For many years and in most cases using a racemic mixture, Chinese scientists identified harringtonine as active antineoplastic agent for the treatment of acute myelogenous leukemia (AML), myelodysplastic syndrome, acute promyelocytic leukemia, and intrathecal therapy for central nervous system leukemia.[99-101] The treatment therapy developed by Chinese produced increased survival of patients at reduced expenses.[102] The racemic mixture of harringtonine and homoharringtonine is regarded favorable agents to treat aged cancer patients due to their relative mild cytotoxicity with efficacy against leukemia of different kinds.[103] Studies on the alkaloid in the 1980s and 1990s were mostly as a single agent, in combined with interferon-alpha, low-dose cytarabine, and with both in late and early chronic-phase chronic myelogenous leukemia (CML).[100,101,104-106] Similar to many anticancer alkaloids, development into a useful anticancer drug was hindered by difficult production of the alkaloid due to unreliable source supply, toxicity profile of original treatment schedules, large quantity of *Cephalotaxus* trees required, success of tyrosine kinase inhibitors (TKIs) in CML, and uncertainty in role of homoharringtonine to TKIs.[23,107] Purified homoharringtonine showed efficacy against leukemias of various kinds including resistant ones to standard treatment and produced complete hematological remission in patients with late chronic-phase CML.[104] The combination therapy with several anticancer drugs also yields positive results; for instance, combinations of homoharringtonine with prednisone, adriamycin, and thioguanine as well as with Chinese traditional medication employed in phase I clinical trial in patients suffering ACL resulted in complete remission.[108] Mechanism of action in homoharringtonine involves inhibition of protein synthesis in dose- and time-dependent ways by acting on ribosomes of cancer cells, with resultant inhibition of polypeptides synthesis initiation, blockage in the progression of cell cycle from G1 to S phase, G2 into M phase leading to apoptosis.[109,110] The first semisynthetic homoharringtonine known as omacetaxine was developed[111] and experimental studies showed the efficacy before ChemGenex provided a stable source for the development, conduct of future research, and completion of FDA pivotal trial on CML after the failure of several TKIs.[112-114] When phase II clinical trial results were submitted to the Oncologic Drugs Advisory Committee of the US FDA as proposal on use of the drug to treat CML after failure of two or more TKIs, approval was secured in October 2012.[23] The drug holds the record for the longest time in development into the anticancer agent before approved by the US FDA (40 years). The support provided by the FDA through approval of omacetaxine usage to treat a narrow case of CML opened "windows of opportunities" to studies on leukemia. Development of congeners with improved potency toxicity profile and bioavailability is promising in the future.

Acronycin

Acronycin was isolated for the first time from the bark of small Australian tree *Acronychia baueri*[115] and the chemical structure determined.[116] Later, several derivatives were isolated from the bark of *Sarcomelicope simplicifolia, Sarcomelicope argyrophylla, Sarcomelicope glauca,* leaves and bark of *Sarcomelicope dogniensis, Sarcomelicope pembaiensis,* as well as aerial parts of *Melicope leptococca*.[117-119] Since then, structural derivatives have been isolated from members of the family *Rutaceae*, several congeners developed, and successful total synthesis achieved.[119-121] Acronycin and congeners show diverse bioactivities including anticancer effect and are attracting research interest in recent years due to their wide range bioactivities. The biological activities are thought to occur due to the planarity of the aromatic structure of the molecule that intercalates into DNA, leading to interference with cellular replication machinery during replication.[122] The alkaloid and congeners show a selective inhibition of many human pathogenic viruses including DNA and RNA viruses.[123-125] Inhibitory effects of the molecules against cellular and viral enzymes with intercalation ability into nucleic acid has been shown.[126] They showed cytotoxicity on melanoma, colon, lungs, murine tumor cell lines, breast, and other solid tumors but slight activity against murine leukemia models.[127,128] Because of the cytotoxicity of acronycins, phase I–II clinical trials to evaluate their safety in patients with multiple refractory myelomas were performed with limited success.[127] In the *in vitro* models, acronycin caused swelling and destruction of Golgi complexes with less consistency on mitochondria of murine leukemia cells, cell layer culture of cervical carcinoma, melanoma, and SV40-induced hamster tumor cells.[129] The mechanism of action of acronycin and congeners is yet to be established at molecular level, but they inhibited incorporation of cytidine, uridine, and other nucleosides, leading to inhibition of nucleoside transport across plasma membranes and antitumor activity.[130] Studies on SAR to uncover pharmacological activity resulted in understanding the structural features responsible for the antitumor activity and necessity of their arrangement.[131,132] Chemical structure of acronycin [Figure 1e] has added hemiterpene unit attached to C-4 of the parent nucleus and cycled to form pyran ring.[128] Modification of the structure led to the development of several congeners, but none showed more potency than the parent compound in first 25 years of isolation.[133] Further studies on natural acronycins led to the synthesis of the compounds with *in vitro* and *in vivo* activity and were believed to act by alkylation of exocytic NH_2 group of guanine units exposed in a DNA groove by the drug during activity. As a result, the double helix becomes destabilized with the resultant formation of single-stranded DNA.[134] An interesting potent congener S23906-1 showed the antitumor effect on solid tumor models during the preclinical trial and also during phase I leading to the current phase II. Mechanism of action of the congener involves alkylating N2 of guanine in a minor groove of DNA with the resultant induction of DNA helix opening.[135,136] The treated cells with a pharmacological concentration are detected in S-phase; addition of DNA polymerase inhibitors resulted in blockage of their division; removal of the congener from the culture media did not change the cytotoxic effects compared to continual treatment; probably, cells could not repair congener-induced adducts.[136,137] Congeners based on modifications of pyran or chromene part of acronycin such as dimethylpyrano (2, 3-c) xanthen-7-one 6b and the 1,2-substituted derivatives present higher antitumor activity than the original alkaloid.[138] Understanding mechanism of action of acronycin and heterocyclic family is attracting research interest. Topoisomerase I and II, protein kinases, are emerging and allowing the design of novel acridine-based patterns.

Thalicarpine

Thalicarpine [Figure 1g] is a novel dimeric alkaloid isolated from roots of several species belonging to genera *Thalictrum*. The alkaloid was synthesized, and structural configuration determined.[139-141] Thalidasine, thalifoetidine, thalamelatine, and berberine alkaloids showed cytotoxicity in monolayer-cultured KB cells.[13,141] The thalicarpines inhibited protein synthesis in monolayer KB cells and Walker 256 carcinoma of rat,[13,142] synthesis of DNA, RNA, proteins in cultured L1210 cells, as well as first step in the biosynthesis of nucleotide triphosphate.[143] Partial and reversible DNA synthesis inhibition occurred due to inhibited thymidine incorporation into cells, inhibited RNA synthesis reversed when cells were washed free of thalicarpine, while inhibited protein synthesis occurred at first stage of biosynthetic scheme.[144] Research on rat ovarian tumor cell line showed higher cytotoxicity of the alkaloids in cisplatin-resistant cell lines than in sensitive parental line.[145] The thalicarpines are notable for multiple and diverse mechanisms of action that is attributed to all or partly responsible for the chemotherapeutic activity. The mechanism of action involves binding and inhibition of drug resistance efflux pump (p-glycoproteins), induction of single-strand break in DNA with arrest of cancer cells at G2/M or G1 phase of cell cycle as well as cardio- and cyto-toxicity.[146] After positive response on *in vitro* cultured cell lines, drug development proceeded to clinical trials. It passed phase I trial but did not show a complete or partial response in any tumor in man during phase II and because of this clinical trials discontinued.[147,148]

Ellipticine

Ellipticine along with elliptine (now isoreserpiline), methoxy-ellipticine, and elliptinine were isolated from the stem, root bark, leaf, stem, and root wood of *Ochrosia elliptica*.[149] The alkaloids are distributed in *Aspidosperma*, *Ochrosia,* and several *Apocynaceae* members found in countries near the Indian Ocean. Along with derivatives, ellipticines showed significant antitumor[150] and biological activities.[151] It shows high antitumor potential and cytotoxic activities with cellular and molecular target in mechanism of action on different tumor types such as leukemia, myeloma, ependymoblastoma, melanoma, breast and colon cancers, and Erlich carcinoma.[152,153] The alkaloid and derivatives showed a multitude of targets in DNA and other double helical polynucleotides, but the precise molecular action responsible for the antitumor activity is unknown. It is believed to cause inhibition of topoisomerase II activeness, resulting in antiproliferative effect[154] and can be considered a drug whose pharmacological efficiency and genotoxic side effects depend on activation by cytochrome P450 and peroxidases in target cells.[155-158] The ellipticine intercalates DNA and other polynucleotides, leading to change in helix topological forms.[157] It also affected ATP synthesis in the mitochondria by accumulating in the inner membrane during energizing and neutralizes negative charges arising as the membrane became energized with resultant inhibition of ATP synthesis. Further, inhibition on uncoupling of the oxidative phosphorylation and activities of cholinesterase enzymes systems occurred due to hydrophobicity and a positive charge in the molecules.[16] The ellipticine did not show hematological toxicity but showed limited toxic side effects, interferes with the catalytic activity of topoisomerase II along with the oxidizable phenolic group on DNA structure leading to cleavage and antitumor activity.[156] The absence of methyl group at C-16 and 19 in the chemical structure [Figure 1d] resulted in derivatives lacking antitumor activity. The C-16 methoxy or thiomethyl derivatives also lacked antitumor activity, but the substitution of hydroxyl, methoxy, ester, or amino group at C10 would enhance binding affinity for DNA. However, replacement of N-4 with hydroxyalkyl, various alkyl, and aminoalkyl groups resulted in derivatives with a higher degree of binding to DNA.[157] Acronycin was synthesized in the 1st year of isolation, later efficient and total synthesis with 9-methoxy-ellipticine developed, reviewed.[151] Search for derivatives with stronger DNA-affinity led to the synthesis of derivatives such as 9-hydroxyellipticine and 2-methyl-9-hydroxy-ellipticinium that showed more DNA-binding affinity and antitumor activity than the parent compound. Along with derivatives, ellipticine showed positive *in vitro* antitumor response in many cancer cell lines. Many of the derivatives passed phase I and II clinical trial stages, but the mechanism of action is unknown. In clinical trials, for instance, 9-methoxy-ellipticine-lactate showed remission in AML, and 2-methyl-9-hydroxyellipticine acetate showed clinical responses in thyroid and renal cancer as well as bone metastases from advanced breast cancer and soft-tissue sarcoma.[158] The pharmacological efficiency or genotoxic side effects of ellipticine depend on enzymatic activation of the alkaloid in the target tissue. Research on the molecule is at evaluation of antitumor effects on *in vitro* cultured cell lines with many promising results.

Usambarensine

Usambarensine is a tumor alkaloid isolated from roots of *Strychnos usambarensis*, a small tree from Sub-Saharan Africa. About sixty indole alkaloids, majority dimeric terpenoids have been isolated from the tree. The root bark contains tertiary and several quaternary alkaloids that have anhydrous bases and includes retuline class C-dihydrotoxiferine, C-calebassine, C-curarine, and monomeric C-fluorocurarine. The afrocurarine, akagarine, harmane and melinonine F, malindine, isomalindine, and four dimeric usambarensines from roots of the species are of corynanthine class. Several of these alkaloids showed promising anticancer properties; however, yet, not much of research on antineoplastic activity has been carried so far.[159-161] Strychnopentamine, chrysopentamine, and isostrychnopentamine are potential anticancer agents; strychnopentamine inhibited RNA synthesis through induction of cytological changes in vacuoles, blebs, and lamellar bodies in the B16 mouse melanoma cells cytoplasm;[160-161] isostrychnopentamine (present in leaves) induced apoptotic cell death in treated HCT-116 colon cancer cells during exponential growth phase. The apoptosis occurs through provoking cell cycle arrest in G2-M phase and induction of p21 in a p53-dependent way without modification of p53 expression or catalytic activity effect on human topoisomerase I and II.[160-161] Treated melanoma cells showed inhibition of nucleic acid synthesis due to intercalation of DNA. The apoptosis induction occurred without interference from the catalytic activity of topoisomerase II in the leukemia cells. Usambarensines showed the high toxic effect on B16 melanoma cells and inhibited the growth of leukemia as well as carcinoma cells. Treated human HL60 leukemia cells showed cytotoxicity effects on cell cycle through loss of the cells in G1 phase accompanied by a substantial increase in the sub-G1 region. The treated cells showed severe fragmentation in DNA with an enhanced proteolysis activity of DEVD-caspases.[160-161] Molecular basis of diverse biological effects of the molecules is unknown and limited studies are carried out on antitumor properties.

Matrines

Matrines are tetracyclo-quinolizindine alkaloids isolated from roots in members of the genus *Sophora*. The molecules were isolated from *S. flavescence*, *S. japonica*, *S. subprostata* and above ground part of *S. alopecuroides*.[162,163] Extract of *Sophora* has been available in the West for many years, and alkaloid fraction of the roots having a standardized level of oxymatrine and matrine made available to traditional medicine practitioners under the name oxymatrine and in tablet form. Extracts of *S. japonica* contain many alkaloids, but matrine and oxymatrine are the highest, altogether comprising 2% of dried rootstock. The matrines are used to treat many diseases such as viral hepatitis, skin inflammations, and cardiac arrhythmia.[164] Kushen, a dried root of *S. flavescence* containing matrine, oxymatrine, and many products containing the dried roots are approved by Chinese state food and drugs administration to treat cancer. Their anticancer effects occur through blockage of carcinogenesis stages and progression. Matrines are also used to treat effects of leukopenia, uterine cervical cancer, leukemia, and as essential ingredients to treat esophageal and laryngeal cancer.[165] Evidence supported their effects in modulating the immune response through a reduction in invasion of metastasized hepatocellular carcinoma cells.[166-179] Alkaloids of *S. subprostata* inhibited the growth of tumor cells, invasiveness and metastasis-induced gastric cancer MKN45 cell apoptosis and could affect immune functions.[167] Further, they reduced adhesion and migration of Hela cells[170] inhibited the growth of nonsmall cell lung cancer A549 as well as hepatoma SMMC-7721 cells through apoptosis *in vitro* and *ex vitro*.[168] High antiproliferative effects were associated with an increase in cells arrested in G1 phase, mediated through apoptosis induction *in vitro* and *in vivo*, and was therefore regarded to be the possible mechanism of antitumor effects in matrines.[169] The Beclin 1 is also involved in matrine-induced autophagy, and pro-apoptotic mechanism of action in matrines is likely related to upregulation of Bax expression.[170] In-depth studies on the pharmacology and clinical application of matrines have been ongoing for decades and are the focal interest of Chinese medical research. The mechanism of the anticancer effect at the molecular level is poorly clarified. Studies on anticancer efficacy along with associated molecular mechanisms are ongoing. Research on matrine and oxymatrine antineoplastic activity is limited to observations of superficial phenomenon without systematic evaluation and few clinical trials carried out. Evolution of molecular techniques in the 21st century will aid studies on the mechanism of antitumor activities, as well as clinical trials to evaluate the safety and efficacy in use of matrine and oxymatrines against various human cancers.

Other Alkaloids with Anticancer Properties

in addition to the discussed alkaloids, there are others that show antitumor properties with *in vitro* models, *in vivo* models, or both; however, studies are at early stage of systemic evaluation of their anticancer properties so far. Among the alkaloids including benzophenanthridines, chelerythrine, and chelidonine were isolated from *Chelidonium majus*, *Zanthoxylum clava-herculis*, *Macleaya cordata,* and *Toddalia asiatica*. The fagoronine found in *Zanthoxylum zanthoxyloides* and other species in the genus *Zanthoxylum*. Chelerythrine chloride, nitidine, and nitidine chloride were isolated from roots of *Zanthoxylum nitidum*. Girinimbine and carbazole alkaloid were isolated from *Murraya koenigii*, and β-carboline alkaloids were isolated from *Geissospermum vellosii*.

CONCLUSION AND FUTURE PROSPECTS

In search of potential anticancer agents from trees, great success that span over decades is made through discovery of nature's gift in vast array of alkaloids with mechanisms of action and target commensurate with tumor types afflicting human society. The success was achieved through screening of the trees for natural products with anticancer properties and came with limitations on their use for human cancer chemotherapy due to cytotoxicity and other side effects. Extensive structural modification of the parent molecule to develop congeners that overcome limitation(s) of natural availability and solubility along with higher potency on the neoplastic cells is still explored. The stage of antineoplastic drug development in the molecules is variable; some are developed and approved drugs for use in cancer chemotherapy, others at clinical trial stages, while anticancer activity of others is discovered, leaving more research opportunities for drug development. Pharmacological activity, molecular targets, and mechanism of work of the neoplastic agents are areas of great interest. The SAR, drug delivery, and mechanism of action of the molecules at cellular and molecular level are also attracting research interest. In some cases, clinical trials gave discouraging results. As a consequence, drug development is not realized. Extraction from a natural population or cultivation, biotechnological methods, and chemical synthesis are alternatives approaches for the supply of these molecules. Considering the increasing prevalence of cancer cases in humans, slow growth of these life forms in nature under *in vitro* or *in vivo* conditions along with endangered status of majority of anticancer alkaloid-yielding tree species, application of biotechnology in plant cell and tissue culture or fermentation technology of alkaloids-producing microbes and metabolic engineering are the workable alternatives for the supply of the molecules. Recent progress in genomics on the characterization of genes, as well as enzymes involved in the biosynthesis of many of the various alkaloids shows great promise toward developing transgenic for commercial production of the metabolites. Many hidden treasures in promising alkaloids are unexplored from tree species, when discovered, could bring a new dimension or the 21st century revolution in the chemotherapeutic utility of anticancer alkaloids isolated from trees. It is hoped to be commensurate with cancer types afflicting human society around the world.

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Conflicts of interest

There are no conflicts of interest.

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