Annals of R.S.C.B., ISSN: 1583-6258, Vol. 26, Issue 1, 2022, Pages. 64 - 74
Received 08 November 2021; Accepted 15 December 2021.

Emerging Therapeutic Efficacy of Alkaloids as Anticancer Agents

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Abstract

Cancer is a genetic disease caused by genetic alterations that affect cell functioning, specifically cell growth, and division. It is also known for being a significant cause of death worldwide. Due to all the setbacks like adverse side effects of conventional anticancer therapeutics, the field of ethnopharmacology has caught the attention of scientists globally. This led to the discovery of various potential plant-derived anticancer drugs. Alkaloids are the most remarkable plant secondary metabolites with potential toxicity proving remarkable therapeutic effects against a diverse range of malignancies and other diseases in vitro and in vivo. Alkaloids were initially used in defense of various infections and pathogens. Over the last decade, many alkaloids have been isolated and studied, revealing different fascinating alkaloid properties. These include numerous neuroactive substances like caffeine and nicotine, life-saving medications like emetine, which can treat oral intoxication, and the widely popular anticancer compounds like vincristine and vinblastine. Here we discuss different types of alkaloids that were isolated and explored in the preclinical trials, as well as various cancer metabolic pathways and how various alkaloids are proven to influence them.

Keywords

Alkaloids, Anticancer, Vinca alkaloids, Cancer, Cancer pathways

Introduction

Cancer is characterized by uncontrolled cell division and proliferation unique to multicellular animals, which sometimes can invade neighboring tissues. Human cells typically grow and multiply with the help of cell division to develop new cells as required by the body. Cells die as they become old or injured, and new cells replace them following various cell cycle regulators like apoptosis, proliferation, etc. This ordered process can be disrupted by gene abnormalities, causing abnormal or damaged cells to grow and increase unnecessarily. Tumors, which are masses of tissue, can develop from these cells. Tumors may either be benign (non-cancerous) or malignant (cancerous). According to the World Health Organization (WHO) cancer, is the second-largest cause with high mortality among 70 years age group in 112 of 183 nations, while it is the third in others(Department of Data and Analytics DNA. Division of Data Analytics and Delivery for Impact. WHO. Geneva, 2020). As a result, it is a critical issue that has a massive impact on the population's health. A specific cancer diagnosis has been a significant challenge to achieve therapeutic efficiency due to tissue level

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Received 08 November 2021; Accepted 15 December 2021.

variability. Drug resistance is also one of the major issues as it is multifaceted. Due to their quick action and widespread availability, alkaloids have shown to be an excellent paradigm for studying natural components with insecticidal properties.

The most frequent cancer therapies are chemotherapy and radiation. The development of negative impacts from chemotherapy and radiotherapy, on the other hand, restricts therapeutic utilization. Natural dietary supplements, including nutrients like Grape seed extract, Ginseng extract, and curcumin, help people recover from severe illnesses and reduce the adverse effects of chemotherapy and radiotherapy like oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, hematological system injury, cardio toxicity, and neurotoxicity caused by chemotherapy and radiotherapy.(Chandrasekar, Sivagami, & Babu, 2018b; Patil et al., 2018; Thakur et al., 2020) The gut micro biota has a role in drug action modification, and it may be used to assess the risk of severe gastrointestinal toxicity. Herbal medication has the potential to help with digestive issues. (*Chemotherapy and Radiotherapy-Induced Side Effects.Pdf*, n.d.; *Dr. PSL 2021View of A Study on the Expression of CCL5,CXCR4 and Angiogenic Factors by Prostate Cancer Stem Cells.Pdf*, n.d.; *Dr.PSL 2012 Molecular Docking Paper OfA.NigerRNase .Pdf*, n.d.; Chikati, Gulati, Garimella, & Chalumuri, 2021; Ghouse, 2020; Lovly & Teresa, 2018) Although there are many chemotherapeutic procedures being used to treat cancer, the underlying reason for high mortality is cancer relapse and drug resistance. Research on various phytochemicals, the natural chemicals derived from plants showed anticancer activity and is effective on other ailments(*2014 Evaluation of Antimicrobial and Phytochemical Properties of Some Indigenous Indian Plants. .Pdf*, n.d.; Chandrasekar, Sivagami, & Babu, 2018a; Gupta, Khan, Verma, & Pathak, 2013; Koli, Patel, Chaudhari, & Patil, 2018; Naik, Babu, Latha, & Kolluru, 2018; D. Sharma, Prashar, & Saklani, 2012; V. Sharma, 2018; Yadav & Mohite, 2020). Alkaloids are one among these phytochemicals, which are usually colorless and odorless crystalline solids. However, they can also appear as yellowish liquids.(Ruano et al., 2016) Various studies showed the potentiality of alkaloids and their strong biological effects on animal and human models with minimal doses. In traditional medicine, alkaloids were widely known and used for their diverse activity by people from ages. However, they lacked direct means for isolating pure compounds.

Different types of Alkaloids

Alkaloids are naturally occurring organic nitrogen-containing bases possessing diverse and vital physiological effects on humans and other animals. (Bhattacharya & Naitam, 2019; Levy, 2020) Based on their biosynthetic pathway, molecular structure, and molecular precursor, alkaloids could be divided into three different types: a) True alkaloids (heterocyclic), b) protoalkaloids (non-heterocyclic), and c) pseudo alkaloids. True alkaloids and protoalkaloids are derived from amino acids, whereas pseudo alkaloids are not derived from these /compounds. (Dey et al., 2020)

(a) Heterocyclic alkaloids (true alkaloids): They are chemically complex and physiologically active cyclic amino acid derivatives. Because of the presence of intra-cyclic nitrogen atoms and enormous biological activity, these highly reactive heterocyclic alkaloids derived from nature can form salts that are water-soluble in nature with organic acids such as tartaric, acetic, oxalic, lactic, malic, and citric acids. Alkaloids discovered in these groups include nicotine, cocaine, quinine, dopamine, morphine, geissospermine, piperine, berberine, and gasoline, with cocaine, morphine, and quinine being the most prevalent genuine alkaloids found in nature. (Dey et al., 2020)

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(b)Protoalkaloids (Non-heterocyclics): Protoalkaloids have a nitrogen atom outside the ring that persists as a side chain rather than part of the heterocyclic system is derived from amino acids or biogenic amines. Mescaline, colchicine, cathinone, and other proto alkaloids are examples; they are uncommon in nature. Mescaline is a phenyl ethylamine alkaloid derived from the plant Lophophora williamsii, better known as peyote. (Birajdar et al., 2013; Dey et al., 2020)

(c) Pseudo alkaloids: Pseudo alkaloids are compounds whose basic carbon skeletons aren't derived from amino acids. In reality, pseudo alkaloids are produced by amination or transamination of amino acid precursors or post cursors. Pseudo alkaloids could be acetate and phenylalanine-derived or terpenoid, as well as steroidal alkaloids. Pseudo alkaloids include coniine, capsaicin, ephedrine, solanidine, caffeine, theobromine, and pinidine. (Dey et al., 2020)

Alkaloids in pre clinical trials and their derivatives

1. Vinca alkaloids: Vinca alkaloids are widely popular for their potent anticancer properties in various cell types. Vincristine, vinblastine, vinorelbine, vindesine, and vinflunine are the five primary vinca alkaloids. Vincamine and vinpocetine are two minor vinca extracts (lesser periwinkle) that have clinical applications. Vincristine and vinblastine were extracted from natural sources in 1958, and the other derivatives, vincristine, vinorelbine, and vinpocetine, were synthesized later on. (Baran, Bidhan, Krishi Viswavidyalaya, Das, & Sharangi, 2017; *Vinca Alk 2016.Pdf*, n.d.)

Vincristine: Vincristine(VCR) is the first natural vinca alkaloid, derived from the leaves of *Catharanthus roseus* (Baran et al., 2017) and has been used in tumor therapy since the 1960s due to its cell cycle-specific (M-phase) antineoplastic properties. It is often used in combination with other chemotherapeutic drugs to treat various cancers (Grindey, 1989; Hassanpour & Dehghani, 2017; *Vinca Alk 2016.Pdf*, n.d.; Zhang, Kong, Wang, & Du, 2018)

Vinblastine: It is derived from the periwinkle plant C. roseus (Baran et al., 2017). Vinblastine is widely used in combination with other cytotoxic agents to treat diseases like disseminated Hodgkin's disease at stages III and IV non-Hodgkin's lymphoma, histolytic lymphoma, and advanced carcinoma/a of the testis. It also has been used to treat bladder cancer, melanoma, and renal cell cancer. (Grindey, 1989; Thirumaran, Prendergast, & Gilman, 2007; Vinca Alk 2016.Pdf, n.d.; Zhang et al., 2018)

Vinorelbine: It is a semi-synthetic vinca alkaloid which, in other terms, is also called nor-5'-anhydrovinblastine (Navelbine). (Degardin et al., 1994; Hassanpour & Dehghani, 2017). The preclinical studies vinorelbine shows a broad spectrum of antitumor action. However, when administered intravenously, vinorelbine is known to cause venous irritation and phlebitis, which demands urgent new drug delivery systems (Degardin et al., 1994; Grindey, 1989; *Vinca Alk 2016.Pdf*, n.d.)

Vindesine: Vindesine is also called desacetyl-vinblastine-amide. It exhibits similar effects to those of vinblastine. In conditions like pediatric solid tumors, blast crisis of chronic myeloid leukemia; acute lymphocytic leukemia; malignant melanoma; metastatic colorectal; and breast, renal, and esophageal carcinomas, vindesine inhibits the net tubulin addition of the microtubules at their assembly ends. (Grindey, 1989; *Vinca Alk 2016.Pdf*, n.d.)

Vinflunine: Vinflunine is another semi-synthetic vinca alkaloid, which is currently being clinically evaluated. According to preclinical information, second-generation vinca alkaloid, vinorelbine, and third-generation compound vinflunine have shown promising results against cancer. Among which vinflunine is emerging as an effective anticancer agent as it is comparatively less neurotoxic than

vinorelbine and has superior antitumor activity compared to other vinca alkaloids. (*Vinca Alk 2016.Pdf*, n.d.; *Vinfluine.Pdf*, n.d.)

2. Colchicine: Colchicine is an alkaloid that has been extracted from the plant Autumn crocus (Colchicum atumnale)(Information, 2021). It is a tricyclic alkaloid and was reported to be an effective treatment for gout attacks, dating back to the first century C.E. Similar to vinorelbine, colchicine acts against microtubulin assembly by interacting with beta-tubulin and disrupting the cytoskeleton of the neutrophils. Recent advancements hint that colchicine may interfere with the intercellular assembly that mediates IL-113 activation of the inflammasome complex found in neutrophils. (Information, 2021)

3-demethylated colchicine: (3-DMC Colchicine biotransformation into regiospecific 3-demethylated colchicine (3-DMC), a pharmacologically active and strong anticancer medication is achieved by immobilization of recombinant microbial monooxygenases, which is a unique and promising technique for its synthesis. A study published in 2013 (*3-Demethylated Colchicine (3-DMC).Pdf*, n.d.) looked at the capacity of recombinant Escherichia coli expressing P450 BM-3 to convert colchicine into 3-DMC when it was immobilized in calcium alginate beads.(*3-Demethylated Colchicine (3-DMC).Pdf*, n.d.; Dey et al., 2020)(Chikati et al., 2021)

Thiocolchicine: Thiocolchicine is an antimitotic alkaloid, which acts as an apoptosis inducer that inhibits tubulin polymerization and microtubule. (*Thiocolchicine 2019.Pdf*, n.d.) In a study on derivatives of cancer, it was found that the two derivatives 7-deacetyl-10-thiocolchicine and 4-iodo-7-deacetyl-10-thiocolchicine analogues showed significant effect as chemotherapeutic agents against a wide range of cancers. (*S0968089621000225*, n.d.)

4. Atropine: Atropine is a synthetically derived form of the endogenous alkaloid isolated from the plant Atropa belladonna. Atropine functions as a sympathetic, competitive antagonist of muscarinic cholinergic receptors, thereby abolishing the effects of parasympathetic stimulation. This agent may induce tachycardia, inhibit secretions, and relax smooth muscles. Plants in the Solanaceae family generate alkaloids such as atropine. Deadly Nightshade (Atropa belladonna). Blockage of the heart and a reduction in the tone of the heart the sphincter of the lower esophagus.

5. Quinine: Quinine, also known as cinchona alkaloid, is a natural compound derived from the bark of the Rubiaceae plant and the cinchona tree. Quinine is a malaria the antidote that has saved millions of lives since its discovery and deployment. It is primarily utilized in the treatment of plasmodium vivax and falciparum malaria caused by chloroquine-resistant strains of plasmodium falciparum. (Du, 2018) It includes various derivatives like chloroquine, mefloquine and quinarcrine which are used mostly in modern malaria therapy. Chloroquine is also used to treat all types of malaria, as well as chemotherapy, non-gastric amebiasis, and amebic liver abscesses.. In case of chloroquine –resistant malaria Mefloquine is used, though its use is limited because of resistance and neuropsychiatric side effects. (*Observational Studies*, 2016). Quinacrine is an acridine derivative that is both chemically and therapeutically comparable to 4-aminoquinolines. During World War II, it was the major medicine for malaria prevention and treatment. It is now rarely used to treat malaria, although it is used to treat amebiasis.(Vardanyan & Hruby, 2006)

6. Lobeline: Liobelin is a pyridine alkaloid found in various plants, particularly in tobacco. Lobeline is a partial nicotinic agonist and is currently being investigated as a therapeutic drug for several addictive disorders, mainly smoking cessation. A synthetic, *des*-oxy analog of lobeline has a good affinity for the vesicular monoamine and dopamine transporter. (Vardanyan & Hruby, 2006)

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7. Ergot alkaloids: The most active ergot alkaloids are amides of lysergic acid, derivatives of ergotine. Ergot alkaloids are substances generated by Claviceps purpurea, a parasitic fungus. Their agonist, partial agonist, and/or antagonistic activities at biogenic amine receptor sites are primarily responsible for these effects. Ergot alkaloids boost uterine motility, affect cardiovascular function in various ways, and inhibit prolactin release. The ergot alkaloids are incredibly poisonous, causing nausea, vomiting, poor circulation, a quick and weak pulse, and even coma. (Hodgson, 2012)

8. Sinomenine: In a lung cancer study, it was discovered that sinomenine increases the percentage of apoptotic cells while lowering cell proliferation and migration. The 7 nAChR antagonist mecamylamine and the allosteric modulator PNU-120596 also blocked sinomenine's actions, but there was no impact when the mice were pretreated with the muscarinic acetylcholine receptor antagonist atropine. In the meantime, sinomenine inhibited the expression of 7 nAChR in vitro and in vivo, as well as the signaling molecules pERK1/2 and ERK1/2, as well as the transcription factors TTF-1 and SP-1. Sinomenine, on the other hand, increased the expression of another transcription factor, Egr-1. The findings suggested that sinomenine can inhibit lung cancer in a negative feedback mode via the 7 nAChR.(Bai et al., 2021)

9. Morphine: Various human cancer cell lines have been shown to be inhibited by morphine (IC50/2.7-8.8 mM) in studies. The research was then expanded by employing newly manufactured morphine derivatives, such as KT-90 and KT-87, which are five times more effective than morphine as analgesics. KT-90 was discovered to be 80 times more effective than morphine at inhibiting the proliferation of human cancer cell lines (IC50/42-70mM) (Lakhanpal et al., 2016; Sueoka et al., 1998) It is considered to be the most abused major stimulant in the world, but according to the Drug Enforcement Administration. Unlike other local anesthetics, cocaine shows additional effects, including its ability to block the reuptake of the neurotransmitters like dopamine (DA), norepinephrine, and serotonin (5-HT).

10. Tubocurarine: The alkaloid tubocurarine is the active ingredient in the South American arrow poison, curare (obtained from *Chondrodendron tomentosum*), and is used as a muscle relaxant in surgery. A strong positive connection between gamma globulin and tubocurarine dose was observed in individuals undergoing laparotomy for diverse reasons.(Theodorsen & Bjelke, 1971)

5. Signaling Pathways that can be targeted in Cancer treatment:

Cancer is a multifactoral heterogeneous metabolic disease that causes an irreversible impairment in cellar homeostasis. This impairment creates tumor growth conditions involving the following six significant hallmarks: 1. Uncontrolled cell division and differentiation, 2. Up-regulated proliferative signaling, 3. Up-regulated angiogenesis, 4. Replicative immortality, 5. Metastatic invasion, 6.Defiance of cell death. (Robinson, 1974)

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Table 1: Molecular pathways targeted in cancer treatment

Growth and Differentiation	Angiogenesis	Proliferation	Replicative Immortality	Metastasis	Apoptosis
Rb	VEGF	Tyrosine Kinase	Telomerase	(-) MMP-2,9	DNA fragmentation
		Ras			Fas/FasL pathway
TGF ß	MIC-1	Cyclins and CDKs	c-MYC		Caspases
					Proapoptotic proteins
		Mtor			
TP53	Thrombospondin	MAPK			Antioxidants: SOD,CAT.GPx.GSH and vitamins C and E
		P13 – Kinase	Max		
		Raf			

Genetic mutations in the cells lead to altered signaling pathways, including cell-cycle progression, apoptosis, and cell growth which are the reasons for various cancers and tumors. However, individual tumors and tumor types differ based upon the mechanisms, extent, and co-occurrence of alterations in these pathways. They were using factors like mutations, mRNA expression, gene fusions, copy-number changes, and DNA methylation in 9,125 tumors profiled by The Cancer Genome Atlas (TCGA), the mechanisms and patterns of somatic alterations in ten canonical pathways: cell cycle, Myc, Notch, Hippo, Nrf2, PI-3-Kinase/Akt, RTK-RAS, p53, and b-catenin/Wnt, and TGFb signaling (Birajdar et al., 2013; Gupta et al., 2013; Sanchez-Vega, Mina, & Armenia, 2019)

It is a regulator of apoptosis produced by pemetrexed, is regulated by vinca alkaloids. Tubulin binding chemicals, which interfere with microtubule assembly and cause mitotic arrest, are another common and influential family of anticancer medicines(Chikati et al., 2018; *Dr.PSL 2014 Access Establishment and Characterization of Two Primary BC Cell Lines from Young Indian Breast Cancer Patients Mutation Analysis.Pdf*, n.d.; Lakhanpal et al., 2016; Pandrangi et al., 2014). However, the majority of these molecules are harmful, necessitating the development of new chemicals.

6. Pathways that are mostly affected by Alkaloids:

Alkaloids have been linked to cancer prevention and management, such as avoiding and regulating oxidative stress and inflammation, or both. Vinca alkaloids such as vincristine, vinblastine,

vinorelbine, and vindesine have shown anticancer activity against MCF-7 and MDA-MB 231 breast. During chemotherapy, drug resistance is a regular occurrence. Some chemotherapeutic-resistant cell lines have exhibited sensitivity to alkaloids, such as MCF-7, a docetaxel-resistant cell line, which was treated with the alkaloid colchicine in a study by (Wang et al., 2021) With the advancement of cancer treatment development, there has been a trend toward new "targeted" therapies to minimize the side effects and toxicity of "cytotoxic chemotherapies" like the vinca alkaloids. (*A Review On-Herbs in Anticancer*, 2022; *Microtubule Destabilising Agents _ Enhanced Reader.Pdf*, n.d.). Berberine is a phenanthren alkaloid isolated from the roots and bark of herbs such Berberis, Hydrastis canadensis, and Coptis chinensis. Berberine was found to effectively suppress growth by causing cell cycle arrest in anoikis-resistant MCF-7 and MDA-MB-231 cells in a study.(Gahlot, Lal, & Jha, 2013; *The Alkaloid Berberine Inhibits MCF-7 and MDA-MB-231 Breast Cancer Cell Lines _ Elsevier Enhanced Reader.Pdf*, n.d.) The authors also discovered that docetaxel-resistant MCF-7 cells were cross-resistant to vinca alkaloids but sensitive to colchicine, 2MeOE2, ABT-751, and CA-4P, all of which target microtubules.

Another study found that vinca alkaloids successfully inhibited the growth of pemetrexed-resistant tumors in vivo trials with vinblastine and in vitro studies with vincristine. Vinblastine, vincristine, vindesine, and vinorelbine are established antimitotic medicines and demonstrated that structural changes between these compounds influence their anticancer activities and toxicity. The non-histone DNA-binding protein high mobility group box 1 (HMGB1) is involved in inflammation, cell migration, cell death, and tumor metastasis. It has a high affinity for receptors for advanced glycation end products linked to inflammation, tumor cell growth, migration, and invasion(*HMGB1 and RAGE in Inflamation 2010.Pdf*, n.d.; Kaur, 2013). In this sense(Cancer, 2019) the anticancer potential of the alkaloid papaverine was investigated in temozolomide-sensitivity U87MG and TMZ- resistant T98G and TMZ- resistant T98G from human glioblastoma (GGB). In human glioblastoma temozolomide- sensitive U87MG and TMZ- resistant T98G cells, papaverine inhibited the high mobility group box 1 protein preventing tumor growth promotion(Lakhanpal et al., 2014; Malla, Pandrangi, Kumari, Gavara, & Badana, 2018).

The antioxidative transcription nuclear factor Nrf2 has been found to increase in cancer cells such as colonic, thyroid, endometrial, lung, breast, and pancreatic cancer cells during tumor malignancy. This may result in changes that have an impact on the gene., (*Inhibition of the Nrf2 Transcription Factor by the Alkaloid 2019.Pdf*, n.d.) The alkaloid trigonelline reduced Nrf2 protein nuclear levels but not overall expression. (*Inhibition of the Nrf2 Transcription Factor by the Alkaloid 2019.Pdf*, n.d.). Amusingly, no adverse effects have been reported for trigonelline in human studies.

7. Conclusion and further directions

Alkaloids are currently promising compounds to be used in combination with other anticancer therapies or cancer treatment alone. Probably the medicinal properties of these alkaloids made them be the first interest to scientists for over thousands of years owe their effect to be used as potential drugs against various diseases and cancer types. This line of interest is still a major one in that pharmacologists explore the mechanisms by which certain alkaloids exercise their powerful effects on animals. Secondly, organic chemists became interested in alkaloids because of the complex problems in structure determination and synthesis. Additionally, with the advent of isotopic tracer techniques in the early 1950's biochemists began to trace the metabolic pathways by which plants synthesized their alkaloids from common substrates. However, further studies are still necessary to

fully understand their molecular, cellular mechanism of action and their toxicity and pharmacological.

9. Acknowledgements: SLP gratefully acknowledges DBT (BT/PR30629/BIC/101/1093/2018), New Delhi; UGC (Ref No: No.F.30-456/2018 (BSR) and SERB (Ref No.: PDF/2015/000867) for the financial support.

10. Author Contributions: Wrote the manuscript: SSC and SLP. Tabulation and arranging the data: SG. Conceptualized the study: SLP. Overall supervision of the study: SLP

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