Journal of Medicinal and Aromatic Plant Sciences 44(1-2), 2022, 1-11

REVIEW ARTICLE

Natural indoles: A brief sketch of their chemistry and pharmacology

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Article History

Received: January 20th, 2022
Revised: May 15th, 2022
Accepted: May 18th, 2022

Key Words

Biosynthesis
Indole
Leukemia
Microtubule destabilizer
Vinca alkaloids

ABSTRACT

Natural products and their semisynthetic analogues have immensely contributed to drug development. Alkaloids have been an essential class of pharmacological agents. Among diverse types, indole has been a crucial biodynamic moiety. Due to the broad-spectrum pharmacological profile, the indole class has been an essential core for drug development by medicinal chemists. Vinca alkaloids, Rauwolfia alkaloids and yohimbines have been the centre of attraction in alkaloid-based drug development. These indoles based clinical drugs have served a lot to humanity, and still, many more synthetic and semisynthetic drugs of this class are under clinical development. The present review highlights the chemistry and pharmacology of some of the indole class clinical drugs.

INTRODUCTION

Indole: A biodynamic core

Indole is one of the most promising heterocyclic moieties possessing diverse pharmacological activities like SARS coronavirus 3CL protease inhibitors, anti-HIV activity, anti-tuberculosis activity, anticonvulsant and HIV-TB coinfection, including anticancer (Kaushik *et al.,* 2013; Ponra *et al.,* 2016; Sarvanthi *et al.,* 2016). Indoles are also associated with the inhibition of several cellular pathways like NFkB/mTOR/PI3K/AkT and the regulation of estrogen-mediated activity. Chemically, indole is a bicyclic planar aromatic compound with a benzene ring fused with a pyrrole ring at the C2-C3 position. It can bind with various receptors to induce biological responses (Himes RH, 1991; Vacca *et al.,* 1999). Several 3-substituted indole derivatives have exhibited remarkable antineoplastic properties, *viz.* cell proliferation inhibition of human colon carcinoma (HT-29), human ovarian adenocarcinoma (SK-OV-3), and also c-Src kinase activity. Significantly, 3-pyranyl indoles have shown good anticancer activity against MCF-7 breast cancer cell lines compared to standard drugs (Chen *et al.,* 2005).

Indole was first isolated by treatment of the indigo dye with oleum. The name indole is derived from the word's *indigo* and *oleum*. The indole core is also found in many natural products such as the *Vinca* alkaloids, fungal metabolites, and marine natural products etc. Many important compounds containing indole nuclei are found in nature (Figure 1). Skatole is a simple alkyl indole found in faecal. Tryptophan is an essential amino acid that is the precursor of many proteins like heteroauxin (Indole-3-acetic acid), a plant hormone. Tryptophan is converted to tryptamine in the presence of bacteria (Kaushik *et al.,* 2013). Toad's release bufotonine on the skin and are also found in toxic mushrooms,

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Institutional communication no. CIMAP/PUB/ 2022/10
Doi: https://doi.org/10.62029/jmaps.v44i1.Yadav

West Indian snuff, and psilocybin. Some notable alkaloids are Ergot alkaloids-ergometrine for its direct action on the contraction of uterine muscles, and ergotamine for the treatment of mammary carcinoma. The *Rauwolfia* alkaloids, and specifically reserpine, which is used as tranquillizers and the dimeric alkaloids of *Catharanthus*, vinblastine and vincristine for anti-leukemic activity. A large number of potential bioactive have been established on the indole core (Figure 2)

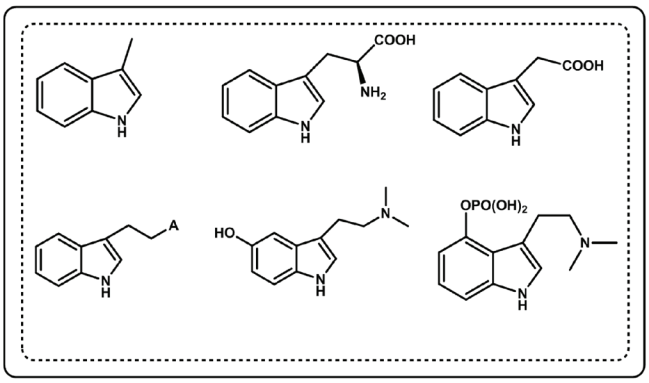

Figure 1: Indole derivatives from natural sources

Biosynthesis of indole core

Indole core is biosynthesized from anthranilate *via* the Shikimic acid pathway (Figure 3). This pathway possesses seven intermediate steps (Santos-Sanchez *et al.*, 2019; Parthasarathy *et al.*, 2018). It starts with an Aldol type condensation of phosphoenolpyruvic acid (P.E.P.) (from glycolytic pathway) and D-erythrose-4-phosphate (from Pentose phosphate cycle) to yield 3-deoxy-D-arabino-heptulosonic acid-7-phosphate (DAHP). In the next step DAHP losses phosphate unit and converts to an enolic type intermediate i.e. 3-dehydroquinic acid (D.H.Q.). D.H.Q. now dehydrates to give a conjugated compound, i.e. 3-dehydroshikimic acid (D.H.S.). In the fourth step, D.H.S. is reduced to Shikimic acid-3-phosphate (S.P.). In the next step addition of phosphor-enolpyruvic acid acid to Shikimic acid-3-phosphate affords 5-enol-pyruvylshikimic acid-3-phosphate (EPSP). In the final step, trans elimination of phosphate unit takes place to give chorismate.

Furthermore, 1, 4-nucleophilic substitution at chorismate by ammonia to give 2-amino-

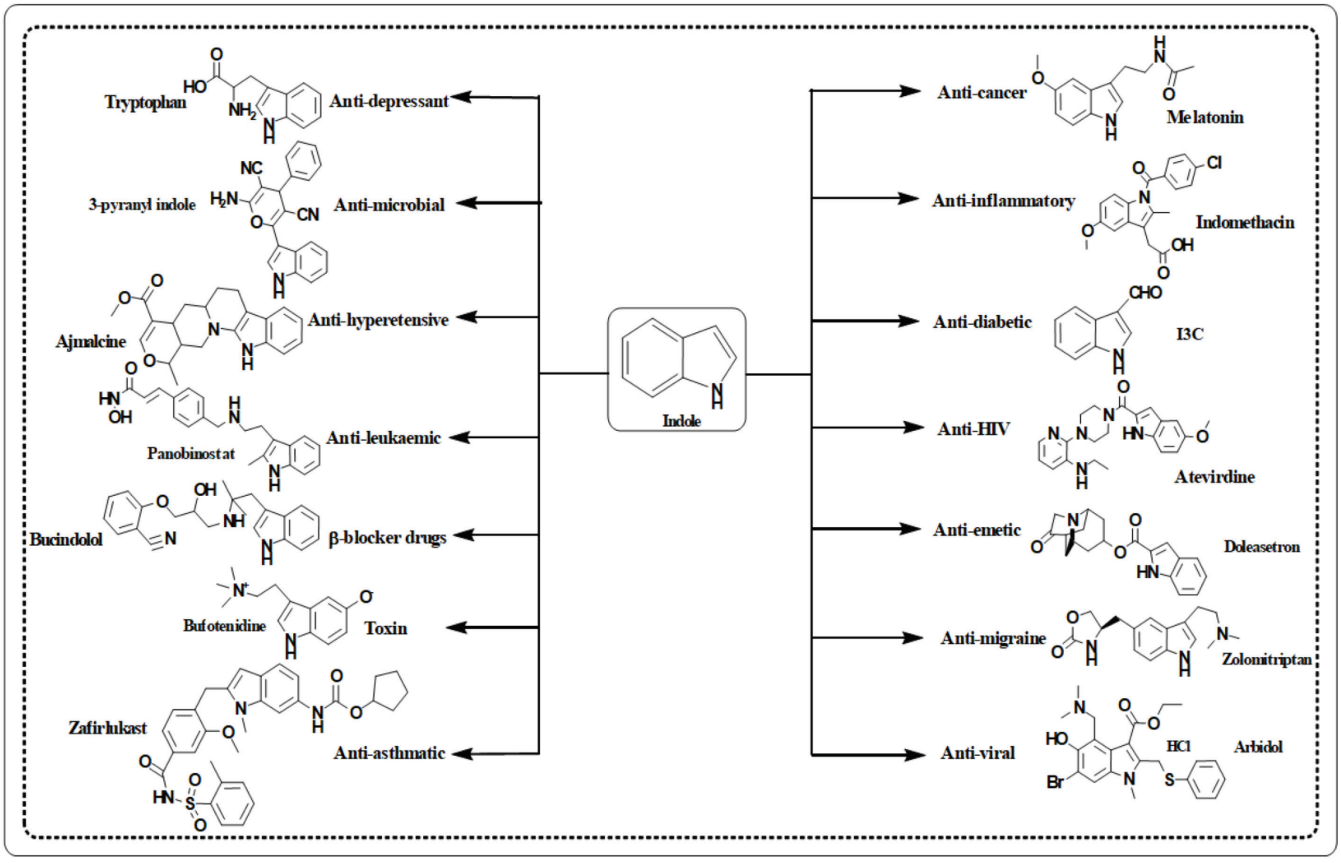

Figure 2: Diverse biological activities of Indoles

2-deoxyisochorismate (ADIC) followed by its elimination of pyruvate to afford the anthranilate. Now phosphoribosyl pyrophosphate (PRPP) transfers a phosphoribosyl group to anthranilate to yield phosphor-ribosylanthranilate (P.R.A.). N-(5-phospho-beta-D-ribosyl) anthranilate (PRA) isomerises into 1-(2-carboxyphenylamino)-1-deoxy-D-ribulose-5-phosphate (CdRP) *via* Amadori rearrangement. There are a series of proton transfer steps in this rearrangement leading to an enolamine, which then undergoes tautomerism to the ketoamine form (CdRP). CdRP on subsequent cyclization and decarboxylation at phenyl ring generate indole ring indole glycerol-3-phosphate (IgP), which is further converted to tryptophane.

Due to broad-spectrum biological activities, indole has gained the attention of medicinal chemists. Since the first synthesis of indole in 1866, several synthetic methods for the preparation of indole nuclei have been reported (Figure 4).

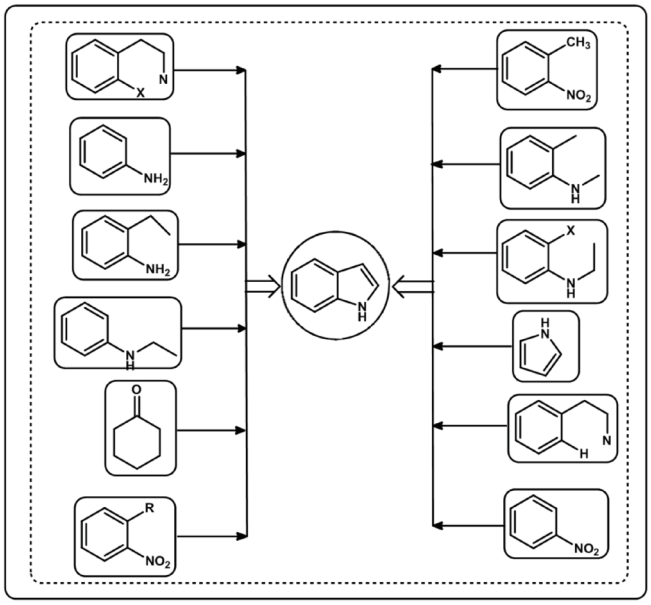

Figure 4: Various approaches for the synthesis of indole core (Yao *et al.,* 2021; Inman *et al.,* 2013)

Natural indoles

Vinca alkaloids are one of the most popular natural products belonging to a critical anticancer drug class (Figure 5). *Vinca* alkaloids inhibit cell proliferation by affecting the microtubule dynamics during mitosis, and this causes a characteristic blockage during mitosis leading to apoptosis. *Vinca* alkaloids include Vinblastine (V.L.B.) and Vincristine (VCR), which are obtained from the

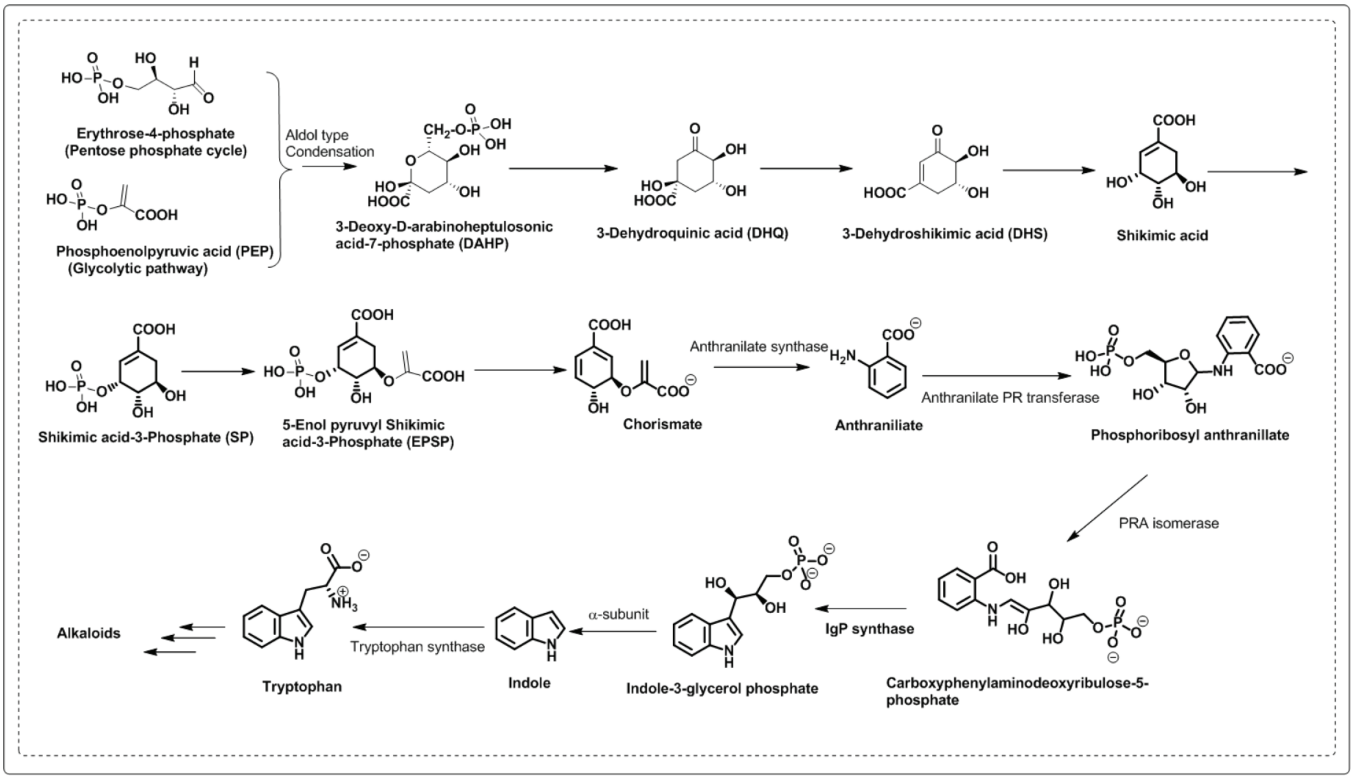

Figure 3: Biosynthetic pathway of indole core

Madagascar periwinkle, i.e., *Catharanthus roseus* G. Don. (Apocynaceae) (Tellingen Van *et al.,* 1993; Noble *et al.,* 1958).

Vinblastine

Vinblastine (V.L.B.) was extracted from *Vinca rosea* Linn., a common flowering herb known as the periwinkle (more appropriately known as *Catharanthus roseus* G. Don) (Figure 5). In cell division cycle analysis, it is a stathmokinetic (arresting cell cycle at metaphase) oncolytic agent (Noble *et al.,* 1958). The function of vinblastine is concentration-dependent. It suppresses microtubule dynamics at very low concentration and reduces microtubule polymer mass at higher concentration. However, it is associated with some side effects. The common ones are nausea and vomiting, stomach pain, constipation, diarrhoea, jaw pain, headache, or other aches, thinned or brittle hair. The exposed areas of the skin may become easily sunburned due to the side effects of vinbastine (Yang *et al.,* 2010; Jordan *et al.,* 2004). Vinblastine is potentially effective against various cancers such as Hodgkins lymphoma, non-Hodgkins lymphoma, breast cancer, testicular cancer, mycosis fungoides, Kaposi's sarcoma related to acquired immunodeficiency syndrome (AIDS), Letterer-Siwe disease, non-small cell lung cancer, bladder cancer, head and neck cancer, cervical cancer, idiopathic thrombocytopenia purpura, and autoimmune hemolyticanemia. In bacterial infections, Vinblastine sulphate is used with antibiotics (Gobbi *et al.,* 2003; Van Der Heijden *et al.,* 2004).

Vinblastine is metabolized to about thirty-five metabolites. The metabolic reactions are mainly ester hydrolysis (C4), Olefinic hydroxylation (C6 & C7), *O*-methylation (C16), *N*-methylation, aromatic hydroxylation (C12′ & C13′), hydroxylation (C17 & C20), *O*-demthylation (C16) etc. (Chagas & Alisaraie, 2019). Its metabolite deacetylvinblastine is more effective than vinblastine (Owellen *et al.,* 1977**)**.

Recently, vinblastine loaded polymeric nanoparticle (VBL−NP) has been prepared by single step molecular imprinting process, avoiding the waste and incomplete removal of the template, and evaluated as targeting carriers for V.B.L. delivery after modification. Using acryloyl amino acid co-monomers and disulfide cross-linkers, VBL−NPs were synthesized and then conjugated with poly (ethylene glycol)−folate with a dynamic size of VBL-NPs-PEG-FA 258.3 nm and 46% efficacy (Zhu *et al.,* 2019). It enhanced tumour targeting efficacy of VBL and decreased toxicity to normal cells. Recently, dextran-coated superparamagnetic nanoparticles of vinblastine have been prepared for its slow release in pancreatic cells (Albukaty *et al.,* 2020)

Vincristine

Vincristine (VCR), commonly known as leurocristine (brand name, Oncovin), is a *Vinca* alkaloid isolated from the *Catharanthus roseus* (Madagascar periwinkle) first time in 1961 (Figure 5). It is effective against several types of human cancers i.e., acute lymphocytic leukemia, acute myeloid leukemia, neuroblastoma, Hodgkin's disease, and small cell lung cancer. It is also a mitotic inhibitor and is used in cancer chemotherapy (Van Tellingen *et al.,* 1993; Noble *et al.,* 1958; Van Der Heijden *et al.,* 2004). It was approved by US FDA in 1963 and marketed by Eily Lilly Co. U.S.A. It has been included in the World Health Organisation's list of essential medicines (WHO, 2019).

Vincristine binds to α, β-tubulin dimers, inhibiting microtubule assembly. Disruption of the tubulin-microtubules dynamic equilibrium arrests mitosis in metaphase (Jordan *et al.,* 2004). *Vinca* alkaloids affect the rapidly dividing cell types, including cancer cells and those of intestinal epithelium and bone marrow. Peripheral neuropathy, hyponatremia, constipation, and hair loss are the main side effects of vincristine (Del Pino, 2010). It is given *via* intravenous infusion for the use in various types of chemotherapy regimens. However, it should not be given intrathecally (*via* the Spinal cord) as it causes paralysis or death. It is used mainly in non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen, acute lymphoblastic leukaemia, and in treatment for nephroblastoma (Wilms tumour, a kidney tumour most common in young children). It is combined with prednisone to treat childhood leukaemia (Zaragoza *et al.,* 1995). A spectrophotometric method was developed and validated, aiming to quantify the vincristine (VCR)-loaded in nanoparticles. Hence, a successful synthesis of mesoporous hydroxyapatite nanoparticles with the mean size of 285.32 ± 10.29 nm and a superficial area of 103.5 m^2/g, containing significant quantities of chemotherapeutic drug vincristine was developed (Maia *et al.,* 2017).

Now several nanoparticles/formulations of vincristine are under development with polyethylene glycol-folate (Wang *et al.,* 2014), lysosomal gold nanoparticle conjugate (Liu *et al.*, 2015), and vincristine loaded folic acid–chitosan conjugated nanoparticles (Salar and Kumar, 2016).

Semisynthetic analogues of vinblastine

Vinorelbine

The Pierre Potier group first invented vinorelbine at CNRS France in the 1980s (Figure 5). It was successfully launched in France in 1989 to treat non-small cell lung cancer (NSCLC) and in 1991 for metastatic breast cancer. It was approved in the U.S.A. in 1994 for medical use against NSLC. It has been included in the 'WHO is the list of Essential medicines' (WHO, 2019). Vinorelbine is the first semisynthetic analogue that can be prepared from vindoline, catharanthine and leurosine. Abbott Healthcare marketed it in India under the brand name Navelbine against breast cancer and non-small cell lung cancer (Faller *et al.,* 2011). It is also active against rhabdomyosarcoma (Skeletal muscles) (Casanova *et al.,* 2002). The antitumor activity of vinorelbine is due to the inhibition of mitosis at metaphase through its interaction with tubulin. Vinorelbine binds to the microtubular proteins of the mitotic spindle, leading to crystallization of the microtubule and mitotic arrest or cell death (Jordan *et al.,* 2004). Vinorelbine has also been approved in the oral formulation in Europe, but in U.S.A. it is approved only in injection form.

Like other *Vinca* alkaloids vinorelbine may also interfere with amino acids, cyclic A.M.P., and glutathione metabolism, calmodulin-dependent Ca^{2+}-transport ATPase activity, cellular respiration, nucleic acid and lipid biosynthesis. The common side effects of vinorelbine are lowered resistance to infection, bruising or bleeding, anaemia, constipation, diarrhoea, nausea, numbness or tingling in hands or feet (peripheral neuropathy), tiredness and a general feeling of weakness (asthenia), inflammation of the vein into which it was injected (phlebitis). Seldom severe hyponatremia is also seen. Hair loss and allergic reactions are less common adverse effects. The dose-limiting toxicity of vinorelbine is leucopenia. Transient increases in SGOT and SGPT have been noted in rats and dogs but not in monkeys (Gregory and Smith, 2000). It is approved to treat non-small cell lung cancer and metastatic breast cancer (Marty *et al.,* 2001; Casanova *et al.,* 2002). The efficacy of vinorelbine (V.R.L.) in treating non-small-cell lung cancer (NSCLC) is constrained by its dose limiting toxic effects such as leukopenia, its vesicant activity, and reduced bioavailability in oral form. Nanoparticle (N.P.) encapsulation has the potential to overcome these problems by shielding the drug in circulation and explicitly targeting the drug to the tumour. Thus, the development of a polymeric N.P. delivery vector and encapsulation of V.R.L. would enhance its anticancer activity and reduce inflammation in non-cancer cells.

Vindesine

Vindesine (V.D.S.) is a semisynthetic analogue of vinblastine marketed in India under the brand name Eldisine. According to Eli Lilly's patent, the carboxylic ester of vinblastine at the 16 positions is converted to amide in reaction by refluxing with ammonia to form vindesine (17-desacetylvinblastine-16-amide) (Figure 5) (Eli Lilly,1974; Barnett *et al.,* 1978).

Vindesine is used as a chemotherapy drug as it blocks the rapid proliferation of certain types of cancerous cells and generally used in combination with other chemotherapeutic drugs for the treatment of various malignancies such as leukaemia, lymphoma, melanoma, breast cancer, and lung cancer (Martino *et al.,* 2018). Vindesine acts by causing the arrest of cells in metaphase mitosis through its inhibition of tubulin mitotic functioning. The drug is cell-cycle specific for the S phase. It has been efficient in childhood acute lymphoid leukaemia (ALL), non-Hodgkin's lymphoma, a blastic crisis of chronic myeloid leukaemia, and oesophageal carcinoma. It has also shown activity in Hodgkin's disease, breast and germ cell carcinomas, and melanoma. Intolerance is mainly neurologic, with parenthesis, without motor impairment, hematologic, leukopenia, and sometimes alopecia, asthenia, and muscle pains. The maximally tolerated dose is 4–5 mg/m^2/week, the dose-limiting toxicity being myelosuppression (Bayssas *et al.,* 1980).

Yohimbine

Yohimbine is an indole alkaloid also known as quebrachine (Figure 6). It was isolated from the bark of the *Pausinystalia yohimbe* (*Corynanthe yohimbe*) tree in Central Africa in 1896 by Adolph Spiegel. It is used

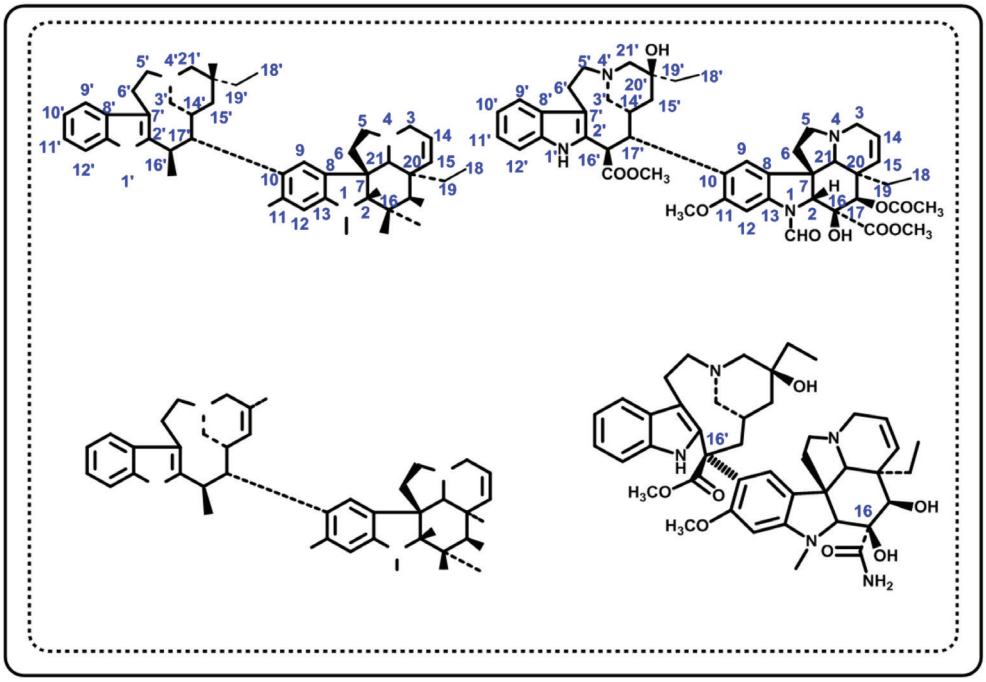

Figure 5: Structure of *Vinca* alkaloids and their semisynthetic derivatives

as a drug in dogs and deer for reverse sedation. For erectile dysfunction, yohimbine has been studied as a potential drug. However, there is insufficient evidence of its effectiveness in rats. For improving sexual function, extracts of yohimbe have been marketed as a dietary supplement (Andersson *et al.,* 2001). Yohimbine was also tested for type-2 diabetes, carrying polymorphisms of the α-2A-adrenergic receptor gene. Van Tamelen proposed a 23-step synthesis to become the first person to achieve the synthesis of yohimbine (Tamelen *et al.,* 1958). Later on, enantioselective synthesis of (+) yohimbine was also developed (Herle *et al.,* 2011).

Yohimbine blocks pre-and post-synaptic α-2 receptors **(**Millan *et al.,* 2000). Blocked post-synaptic α-2-adrenergic receptors cause only minor corpus cavernosum smooth muscle relaxation since most adreno-receptors in the corpus cavernosum are of the α-1 type. At the same time, presynaptic α-2 receptors facilitate the release of several neurotransmitters in the central and peripheral nervous systems. Thus, in the corpus cavernosum, the release of nitric oxide and norepinephrine takes place. Whereas nitric oxide released in the corpus cavernosum is the major vasodilator contributing to the erectile process, norepinephrine is the major vasoconstrictor through stimulation of α-1 receptors on the corpus cavernosum smooth muscle. Under physiological conditions, however, nitric oxide attenuates norepinephrine vasoconstriction. The toxicity of yohimbine depends upon dosage. It either decreases or increases blood pressure because it has the highest affinity for α-2 receptors while low affinity towards α-1 receptors. Higher dosage may induce adverse effects such as rapid heart rate, overstimulation, abnormal blood pressure, cold sweating, and insomnia (Saenz *et al.,* 2000; Baxter *et al.,* 1994).

Ajmalicine

Ajmalicine, another indole alkaloid, is isolated from the roots of *Rauwolfia serpentina* (L) Benth. (Apocynaceae) Furthermore, known as δ-yohimbine or raubasine (Figure 6) (Srivastava *et al*., 2006). It is also found in various plants such as *Catharanthus roseus* and *Mitragyna speciosa*. It is mostly used as an antiarrhythmic agent (Kurz *et al.,* 1981). It acts as an α1-adrenergic receptor antagonist with preferential actions over α2-adrenergic receptors underlying its hypotensive effect rather than hypertensive effects (Roquebert and Demichel, 1984). However, it is less pronounced than that of propranolol (β-blocker) but superior, in terms of the ratio of prolongation of refractory phase over the reduced condition, to that of procainamide and quinidine. That's why this drug has been extensively used in Europe to treat arrhythmias.

Ajmalicine has been marketed under various brand names such as Card-Lamuran, Circolene, Cristanyl, Duxil (H. Care India), Duxor, Hydroxysarpon, Iskedyl (Hanwha Pharma), Isosarpan, Isquebral, Lamuran, Melanex (Young Pharmaceuticals), Raunatin (Health Pharmaceucal Co.), Saltucin Co, Salvalion, and Sarpan. Ajmalicine is structurally related to yohimbine, rauwolscine, and other yohimban derivatives (Leon *et al.,* 2009; Roquebert *et al.,* 1984).

Reserpine

Reserpine was first isolated in 1952 from the dried roots of *Rauwolfia serpentina* (Indian snakeroot) (Figure 6) (J. Monachino, 1954) and also known as Sarpagandha, used for centuries in India for the treatment of insanity, as well as fever and snakebites. It was marketed under various trade names like Raudixin, Serpalan, and Serpasil. The structure of reserpine was elucidated in 1953, and the natural configuration was published in 1955 (Klohs *et al.,* 1953). R. B. Woodward proposed the first total synthesis in 1956 (Woodward *et al.,* 1956); after that, several more approaches were developed to synthesize Reserpine (Khan *et al.,* 2018). Reserpine is used as antipsychotic and antihypertensive drug. It also has been used for the control of high blood pressure and for the relief of psychotic symptoms (Baumeister *et al.,* 2003). Reserpine was the first compound that was reported as an antidepressant in a randomized placebo-controlled trial.

Reserpine blocks the vesicular monoamine transporter irreversibly (VMAT), which is responsible for the transportation of free intracellular norepinephrine, serotonin, and dopamine in the presynaptic nerve terminal into presynaptic vesicles for subsequent release into the synaptic cleft (exocytosis). These are metabolized as unprotected neurotransmitters (as well as by COMT) in the cytoplasm, and M.A.O. consequently never excite the post-synaptic cell. It is also used to treat dyskinesia symptoms in patients who have Huntington's disease. Reserpine is used as a long-acting tranquillizer to subdue excitable or difficult horses. It has been used illicitly for the sedation of show horses, for-sale horses, and in other circumstances where a "quieter" horse might be desired. Reserpine causes depression leading to suicide. However, this was reported in uncontrolled studies using doses averaging 0.5 mg per day. Nasal congestion, nausea, vomiting, weight gain, gastric intolerance, gastric ulceration (due to increased cholinergic activity in gastric tissue and impaired mucosal quality), stomach cramps and diarrhoea are the common adverse effects. Reserpine is avoided during breastfeeding if possible because breast milk is harmful to breast-fed infants (Barcelos *et al.,* 2011; Shamon *et al.,* 2016; López-Muñoz *et al.,* 2004).

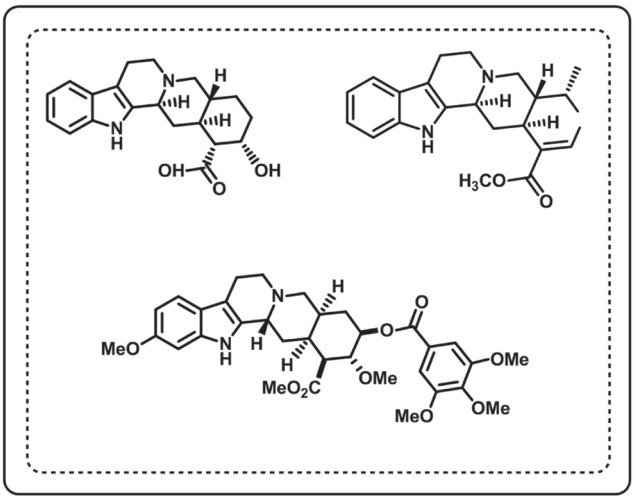

Figure 6: Chemical structure of Yohimbine, Ajmalicine and Reserpine

Clinical trials

All these indole based clinical drugs are being further explored for various disease conditions either alone or in combination with other clinical drugs for synergistic effects (clinicaltrials.gov, 2022). Multiple clinical trials are being held, as displayed at clinicaltrials.gov. Some of the trials are ongoing, few are completed, and few are terminated or withdrawn. Most of these are repurposing of these clinical drugs. There are more than twelve hundred recorded trials for vincristine. Several combinations are like Vit. B12, irinotecan, prednisolone, volasertib, venetoclax, mitoxantrone, inotuzumabozogamicin, ketoconazole, temozolomide etc. Vinblastine has more than two hundred registered trials either alone or combined with carboplatin, temsirolimua, bevacizumab, nilotinib, doxorubicin hydrochloride, pembrolizumab, methotrexate, temozolomide, cisplatin etc. Vinorelbine (Navelbine) has more than four hundred registered trials. Some of the combination drugs are apatinibmesylate, cisplatin, pyrotinib, mocetinostat, gemcitabine, and trastuzumabemtansine etc. Another semisynthetic drug vindesine has more than fifty records. Some of the combination drugs are vilopronic acid, doxorubicin, chidamide, bortizomib, nilotinib,

rituximab, zanubrutinib, orelabrutinib etc. Most of these *Vinca* alkaloids studies are against various types of cancers or their associated side effects.

Yohimbine showed more than forty clinical trials. Most of these studies are alone. Only a few are with the combination drug naltrexone. These studies are mostly related to cognition or related disorders. There are about ten trials registered for reserpine. Presently, there was no study registered for ajmalicine. Most of the studies are alone, but a few are combined with tetrabenazine, gebapentin or lamotrigine related to hypertension, CVD, Parkinson etc.

Some of the important experiments are being included in Table 1 below.

CONCLUSION

Indole core exhibits broad-spectrum pharmacological activities due to its ability to bind with multiple receptors with high affinity. Therefore, it is also considered one of the most privileged pharmacophores. Indole core is biosynthesized in plants with good chemical diversity. There are many bioactive indoles isolated from plants, and many of them have been developed as clinical drugs. Vincristine, vinblastine, reserpine, ajmalicine, yohimbine etc., are some of the successful plant-based indole alkaloids used as clinical drugs. The semisynthetic derivatives of these natural indole based drugs have also been developed as successful drugs, and several are under clinical trials. Further,

Table 1: Indole based drugs under different types of clinical trials

S. no.	Drugs	Details	Type of trial
1.	Vincristine	More than a hundred clinical trials are going on to treat acute lymphoblastic leukaemia and acute myeloid leukaemia.	Alone or in combination with Vit. B12, irinotecan, volasertib, prednisolone, temozolomide venetoclax, mitoxantrone, inotuzumab ozogamicin, ketoconazole, etc.
2.	Vinblastine	Several clinical trials aganist A.M.L., solid tumours, glioma, brain tumour etc.	alone or in combination with carboplatin, temsirolimua, bevacizumab, nilotinib, doxorubicin hydrochloride, pembrolizumab, methotrexate, temozolomide, cisplatin etc.
3.	Vinorelbine	More than a hundred clinical trials are in progress, either alone or in combination with other drugs against Colon cancer, non-small lung cancer, metastatic breast cancer, Triple-negative breast cancer, Ovarian cancer etc.	In combination with apatinib mesylate, mocetinostat, cisplatin, gemcitabine, pyrotinib, and trastuzumab emtansine etc.
4.	Vindesine	Four clinical trials are underway against small cell lung cancer, hodgkins lymphoma, lung cancer etc. In combination of other drugs.	Some of the combination drugs are doxorubicin, vilopronic acid, bortizomib, chidamide, orelabrutinib, nilotinib, zanubrutinib, rituximab etc.
5.	Yohimbine	Several clinical trials are going on Parkinson's disease, type 2 diabetes, erectile dysfunction, phobic disorder, depression, narcotic drug-related disorders etc.	Mostly alone. Only a few with the combination drugs naltrexone.
	Reserpine	About ten clinical trials are underway to treat refractory hypertension, cardiovascular disorders, narcotic drug-related disorders etc.	Some of them are alone. While some, in combination with drugs like tetrabenazine, lamotrigine and gabapentin etc.

taking learnings of structure-function relationship, several medicinal chemists have shown interest in diversifying the indole core for bioactive molecules against various disorders in the human body, including various pathogens (Sravanthi & Manju, 2016; Thanikachalam *et al.,* 2019). Several indole based natural clinical drugs are also under different phases of clinical trials as combination drugs or repurposing of bioactivity. We hope several new clinical drugs will emerge shortly from this pharmacophore.

ABBREVIATIONS

ADIC, 2-Amino-2-deoxyisochorismate; Akt, Protein kinase B (Signalling pathway); ALL, Acute lymphoid leukemia; A.M.L., Acute myeloid leukemia; BEACOPP, Bleomycin, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, and prednisone (Treatment regimen}; COMT, catechol-O-methyltransferase; COPP, Certificate of pharmaceutical product; DAHP, 3-Deoxy-D-arabino-heptulosonic acid-7-phosphate; D.H.S., 3-Dehydroshikimic acid; EPSP, 5-Enol-pyruvylshikimic acid-3-phosphate; M.A.O., Monoamine oxidase; MOPP, Mechlorethamine, vincristine, procarbazine, and prednisone (Treatment regimen); NFkB, Nuclear factor kappa B; NSCLC, Non-small cell lung cancer; SARS, Severe acute respiratory syndrome; PI3K, Phosphotidylinositol-3-kinase; P.R.A., Phosphoribosylanthranilate; PRPP, Phosphoribosyl pyrophosphate; CdRP,1-(2-Carboxyphenylamino)-1-deoxy-D-ribulose-5-phosphate; IgP, Indole glycerol-3-phosphate; V.B.L., Vinblastine; VCR, Vincristine; US-FDA, United States-Food and drug Administration; PEG-FA, Poly (ethylene glycol)-folate; SGOT, Serum glutamicoxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; MOPP, Mechlorethamine, vincristine, procarbazine, and prednisone (treatment regimen); mTOR, Mammalian target of rapamycin; V.D.S., Vindesine; VMAT, vesicular monoamine transporter.

ACKNOWLEDGEMENT

Ms Tanya Yadav thanks to CIMAP-HRD and Director CSIR-CIMAP, Lucknow for permitting her six-month Graduate training course at the institute and providing facilities to work on indoles.

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