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Review article

Indoles as therapeutics of interest in medicinal chemistry: Bird’s eye view

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ABSTRACT

Indoles constitute extensively explored heterocyclic ring systems with wide range of applications in pathophysiological conditions that is, cancer, microbial and viral infections, inflammation, depression, migraine, emesis, hypertension, etc. Presence of indole nucleus in amino acid tryptophan makes it prominent in phytoconstituents such as perfumes, neurotransmitters, auxins (plant hormones), indole alkaloids etc. The interesting molecular architecture of indole makes them suitable candidates for the drug development. This review article provides an overview of the chemistry, biology, and toxicology of indoles focusing on their application as drugs. Our effort is to corroborate the information available on the natural indole alkaloids, indole based FDA approved drugs and clinical trial candidates having diverse therapeutic implementations. This compiled information may serve as a benchmark for the alteration of existing ligands to design novel potent molecules with lesser side effects.

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1. Introduction

With identification dating back to 1860’s by Baeyer and coworkers while studying the structure of indigo [1], indole has gained immense popularity as a pharmacophore in numerous pharmacological conditions. Its interesting molecular architecture attracts the eye balls of organic and medicinal chemists to design derivatives of medicinal interest. Chemically, this heterocyclic ring system is a fusion of six-membered benzene and five-membered pyrrole ring [2]. The chemistry of this bicyclic arene is vast, well established and consolidated in a variety of reviews [3,4]. Electrophilicity of the nucleus has been well described in literature that leads to synthesis of various indole derivatives via nucleophilic addition and cycloaddition [5]. This property of indole improves its interesting molecular architecture gained immense popularity as a pharmacophore in numerous workers while studying the structure of indigo [1]; indole has highest electron density and is the most reactive position for electrophilic substitution while the slightly acidic nature of the NH makes it susceptible to N-substitution reactions under basic conditions [12].

The unsubstituted indole (C₈H₇N) is a colourless crystalline solid with unpleasant odour. The compound has a melting point range of 52–54 °C (126–129 °F) and boiling point of 254 °C. The molar mass of the compound is 117.15 g/mol and a density of 1.17 g/cm³ [13]. The mass spectrum of indole has been reported to show a molecular ion peak at m/z 117 (base peak). There appear two strong peaks at m/z 90 (relative abundance 40%) and 89 (24%) due to the loss of HCN and H₂CN, respectively [14]. The ¹H-NMR spectra of indole show the presence of seven peaks due to seven protons. The proton attached to the nitrogen of the ring appears maximally down field as a singlet at 7.81 ppm. The aromatic protons showed multiplet in the range of 7.64 to 6.52 ppm (7.64, 7.27, 7.18, 7.11, 7.04, 6.52).

2. Chemistry

The indole nucleus is a planar bicyclic molecule containing 10π electrons (8π electrons from double bonds and 2π from lone pair of electrons from nitrogen), thus it is aromatic according to Huckel’s rule. It acts as a feeble base and protonates only in the presence of strong acids. The third position of the nucleus has the highest electron density and is the most reactive position for electrophilic substitution while the slightly acidic nature of the NH makes it susceptible to N-substitution reactions under basic conditions [12].

The indole is a prominent phytoconstituent across various plant species and is produced by a variety of bacteria. The natural occurrence of this nucleus can be owed to its presence in essential amino acid ‘tryptophan’ [6]. The indole-derived phytoconstituents and bacterial metabolites are a result of biosynthesis via coupling of tryptophan with other amino acids. For this reason, it is a constituent of flower perfumes, pharmacologically active indole alkaloids and some animal hormones such as serotonin and melatonin. Some naturally occurring indole alkaloids have gained FDA approval, including vincristine, vinblastine, vinorelbine and vindesine for anti-tumor activity; ajmaline for anti-arrhythmic activity and physostigmine for glaucoma and Alzheimer’s disease. Taking inspiration from these natural compounds several synthetic drugs were synthesized that have reached the patient’s bedside, such as indomethacin (NSAID), ondansetron (chemotherapy induced nausea and vomiting), fluvastatin (hypercholesterolemia), zafirlukast (leukotriene receptor antagonist) etc (Fig. 1). The success of the above mentioned compounds indicates the importance of the ring system in multi-disciplinary fields including pharmaceutical and agrochemical industry.

Among the several reviews published earlier, the focus was the description of chemistry and synthetic routes followed for the preparation of nucleus and its derivatives [3,4,7,8]. Some other reviews have also been published focusing on a particular activity of the indole derivative [9-11]. Our effort is an exhaustive compilation of the pharmacological aspects of the natural as well as synthetic derivatives with indole moiety present in literature. This compiled information may be beneficial for medicinal chemists working in this area to design derivatives with good pharmacological activity.

2.1. Synthetic pathways for indole

The synthesis of indole has been carried out using various starting materials across the literature reports of organic chemistry. The literature reports revealed that different strategies have been explored and widely used for indole construction that include:
and Sundberg indole synthesis [28]. The detail of the above mentioned reactions is summarized in Table 1.

3. Pharmacological implications

In this section, the various activities associated with the indole derivatives, including anti-tumor, anti-microbial, anti-viral, anti-inflammatory, anti-depressant, anti-cholinergic, anti-migraine, anti-emetic, anti-hypertensive, etc., have been described with special focus on the identified natural derivatives, marketed drugs and clinical trial candidates.

3.1. Anti-tumor activity

Cancer is one of the major causes of mortality across the globe affecting billions of people worldwide. Various anti-cancer agents are reported that act via varying mechanisms. A number of molecules are approved by FDA and even more are undergoing clinical evaluation containing indole nucleus.

3.1.1. Natural derivatives

From the category of indole alkaloids, a vast number of compounds have been isolated and evaluated for their cytotoxic potential. Among those vincristine, vinblastine, vindesine and vinorelbine, isolated from Catharanthus roseus, achieved success and were approved for the treatment of various cancerous conditions including leukemia, lymphoma, melanoma, breast cancer, non-small cell lung cancer (NSCLC), etc. These drugs are currently listed in the World Health Organization's list of essential medicines [36]. They show their anti-tumor effect via inhibition of the polymerization of tubules in cancer cells.

First isolated in 1961, vincristine (Oncovin, marketed by Eli Lilly) got FDA approval in 1963 as a part of cancer chemotherapy regimen for the treatment of Hodgkin's, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, nephroblastoma, large B-cell lymphoma, retinoblastoma, rhabdomyosarcoma, Follicular lymphoma, etc [37]. Vinblastine (Velban, marketed by Eli Lilly) was approved in 1963 for the chemotherapy regimen of Hodgkin's lymphoma [37]. Vinorelbine (Navelbine, marketed by Pierre Fabre Group) is a semi-synthetic vinca alkaloid approved in 1994 for the treatment for NSCLC, breast cancer and rhabdomyosarcoma. However, these
<table>
<thead>
<tr>
<th>Name reaction</th>
<th>Reactant(s)</th>
<th>Catalyst/Reaction Conditions</th>
<th>Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartoli indole synthesis</td>
<td><img src="image" alt="Nitrobenzene" /></td>
<td>1. BrMg, THF, -40 °C</td>
<td><img src="image" alt="Indole" /></td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Aq. NH₄Cl</td>
<td></td>
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<tr>
<td>Bischler indole synthesis</td>
<td><img src="image" alt="Aniline" /> + <img src="image" alt="α-bromoacetophenone" /></td>
<td></td>
<td><img src="image" alt="Indole" /></td>
<td>[16]</td>
</tr>
<tr>
<td>Fischer indole synthesis</td>
<td><img src="image" alt="Phenylhydrazine" /> + <img src="image" alt="2-oxopropanoic acid" /></td>
<td>ZnCl₂/PCl₃</td>
<td><img src="image" alt="Indole" /></td>
<td>[17]</td>
</tr>
<tr>
<td>Hemetsberger indole synthesis</td>
<td><img src="image" alt="2-Azido-3-arylpropanoic ester" /></td>
<td>Heat (Δ)</td>
<td><img src="image" alt="Indole" /></td>
<td>[18]</td>
</tr>
<tr>
<td>Julia indole synthesis</td>
<td><img src="image" alt="4-Methoxyaniline" /></td>
<td>1. SOCl₂</td>
<td><img src="image" alt="Indole" /></td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. MgBr</td>
<td></td>
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<tr>
<td>Larock indole synthesis</td>
<td><img src="image" alt="Ortho-iodoaniline" /> + <img src="image" alt="Disubstituted alkyne" /></td>
<td>Pd(OAc)₃, base</td>
<td><img src="image" alt="Indole" /></td>
<td>[20]</td>
</tr>
<tr>
<td>Leimgruber indole synthesis</td>
<td><img src="image" alt="Ortho-nitrotoluene" /></td>
<td>1. Sodium ethoxide, water</td>
<td><img src="image" alt="Indole" /></td>
<td>[21]</td>
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<td>2. Raney Nickel, hydrazine, water</td>
<td></td>
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<td>Madelung indole synthesis</td>
<td><img src="image" alt="Aminoaniline" /></td>
<td>1. Sodium ethoxide</td>
<td><img src="image" alt="Indole" /></td>
<td>[23]</td>
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<tr>
<td></td>
<td></td>
<td>2. Hydrolysis, heat</td>
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<td></td>
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<tr>
<td>Nenitzescu indole synthesis</td>
<td><img src="image" alt="Benzoquinone" /> + <img src="image" alt="β-aminocrotonic acid" /></td>
<td></td>
<td><img src="image" alt="Indole" /></td>
<td>[31]</td>
</tr>
</tbody>
</table>
drugs are associated with various side effects including chemotherapy induced peripheral neuropathy, nausea, vomiting, hairloss, gastrointestinal problems, depression etc. [38].

Prenylated indole diketopiperazine (DKP) alkaloids ‘Okaramine S’ isolated from Aspergillus taichungensis ZHN-7-07 (Ascomycota family) exhibited cytotoxic activity against HL-60 and K-562 cell lines with IC₅₀ values 0.78 and 22.4 μM, respectively [39]. These DKP alkaloids are hybrid natural molecules derived from the coupling of prenylated tryptophan with amino acid such as proline, tryptophan, histidine or alanine. Aspidosperma indole alkaloid ‘jerantinine A’ isolated from Tabernaemontana corymbosa possess cytotoxic activity against vincristine-resistant nasopharyngeal carcinoma cells via G2/M cell cycle blockage, inhibition of tubulin polymerization, microtubule disruption, aneuploidy and cyclin B1 downregulation. Jerantinine A has been shown its cytotoxic activity in breast cancer (MDA-468, MCF-7), colon cancer (HCT-116, HT-29) and lung cancer (A559) cell lines [40]. Literature reports show that reserpine obtained from Rauwolfia serpentina exhibit in-vivo anti-
tumor activity independent of cardiovascular action. In addition, recent studies demonstrate its activity in drug-resistant tumor cell lines [41]. Dihydroteleocidin B, a hydrogenated teleocidin derivative isolated from *Streptomycetes*, acts as tumor promoter via induction of ornithine decarboxylase (OD-Case) and acts by inducing cell adhesion of HL-60 cells [42]. 5,6-Dibromo-N,N-dimethyltryptamine isolated from *Smenospongia auroa* exhibit anti-tumor activity against HCT-116 colon cancer cell lines using MTT assay. The compound showed diminished activity against p53−/− cell line indicating a p53 dependent mechanism [43]. The indole alkaloid Brasilidine A containing isocyno group isolated from the actinomycete *Nocardia brasiliensis* possessed cytotoxic activity. This compound was found to be cytotoxic against murine leukemia, Adriamycin resistant P388, human epidermoid carcinoma and multi-drug resistant cell lines [44]. Meridianins B-E from *Aplidium meridianum* showed cytotoxicity against murine mamalian adenocarcinoma cell line LMM3 with IC50 values 11.4, 9.3, 33.9 and 11.1 μM, respectively [45]. Bengacarboline, a tetrahydro-β-carboline isolated from the Fijian ascidian *Didemnum* sp., has cytotoxic activities against A549 (lung cancer), BxPC3 (pancreatic cancer), LoVo (colon cancer) and MCF7 (breast cancer) cell lines [46,47]. Duo-carmycins are potent antitumour antibiotics from *Streptomyces* sp. with IC50 values of 10−12 M−10−9 M on HeLa cell line [48].

Melosine B and H obtained from the plant *Melodinus cochinchnensis* (family: Apocynaceae) demonstrated moderate cytotoxic activity against human cancer cell lines HL-60, SMMC-7721, A-549, MCF-7, and SW480 with IC50 values ranging from 1.6 to 8.1 μM [49]. The makaluvamines isolated from a sponge of *Zyzya* sp. are potent antineoplastic agents, with bioactivity against human colon carcinoma cell line HCT-116. These molecules act through inhibition of topoisomerase II. The study of mechanism of action of Makaluvamine showed that it produce protein-linked DNA double-strand breaks [50]. Dragmacidin is a bis-indole alkaloid isolated from marine sponge *Dragmacidon* sp. that exhibited in-vitro cytotoxicity with IC50 value of 15 μg/ml against murine leukemia P-388 cell line and 1−10 μg/ml against human lung (A549), colon (HCT8) and mammary (MDAMB) cancer cell lines [51]. Kobayashi et al. reported a cytotoxic bisindole alkaloid hyrtinadine A obtained from an Okinawan marine sponge *Hyrtios* sp., with pyrimidine moiety which has shown to exhibit in-vitro cytotoxicity against murine leukemia L-1210 (IC50 = 1 μg/ml) and human epidermis carcinoma KB cells (IC50 = 3 μg/ml) [52]. Bifulco et al. reported the isolation of two tris-indole alkaloids, gelliusines A and B from a deep water new caledonian sponge *Gellius* or *Orina* sp. that showed anti-cancer activity with an IC50 value between 10 and 20 μg/ml against KB, P-388, P-388/dox, HT-29 and NSCLC-6 cell lines [53]. Eudistomin
K is a novel oxathiazepine ring containing β-carboline, isolated from the tunicate *Eudistoma olivaceum*, exhibited anti-tumor activity against L-1210, A-549, HCT-8, and P-388 cell lines [54].

3.1.2. Synthetic derivatives

Numerous synthetic derivatives have been synthesized and evaluated for anti-tumor activity. Several reviews have been published focusing the indole-based molecules implicated in the treatment of cancerous conditions. Sunitinib and osimertinib are two marketed drugs with indole nucleus implicated for treatment of renal cell carcinoma, gastrointestinal stromal tumor and NSCLC, respectively. Sunitinib (Sutent) is a multi-targeted receptor tyrosine kinase (RTK) inhibitor of platelet derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) along with RET (rearranged during transfection). In 2008, the drug received approval for the treatment of renal cell carcinoma and gastrointestinal stromal tumor [55]. The crystal structure of this molecule available with VEGFR (PDB: 4AGD) shows that nitrogen of the indole nucleus forms hydrogen bond with carbonyl of Glu917 while the carbonyl group on the ring interacts with NH of Cys919 of the pocket. The oxindole ring system substituted with fluoro group forms hydrophobic interaction with Leu1035 residue of the pocket [56]. Osimertinib (Tagrisso) is a third generation inhibitor of mutated (T790 M) epidermal growth factor receptor (EGFR). In 2015, AstraZeneca received license for marketing osimertinib for the treatment of T790 M mutation positive NSCLC [37,57,58]. Recently, Panobinostat (Farydak) received FDA approval for the treatment of multiple myeloma [59]. The drug has been developed by Novartis to act as a pan-selective histone deacetylase (HDAC) inhibitor. It is under Phase III clinical trial for the treatment of Hodgkin’s lymphoma, cutaneous T-cell lymphoma, and under Phase II clinical trial against myelodysplastic syndromes, breast cancer and prostate cancer [60,61]. The drug is also being evaluated for its anti-retroviral potential and is in Phase I/II trial for the same [62]. The drug co-crystallized with HDAC-6 protein (PDB ID: 5EF8) shows that OH forms hydrogen bond interaction with Asp612 and His573 amino acid residues while NH forms hydrogen bonding interaction with Ser531 and benzyl ring forms π-π stacking with Phe643 amino acid residue [63]. Another oral drug by AstraZeneca Alectinib (Alecensa) is ALK inhibitor implicated for crizotinib resistant NSCLC that was approved by FDA in 2015 [64].
Some of the compounds are under evaluation against a plethora of cancerous conditions. These include AstraZeneca’s ATR/mTOR inhibitor AZ-20, that showed activity against HT29 tumor cancer cell line (IC\textsubscript{50} value of 50 nM) [65]. LAQ-824 (Dacinostat) is another HDAC inhibitor (32 nM) developed by Novartis whose clinical effectiveness is being evaluated for the treatment of NSCLC [66]. PCI-34051 is another investigational inhibitor of HDAC8 implicated for the treatment of T-cell lymphoma or leukemia [67]. EI1 (developed by Novartis) is a selective EZH2 (Enhancer of zeste homolog 2) inhibitor effective against wild and mutated (Y641F) form of enzyme [68]. CPI-169 (developed by Constellation Pharmaceuticals) is another inhibitor with ability to block EZH2 enzyme [69]. The EZH2 inhibitors are implicated in the treatment of various types of lymphomas. Orantinib (developed by Taiho Pharmaceuticals) is a potent and bioavailable receptor tyrosine kinase inhibitor capable of blocking vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), thus inhibiting tumor growth and angiogenesis. The drug however got failed in Phase III clinical trials for the treatment of hepatocellular carcinoma, it is now being considered for advanced solid tumors [70]. Motesanib is an experimental drug candidate showing inhibitory activity on VEGFR, PDGFR and stem cell factor receptor. In clinical evaluation, the drug failed to show promising results in Phase II evaluation for effectiveness in advanced NSCLC and metastatic breast cancer [71]. However, it showed positive results in Phase II clinical trials against thyroid cancer [72]. The crystal structure of VEGFR2 kinase domain with motesanib (PDB ID: 3EFL) depicts that NH of amide group of the molecule forms hydrogen bond with Glu885 and carbonyl group with Asp1046; nitrogen of terminal pyridine ring with Cys919 and pyridine ring linked with amide forms π-cation interaction with Lys868 amino acid residue. PF-00562271 is a potent focal adhesion kinase (FAK; IC\textsubscript{50} value = 1.5 nM) and proline rich tyrosine kinase (PYK2; IC\textsubscript{50} value = 13 nM) inhibitor implicated for the treatment of hepatocellular carcinoma [73]. Obatoclax (developed by Gemin X) is an investigational drug with BCL-2 inhibitory activity. The drug has shown effectiveness in various cancerous conditions including leukemia, lymphoma, small cell lung cancer, non-Hodgkin's lymphoma, multiple myeloma, myelofibrosis and mastocytosis [74-77]. It is currently undergoing clinical evaluation for various cancerous states, JN-26854165 (Serdemetan), a product of Johnson and Johnson Pharmaceutical and Research Development Pvt. Ltd., has been clinically evaluated for the treatment of advanced stage or refractory solid tumors. It shows its pharmacological activity via inhibition of HDM2 ubiquitin ligase and activation of p53 [78]. Birinapant (TL32711, Teralogic Pharmaceuticals) is SMAC mimetic antagonist having inhibitory effects on apoptosis. It is a clinical candidate for the treatment of hematological malignancies, solid tumors and acute myelogenous leukemia [79,80].
GSK2606414 and GSK2656157 are products of Glaxosmithkline that act as protein kinase R (PRK) like ER kinase (PERK) inhibitors that are implicated in cell proliferation and differentiation [81,82]. The structure of GSK2606414 co-crystallized with PERK (PDB ID: 4G31) shows that NH$_2$ of pyrrolopyrimidine interacts with Gln888 while nitrogen forms hydrogen bonds with Cys890 amino acid residue; the ring forms π-π interaction with Phe943 amino acid [81]. Enzastaurin is a protein kinase C beta (PKCβ) inhibitor with antineoplastic activity. The drug is undergoing clinical evaluation for the treatment of lymphoma, breast cancer, prostate cancer, NSCLC, leukemia, colorectal cancer, ovarian cancer, renal cell carcinoma and pancreatic cancer [83,84]. Sotrastaurin (developed by Novartis) is a pan-protein kinase C inhibitor that is being clinically evaluated for effectiveness in the treatment of lymphocytic leukemia, lymphoma, melanoma and kidney transplantation [85,86]. Another PKC inhibitor, Go 6976 is a PKCα and β inhibitor (2.3 and 6.2 nM, respectively) that has been reported to inhibit invasion of urinary bladder cancer cells [87]. Rucaparib (developed by Agouron Pharmaceuticals) is an investigational candidate for advanced solid tumor, breast and ovarian cancer with BRCA1 and BRCA2 mutation that shows its effect via inhibition of poly (ADP-ribose) polymerase (PARP-1) [88]. The catalytic domain of PARP-1 in complex with rucaparib shows (PDB ID: 4RV6) that amide linkage in the molecule form hydrogen bonds with Gly863 and Ser904 amino acid residues while indole nucleus forms π-π interaction with Tyr907. TAK-901 (developed by Millennium Pharmaceuticals, Inc.) is an investigational multi-targeted Aurora A/B kinase inhibitor implicated for hematologic malignancies or lymphoma. In addition, the drug has also shown to inhibit JAK2, c-src, Abl kinases [89]. Tivantinib (ARQ-197) is a c-MET inhibitor implicated against solid tumor, NSCLC, colorectal cancer, prostate cancer, hepatocellular carcinoma etc. [90]. AZD-3463, a preclinical candidate designed by AstraZeneca, is an orally bioavailable ALK inhibitor showing effectiveness in crizotinib resistant NSCLC cell line [91]. YH-239-EE is a highly potent p53-MDM2 antagonist with anti-myeloid leukemia activity [92]. THZ1 is a selective and irreversible CDK7 inhibitor that has activity reported in leukemia. The compound has been shown to bind covalently to the Cys312 residue of the active site of CDK7 protein [93].
The chemical structures of the marketed drugs when observed critically show that substitution of indole ring at third position yielded highly potent molecules. Sunitinib and osimertinib show the substitution of nitrogen containing ring systems with diethylamino substitution attached via different linkers. On the other hand, alemtuzumab contains tetracyclic ring system with fused indole ring. This ring system further has nitrogen containing ring (piperidine) followed by morpholine moiety. Panobinostat also contains the indole substituted at third position with aromatic benzyl substituent attached via an ethyl amino linker. A common structural requirement for indole based anti-tumor agents has been shown in Fig. 2.

Other molecules in clinical trials are indole derivatives substituted at third position including AZ-20, dacinostat, CPI-169, orantinib, JNJ-26854165, birvanapant, enzastaurin, sotrastaurin, tivantinib, AZD-3464, YH-239-EE and THZ1. Various types of substitutions have been tried at this position to yield potent derivatives. For the other derivatives, second (obatoclax, rucaparib) and fifth (EI-1, brivanib, PF-00562271, GSK2606414, GSK2656157, TAK-901) positions of indole have been explored. In addition, substitution at nitrogen of indole as well as cyclic derivatives has yielded potent molecules. These substitutions have also yielded potent anti-cancer agents. Considering the substitution pattern, potency and mechanism of action of these indole derivatives, medicinal chemists may design new derivatives with better potency and lesser toxicological implications.

3.2. Antimicrobial activity

Microbial infections are caused by a range of microbes, including, bacteria and fungi, such as, Enterococcus, Aspidosperma, Plasmodium, Staphylococcus, Pseudomonas etc. Resistance of microbial agents has become a global concern and structurally novel molecules with new mode of action are required for the treatment of bacterial infections. A range of microbial agents with indole nucleus have been isolated from natural sources and have also been synthesized.

3.2.1. Natural derivatives

Alstonia scholaris is extensively used as traditional medicine in the treatment of malaria, jaundice, gastrointestinal troubles, cancer, etc. It belongs to Apocynaceae family and contains monoterpenoid, indole alkaloids nareline, vallesamine, vallesamine-N-oxide, picrinine, strictamine, 5α-methoxystrictamine and 16-formyl-5α-methoxystrictamine, strictamine-N-oxide, akummidine, 19-epischolaricine, normavacurine-2-one, 5-hydroxy-19,20-E-alschomine and scholarisines H-O. Out of these identified phytoconstituents, normavacurine-21-one, strictamine and vallesamine-N-oxide show potent inhibitory activity against Enterococcus faecalis while vallesamine and nareline against Pseudomonas aeruginosa [94]. Deethylobiphyllidine, aspidophylline, strychnine, melotene and Limaspermidine are alkaloids isolated from Aspidosperma sp., family Apocynaceae [95]. Reports show that aspidospermine extracted from Aspidosperma show anti-parasitic properties against Plasmodium, Leishmania and Trypanosoma sp. [96]. 6-Bromoaplysinopsin isolated from Smenospongia aurea also showed antimalarial activity against Plasmodium falciparum at concentration of 0.34 μg/ml [97]. Moody and co-workers isolated a potent antibacterial antibiotic indolmycin which is an intermediate for Convolvulatmydine C (4,6-dibromo-3-hydroxyoxoindoline) isolated from Amathia convolute. Indolmycin is a potent antibacterial drug effective against Staphylococcus aureus and Helicobacter pylori at concentration of 0.5 and 0.016 μg/ml, respectively [98,99]. Cryptotripeptine, cryptopine hydrochloride, hydroxycryptopine and neocryptopine (cryptotackirine) are indoloquinoline derivatives isolated from Cryptotepis sanguinolenta display antimalarial activity against Plasmodium falciparum chloroquine resistant strains with IC50 value in the range of 27–63 ng/ml [100,101]. Manzamine A, 8-hydroxymanzamine A and manzamine-A-N-oxide belong to the class of manzamine alkaloids show potent antibacterial activity against different strains of Plasmodium falciparum with IC50 values of 4.5, 6.0 and 11 ng/ml, respectively [102]. Canthin-6-one and 8-hydroxycathin-6-one isolated from Allium neapolitanum exhibited pronounced antibacterial activity with minimum inhibitory concentration (MIC) values of 8–64 μg/ml against Staphylococcus aureus strains and 2–32 μg/ml against Mycobacterium species [103]. Alternatamides A–C are bromotryptamine peptides from Atlantic bryozoan Amathia alternata, which show antibacterial activities against several Gram-positive bacteria including Staphylococcus aureus, Staphylococcus haemolyticus, Bacillus subtilis, Enterococcus faecalis, Enterococcus faecium, Streptococcus pyogenes with MIC values range of 4–32 μg/ml [104]. Uleine is a major indole alkaloid isolated from the bark of Aspidosperma parvifolium (family: Apocynaceae) shows high in vitro anti-malarial activity against chloroquine-resistant Plasmodium falciparum (IC50 < 1 μg/mL) [105]. Dihydroflustramine C, a marine alkaloid isolated from bryozoans of the Flustridae family (Flustra foliacea), has shown antibacterial activity against Bacillus subtilis [106].
3.2.2. Synthetic derivatives

The antimicrobial activity of natural indole alkaloids has inspired synthetic chemists to design and synthesize some novel indole based antimicrobial agents. Desai et al synthesized a series of indole and pyridine based 1,3,4-oxadiazole derivatives antitubercular agents. The compounds were evaluated for their activity against Mycobacterium tuberculosis and Mycobacterium bovis BCG. The most active compound M1 showed activity against Mycobacterium bovis BCG with MIC value of 0.94 μg/ml [107]. Heuseca and coworkers synthesized a series of [3-(4,5-diaryl-1H-imidazol-2-yl)-1H-indole] derivatives with potency against methicillin resistant as well as methicillin sensitive strains of Staphylococcus aureus (MIC = 1 μg/ml against both strains). The highest active compound M2 was also evaluated against other strains and was observed to show potency against Gram positive bacteria instead of Gram negative bacteria [108]. Singh et al synthesized a series of new antimicrobials with indole scaffold and evaluated for their antimicrobial and antifungal potential. The results showed the compounds to possess antifungal activity against Candida albicans. The molecule M3 was emerged as the most potent molecule of the series having both antimicrobial as well as antifungal potential [109]. Shakuja et al synthesized bis spiroindoles that exhibited in-vitro antibacterial against three Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis, and Staphylococcus epidermis), four Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, and Klebsiella pneumonia) and two fungal strains (Aspergillus niger and Candida albicans) [110].

Naidu et al synthesized 1-(4-(benzo[d]isoxazol-3-yl)-piperazin-1-yl)-2-(1H-indol-3-yl)ethan-1-one derivative M4 that showed activity against Mycobacterium tuberculosis H37RV strain (MIC value = 126.86 μM) [111]. Choppara et al synthesized a series of bis—indole analogues that showed antibacterial and antifungal potential against various Gram positive bacterium (Bacillus subtilis), Gram negative bacteria (Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa) and antifungal activity against Aspergillus flavus, Aspergillus niger, Candida albicans using agar well diffusion assay. The lead compound M5 was found to be active against B. subtilis, K. pneumonia, P. aeruginosa and Aspergillus sp [112]. Behbehani et al synthesized a series of indole derivatives and evaluated them against Gram positive, Gram negative bacteria and the fungus Candida albicans. The lead compound from the series named M6, M7 and M8 were found to be effective against Escherichia coli, Staphylococcus aureus, Bacillus subtilis and Candida albicans [113]. Yamuna et al synthesized indole based anti-tubercular agents M10-M12 with MIC value 3.12 μg/mL. The compounds were effective against Mycobacterium tuberculosis H37Rv strain [114]. Mielczarek et al synthesized mono-indole and bis-indole derivatives that were evaluated for their activity against Escherichia coli and Bacillus subtilis. Among the synthesized compounds, the most promising candidate M13 showed moderate activity against the evaluated strains [115].

The medicinal chemists across the globe have synthesized antimicrobial agents via electrophilic substitution of the third position as well as the NH of the indole nucleus. The substitution of
hydrophobic groups with or without linker has been shown to yield compounds with good anti-microbial activities. Moreover, the cycloaddition at the second and third position of the ring also gave compounds with high anti-microbial activities. On the contrary, substituting the third position of indole with small groups such as methyl (M13) yielded compounds with only moderate anti-microbial potential. On the basis of the above knowledge, the substitutional requirements for indole based anti-microbial agents have been shown in Fig. 3.

3.3. Anti-viral activity

Viral diseases are one of the widespread infections around the globe that include common cold, influenza, chickenpox, herpes, gastroenteritis, human immunodeficiency virus (HIV), hepatitis, ebola virus, etc. Antiviral therapy plays a key role in controlling the outbreak of the viral infections. Till date, a number of indole containing molecules have been reported in the literature.

3.3.1. Natural derivatives

Sattazolin is an indole acyloin based natural product that exhibits potent antiviral activity with an ID<sub>50</sub> value of 1.5 mg/mL against herpes simplex virus type 1 (HSV1) and type 2 (HSV2) [116]. Drymaritin, a novel indole alkaloid isolated from Drymaria diandra, is reported to exhibit anti-HIV effects in H9 lymphocytes with an EC<sub>50</sub> value of 0.699 mg/mL [117]. Caulerpin, isolated from the green algae Caulerpa racemosa, is reported to possess antiviral activity against Bovine viral diarrhea virus (BVDV) replication [118]. Minghua Chen and co-workers reported the isolation of seventeen new indole alkaloids and fourteen known analogues from an aqueous extract of the root of Isatis indigotica, and arvelexin show antiviral activity against the influenza virus A/Hanfang/359/95 (H3N2), with IC<sub>50</sub> values of 3.70–12.35 mM [119].

Paromita Bag and coworkers reported the isolation of an indole alkaloid 7-methoxy-1-methyl-4,9-dihydro-3H-pyrido [3,4-b]indole (Harmaline) from an ethnomedicinal herb Ophiorrhiza nicobarica, which demonstrated significant anti-HSV-1 activity against both wild type and clinical isolates of HSV-1 by interfering with the viral immediate early (IE) transcriptional events [120].

Dragmacidins, obtained from a marine sponge of the genus Halicortex, were reported to display modest antiviral activity, and compound, dragmacidin F, containing an unprecedented carbon skeleton that may be derived from cyclization of a partially oxidized form of dragmacidin series derivatives, showed in-vitro antiviral activity against HSV-1 (EC<sub>50</sub> = 95.8 mM) and HIV-1 (EC<sub>50</sub> = 0.91 mM) [121].

Cheng-Jian Tan and coworkers reported the isolation, structural elucidation, and anti-HIV-1 activity of three novel indole alkaloids trigonoliimines A-C with unprecedented polycyclic skeletons. They were isolated from the extract of the leaves of Trigonostemon lili. The anti-HIV-1 activity of trigonoliimines A and B were tested by a microtiter syncytium formation infectivity assay with Zidovudine (EC<sub>50</sub> = 0.02 mM) as a positive control. Trigonoliimine A showed modest anti-HIV-1 activity (EC<sub>50</sub> = 0.95 mM) [122].
Eudistomins are β-carboline derivatives, isolated from different kinds of ascidians (marine tunicates of the family Ascididae), such as *Ritterella sigillinoides*, *Lissoclinum fragile* or *Pseudodistoma auratum*. Recent investigations reported that eudistomins containing the oxathiazepine ring (Eudistomins C, E, F, K, and L) show the most significant antiviral activity against HSV-1, of which C and E, with a phenolic group were active at concentration of 0.005–0.01 mg/disk. Eudistomins C and E are also reported to possess the activities against RNA viruses such as Coxsackie A-21 virus, equine rhinovirus and against DNA viruses [123].

![Eudistomin A](image1.png)

![Eudistomin C](image2.png)

![Eudistomin E](image3.png)

![Eudistomin K](image4.png)

![Eudistomin L](image5.png)

3.3.2. Synthetic derivatives

Arbidol (Umifenovir), manufactured by Russian pharmaceutical company Phamastandard, is a broad-spectrum antiviral agent that has been demonstrated to possess activity against a number of enveloped and non-enveloped viruses by inhibiting the fusion of viral capsid with the host cell membrane. The drug has been shown to possess potency against influenza A, B and C viruses, respiratory syncytial virus, hepatitis B virus, hepatitis C virus, human rhinovirus type 14, coxsackie B3 virus, adenovirus type 7 [124]. The drug in complex with H3N2 influenza virus hemagglutinin (PDB ID: 5T6N) shows that carbonyl group of ethyl ester group forms hydrogen bonding interaction with Lys307 amino acid residue [125].

Delavirdine (Rescriptor), an anti-retroviral agent marketed by VIIV healthcare, was approved by US FDA in 1997 [126]. It acts as non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used for the treatment of human immunodeficiency virus (HIV). It is an inhibitor of chytochrome P450 enzyme CYP3A4 and interacts with many medications. The drug has been found to be hepatotoxic [127,128]. The co-crystal structure of delavirdine complexed with HIV-1 reverse transcriptase (PDB ID: 1KLM) shows that carbonyl group and NH of indole ring forms hydrogen bonding interaction with amino acid Lys103 of the protein [129].

Atevirdine (U-87201E) is a bis-heteroarylpyperazine (BHAP) with *in-vitro* activity against human immunodeficiency virus (HIV-1). It is a Phase I clinical candidate that acts as NNRTI against HIV-1 as well as zidovudine resistant HIV-1 [130].

GSK2248761 (Fosdevirine) is another NNRTI developed by GlaxoSmithKline that is under Phase 2 clinical evaluation. The compound has been reported to have sub nano-molar activity against wild type as well as NNRTI resistant mutant HIV [131]. The evaluation of clinical efficacy of the compound has been put on hold due to reports of seizures in treatment-experienced patients [132].

Golotimod (SCV-07) is an orally bioavailable synthetic peptide containing the amino acids ω-glutamine and ω-tryptophan connected by a gamma-glutamyl linkage with potential immune stimulating, antimicrobial and antineoplastic activities. SciClone Pharmaceuticals Inc carried out Phase 2 clinical trial of the drug for the treatment of hepatitis C (HCV). The clinical data demonstrated SCV-07 to be safe and well-tolerated at both administered doses. Results showed that SCV-07 did not meet the study’s primary efficacy endpoint of a 2-log reduction in viral load from baseline level. A phase 2 study is still on-going with SCV-07 in attenuating oral mucositis in subjects with head and neck cancer; however, no further study is listed for HCV [133].

Panobinostat (LBH589) is an experimental drug developed by Novartis as a non-selective histone deacetylase inhibitor (HDAC inhibitor) for treatment of Multiple Myeloma (Phase III) and Acute Myeloid Leukemia (Phase II). It is currently being used in a Phase I/II clinical trial that aims at curing AIDS in patients on highly active antiretroviral therapy (HAART). In this technique, panobinostat is used to drive the HIV DNA out of the patient’s DNA, in the expectation that the patient’s immune system in combination with HAART will destroy it, this is the first proof of a viral “kick” leading to consistent plasma release of viral particle [59].

BILB-1941 is a NS5B inhibitor that demonstrated antiviral activity in patients chronically infected with genotype 1 hepatitis C virus. It belongs to the category of allosteric non-nucleoside inhibitor of HCV NS5B polymerase that inhibits replication in replicon systems. It also displayed improved ADME profiles, and showed the most optimal balance between antiviral potency and a consistent cross-species pharmacokinetic profile [134].

BMS-79132, a cyclopropyl-fused indolobenzazepine HCV NS5B RNA-dependent polymerase inhibitor, developed by Bristol-Myers Squibb, was found to perform distinguishing antiviral, safety, and pharmacokinetic properties that resulted in its selection for clinical evaluation [135]. The X-ray crystallographic structure of RNA directed RNA polymerase in complex with BMS-79132 shows that sulphamoyl and carbonyl group of carbazole attached to fifth position of indole ring forms hydrogen bonding interaction with Arg503 amino acid residue present in the binding site [135].

MK-8742, a second generation tetracyclic indole-based NS5A inhibitor, is currently under Phase II clinical evaluation for the treatment of HCV infection. In combination with MK-5172, an NS3/4A protease inhibitor, this drug exhibited improvements in the genetic barrier while maintaining potency, yielding amazing results in terms of efficacy (90–100%), tolerability and safety [136].

(7R)-14-Cyclohexyl-7-[(2-(dimethylamino)ethyl)(methyl)amino]-7,8-dihydro-6H-indolo [1,2-e] [1,5]benzoxazocine-11-carboxylic Acid (MK-3281), a phase II clinical candidate discovered in Merck Research Laboratories, is a potent and orally bioavailable second-generation tetracyclic allosteric finger-loop inhibitor of the Hepatitis C Virus NS5B polymerase with indolo-benzoxazocine scaffold [137].

Sulphonylindolecarboxamide (L-737126), reported by Merck
Laboratories, is non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against NNRTI-resistant mutant carrying in-vitro activity against wild and mutant HIV-1 in the low nanomolar range and cytotoxicity for MT-4 cells [138].
Enfuvirtide (T-20; Fuzeon), the peptide anti-HIV drug targeting gp41N-terminal heptad repeat (NHR), was approved by the U.S. FDA in 2003 as the first HIV fusion/entry inhibitor for treatment of HIV/AIDS patients who fail to respond to the current antiretroviral drugs. However, because T20 lacks the pocket-binding domain, it exhibits low anti-HIV-1 activity and short half-life [139].

TMG647055, a non-zwitterionic 17-membered macrocyclic indole, is a potent and selective inhibitor of the HCV NS5B polymerase. This compound was identified to possess nanomolar potency (EC50 = 77 nM) in HCV replicon cells, limited toxicity and off-target side effects, and encouraging preclinical pharmacokinetic profiles characterized by high liver distribution, and it is currently being evaluated in phase II clinical trials in combination with simeprevir [140].

Chemically, indole derivatives demonstrating antiviral activity are substituted at second, third, fifth and sixth positions of the nucleus. Arabidol, delavirdine and ateviridine are the derivatives with substitutions at second position of indole. GSK2248761, golotimod and panobinostat are antiviral molecules that possess electronegative substitutions at second position. BIBL1941 is a derivative possessing 2,3-unsaturated carboxylic acid attached via a linker at fifth position of the indole ring. BMS-791325, MK-8742, MK-3281 and TMG-647055 are indole derivatives cyclized at first and second positions of the ring. In addition, these derivatives are also substituted at fifth position. The structural requirements of indole based anti-viral agents have been shown in Fig. 4.

### 3.4. Anti-inflammatory activity

Inflammation is a complex biological response of body tissue to harmful stimuli such as pathogens, irritants, damaged cells etc. Anti-inflammatory agents find their use in a wide range of pathological conditions including rheumatoid arthritis, osteoarthritis, migraine, gout, spondylitis etc.

Only a few natural anti-inflammatory agents containing indole scaffold have been reported till now. Cycloexpansamine A and B, penicillinolide A isolated from marine cultures of *Penicillium* species are among the few. These are spiroindolinone alkaloids having anti-inflammatory properties [141]. Indole-based indomethacin (Indocid) is a non-steroidal anti-inflammatory drug (NSAID) that acts as non-selective inhibitor of cyclooxygenase (COX-1 and COX-2) that in turn blocks the production of prostaglandins [142]. It was approved by US FDA in 1965 for the treatment of fever, pain and swelling, and has been implicated in a number of clinical indications including ankylosing spondylitis, gout, migraine, osteoarthritis, rheumatoid arthritis, Paget’s disease of bone, juvenile arthritis, etc. [143]. The drug has been shown to have adverse effects such as peptic ulcers, ranitidine, dyspepsia, heartburn, diarrhea, hyperkalemia etc. that occur due to non-selective inhibition of cyclooxygenase (COX).

Tenidap (developed by Pfizer), a COX/5-LOX inhibitor have cytochrome modulating anti-inflammatory drug candidate with anti-rheumatoid activity. The drug was observed to inhibit interleukin 1 synthesis [144]. However, it was rejected by FDA in 1996 due to reported liver and kidney toxicity [145].

Acemetacin (Emflex, manufactured by Merck KGaA), a glycolic acid ester prodrug of indomethacin that acts as NSAID. It has advantage of reduction of gastric damage over indomethacin and has implication in the treatment of osteoarthritis and rheumatoid arthritis [146].

Etodolac (Lodine, manufactured by Almirall Limited), a US-FDA approved (1991) NSAID acting as selective COX-2 inhibitor results in decrease of prostaglandin levels in the body with better gastrointestinal tolerability. The drug is implicated in the treatment of osteoarthritis and rheumatoid arthritis [147].

Several synthetic indole based derivatives have also been evaluated for anti-inflammatory activity. Rani et al synthesized and evaluated indole based chalcones and pyrazolines derivatives, the most active compound (3-[1-acetyl-5-(p-hydroxyphenyl)-2-pyrazolin-3-yl]indole) **AI1** was found to be the most potent, showed higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than the standard drug phenylbutazone [148]. Bhati et al synthesized various indole derivatives and evaluated them for anti-inflammatory, ulcerogenic and analgesic activities. The most active compound **AI2** (41.23% at 50 mg/kg) showed anti-inflammatory and analgesic activities better than phenylbutazone (36.8% at 50 mg/kg), while the compound was associated with lesser degree of anti-inflammatory activity in comparison to indomethacin (52.20% at 5 mg/kg) [149]. Singh et al synthesized a series of bis-indole derivatives and evaluated for their anti-inflammatory activity. The most active compound **AI3** (53.3% at 50 mg/kg dose) of the synthesized series showed higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than phenylbutazone (38.8% at 50 mg/kg dose) [150]. Singh et al synthesized indole derivatives with selectivity indices **AI4** (COX-2 IC50 value = 63 nM) and **AI5** (COX-2 IC50 value = 99 nM) [151]. Experiments done by Radwan et al led to the development of tenidap based anti-inflammatory agents, the compounds showed good anti-inflammatory and analgesic potential. The lead compound **AI6** (44.4% at 70 mg/kg dose) showed anti-inflammatory activity comparable to standard drug indomethacin (29.9% at 35 mg/kg dose) [152]. Nakkady et al evaluated twelve compounds,
out of which the most active compound A17 exhibited 55.31% inhibition at 50 mg/kg dose with ulcerogenic activity less than standard drug indomethacin [153].

The other synthesized derivatives were substituted mainly at third position of the ring. In A14 and A15 the first position was substituted with sulphonlic acid group and these compounds were bis-indole derivatives linked with long chain, whereas in A17 second position was substituted with thiophene group.

3.5. Anti-depressant activity

Antidepressants are the class of drugs used in the treatment of major depressive disorder characterized by pervasive and persistent low mood. Depression is a disorder that is rising at an alarming rate especially in young people. Various indole containing antidepressant drugs have been reported in the literature are discussed below. Tabernanthe iboga is a perennial rainforest shrub of Central Africa that acts as CNS stimulant and has marked ability to attenuate drug addiction and dependence. The iboga alkaloids consist of indole ring are represented by ibogaine [154]. Several indole based compounds of marine origin have been used in past to control anxiety and depression. Methylaplysinopsin isolated from Aplysia reticulata inhibits monoamine oxidase (MAO) and displaces serotonin from its receptors [155]. 6-bromoaplysinopsin and N-3'-ethylaplysinopsin isolated from Smenospongia aurea were reported to have high affinity for 5HT2A and 5HT2C receptors [87]. 5,6-dibromo-N,N-dimethyltryptamine showed antidepressant action in forced swim test and tail suspension test carried out in mice [156].
Some of the synthetic antidepressants have been synthesized in 1990s, and act as reversible inhibitors of monoamine oxidase A (MAO-A). MOA-A is an enzyme that catalyzes the oxidative deamination of serotonin, dopamine and norepinephrine. Thus, inhibitors of this enzyme prevent the breakdown of monoamine neurotransmitters and increase their availability. Three drugs, namely, metralindole (Inkazan), pirlindole (Pyrazidol) and terindole were synthesized in Russia as monoamine oxidase A inhibitors [157,158]. These drugs belong to the class of tetracyclic antidepressants.

Metralindole, pirlindole and terindole are tetracyclic derivatives of indole. Metralindole is a triaza derivative with methoxy substitution at fifth position, while pirlindole and terindole are diaza derivatives with methyl and cyclohexyl group substituted at fifth position of indole, respectively. The various substitution requirements for anti-depressant indole molecules is mentioned in Fig. 6.

3.6. Anti-cholinergic activity

Cholinergic drugs are a class of drugs that modulate the functioning of the neurotransmitter acetylcholine. These drugs find their application in diseases such as glaucoma, Alzheimer’s disease, delayed gastric emptying, asthma, chronic bronchitis, etc.

From the category of natural origin, different indole alkaloids have been isolated from the bark of Rauwolfia reflexa (Apocynaceae) including rauvolfine C, 3-methyl-10,11-dimethyl-6-methoxy carbonyl-β-caroline, macusine B, vinorine, undulifoline, isoreserpiline and rescinnamine. Out of these rescinnamine was found to be potent anticholinergic agent [159].

Physostigmine is an important reversible acetylcholinesterase inhibitor derived from Physostigma venenosum (Calabar bean). It indirectly stimulates nicotinic and muscarinic acetylcholine receptor and used in the treatment of glaucoma, Alzheimer’s disease and delayed gastric emptying. It has been shown to improve long term memory, treatment of orthostatic hypotension, myasthenia gravis and cholinergic disorders. It is antidote for Datura stramonium and Atropa belladonna poisoning [160].
3.7. Anti-migraine activity

Migraine is a severe neurological disorder characterized by throbbing pain in the head. According to a survey by WHO, between 50 and 75% adults all around the world suffer from migraine and 14% adults report severe headache. The triptans and NSAIDs are most widely used treatment of migraine disorders. ‘Triptan’ is a class of tryptamine-based drugs and most widely used for the treatment of migraine that act as agonist on serotonin 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors. These molecules have indole ring as their basic scaffold. Some of the FDA approved triptans include sumatriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan, avitriptan and zolmitriptan.

Sumatriptan (Treximet, Imitrex, Imigran) developed by Glaxosmithkline received FDA approval for the treatment of migraine in 1992 [161]. Naratriptan (Amerge) is another drug of same class marketed by Glaxosmithkline after getting approved in February 1998 [162]. Rizatriptan (Maxalt), a product of Merck, also received approval in 1998 as a second generation triptan [163]. Almotriptan (Axert) received marketing approval in 2001 for the management of heavy migraine attacks (Janssen Pharm)[164]. Pfizer in 2002 got approval for eletriptan (Relpax) which is used as an abortive medication in migraine attacks[165]. Frovatriptan (Frova) has been licensed to Endo Pharms (2001) for the treatment of migraine and short term menstrual migraine [166]. Zolmitriptan (Zomig) marketed by AstraZeneca was approved in 2001 for the treatment of acute migraine attacks [167]. Another triptan class candidate Avitriptan (BMS-108, 048) never received FDA approval is used as an investigational drug [168].

Chemically, the triptan class of drugs contains an indole ring as their basic nucleus. These drugs show their action by acting as an agonist on 5-HT\textsubscript{1B/1D} receptor which is G-protein coupled receptor with ligand gated ion channel. The above mentioned drugs have some common features that are required for their action on the receptor (Fig. 7). The nitrogen (NH) of indole nucleus acts as a hydrogen bond donor to the Ser352 residue in the serotonin receptor pocket. In addition, the ring provides lipophilicity to the drug to form hydrophobic as well as $\pi-\pi$ interaction with Phe residues of the pocket. The presence of protonated nitrogen is also sorted for ionic interaction with acidic residue Asp118 of the pocket. Other groups are required to form hydrogen bonds within the receptor site [169].

Methysergide (UML-491) was a prescription drug for prophylaxis of cluster headaches/migraine headaches, but no longer recommended due to retroperitoneal/retropulmonary fibrosis [170]. It was approved by FDA in 1962, acts as a 5-HT\textsubscript{2B} receptor inhibitor. It is one of the most effective medications for the prevention of migraine, but not for the treatment of an acute attack. Nicergoline (Sermion), ergot derivative used for the treatment of migraine of vascular origin, senile dementia, cerebral thrombosis, atherosclerosis, Raynaud’s disease, Bradycardia, and interstitial nephritis. Chemically, methysergide and nicergoline are cyclic derivatives of indole cyclized at third and fourth positions of the ring.
Some natural products showing serotonin receptor modulatory activity have also been reported. Gelliusine A, isolated from Caledonian sponge Gellius sp. (Demospongiae), had similar features as required for acting on serotonin receptor, i.e. presence of indole nucleus, protonated nitrogen and groups of forming hydrogen bonds (OH) [53].

### 3.8. Antiemetic activity

Antiemetics are a class of drugs effective in the treatment of nausea and vomiting. These drugs are particularly used for the treatment of motion sickness, cancer chemotherapy and drug induced nausea vomiting. Various serotonin 5-HT₃ antagonists have been approved and prescribed as antiemetic especially for the treatment of cancer chemotherapy induced as well as postoperative nausea and vomiting. These antagonists are generally categorized as ‘setrons’ and antagonize the activity of 5-HT₃ receptors present at the terminals of the vagus nerve. These are sometimes also prescribed in irritable bowel syndrome. The marketed drugs of this category including ondansetron, alosetron, ramosetron, dolasetron and tropisetron have indole as basic nucleus in their structure. The structure activity relationship developed for this class of drugs highlighted the importance of an aromatic center (to form hydrophobic interactions), a basic amine moiety (form hydrogen bonds with the receptor) and a carbonyl linker (provide proper distance between the two moieties) [171].

Ondansetron (Zofran), a carbazole containing prototypic antiemetic generally used in cancer chemotherapy, radiation therapy or surgery induced nausea and vomiting, and also indicated in morning sickness and hyperemesis gravidarum of pregnancy and gastroenteritis. It is a product of GlaxoSmithKline approved by FDA in 1991. The side effects associated with the drug includes diarrhea, headache, QT prolongation and allergic reaction [172]. Dolasetron (Anzemet, approved in 1997), an indole containing drug used in the treatment of chemotherapy induced, postoperative and post-radiation nausea and vomiting, and acute gastroenteritis [173]. It is a prodrug with hydrodolasetron being the active metabolite formed by the action of carbonyl reductase enzyme. Tropisetron (Navoban), marketed by Novartis, is another antiemetic that is also used as analgesic in fibromyalgia. The common side effects associated with the drug include headache, constipation and dizziness [174]. Ramosetron (Nasea), is implicated as antiemetic as well as in irritable bowel syndrome like symptoms [175]. Alosetron (Lotronex, GlaxoSmithKline), 5-HT₃ antagonist implicated in irritable bowel syndrome was approved by US FDA in 2000 [176].

Chemically, setrons are indole derivatives possessing heterocyclic ring substitution at third position of the ring linked with carbonyl group. In ondansetron and alosetron, cyclization at second and third positions is observed. The first position is also substituted with methyl group in ondansetron, ramosetron and alosetron. The indole ring substituted with a basic ring system linked with carbonyl group at third position seems to be an important pharmacophore for the 5-HT₃ antagonist activity (Fig. 8).
3.9. Antihypertensive activity

These are a class of drugs that are used for the treatment of hypertension (high BP). Various indole based anti-hypertensive agents have been reported in literature. The reported drugs have varying mechanism of action: α/β blocker, ACE inhibitor, thiazide-like diuretic, AT1 antagonist etc. Perindopril (Coversyl, Coversum or Aceon) and Trandopril (Mavik) are two marketed angiotensin converting enzyme (ACE) inhibitors having octahydro-indole nucleus in their structures. They act by inhibiting angiotensin converting enzyme, a key component of renin-angiotensin-aldosterone system [177,178]. The side effects associated with these drugs include hypotension, dry cough, headache, dizziness, fatigue, nausea and renal impairment. Trandolapril is a prodrug with trandolaprilat (de-esterified form of ethyl ester) being the active metabolite. Trandolaprilat is around eight times more active and has more half-life than the parent drug. The crystal structure of trandolaprilat in complex with angiotensin converting enzyme (PDB ID: 2X93) shows that carboxylic acid group attached to the 2nd position of octahydro-indole ring of the ligand forms hydrogen bonding interaction with Gln265, Tyr504 and Lys495 amino acid residues; another side chain carboxylic acid group forms hydrogen bonds with Glu368, Tyr507 and coordination complex with Zn2+ metal ion; and the quaternarized NH2 interacts with His337 and Ala338 amino acid residues of the ACE enzyme. A similar type of interaction pattern was observed for the prodrug perindoprilat in complex with ACE (PDB ID: 2X94).

Indapamide (marketed by Servier) is a dihydro-indole based thiazide like diuretic used in the treatment of hypertension as well as management of heart failure [179]. The common side effects include fatigue, orthostatic hypotension, allergies and hypokalemia. Carvedilol (Coreg) is well established β-blocker with implication in the treatment of congestive heart failure and hypertension. First approved for use in 1995, the drug has carbazole based architecture [180]. Pindolol (Visken, Novartis) is another selective beta blocker that received FDA approval in 1982 for the treatment of hypertension [181]. It is also implicated in angina pectoris, arrhythmia, acute stress and depression.

Chemically, perindopril and trandolapril are octahydro-indole derivatives substituted with carboxylic acid at second position and a hydrophobic group and ethyl carboxylic ester attached at first position with a linker group. Indapamide is also substituted at first position with 4-chloro-3-methylsulphonylphenyl group attached via carboxamide linker. Carvedoiol and pindolol are beta blockers that have substituted ether groups at fourth position of the indole ring.

In addition, Ogawa et al have recently evaluated some novel indole based mineralocorticoid receptor antagonists having anti-hypertensive activity. The evaluated compounds showed good anti-hypertensive activity and lead compound H1 showed an IC50 value of 21 nM against human mineralocorticoid receptor [182]. Zhu et al evaluated the AT1 receptor antagonist activities of N-Phenyl indole analogues and the lead compound H2 had IC50 value of 0.36 nM in-vitro against the angiotensin II type 1 receptor [183].

Some indole based natural phytoconstituents have also been reported to possess antihypertensive activities. Reserpine (Rau-dixin) is an indole alkaloid with anti-hypertensive and anti-psychotic properties. The anti-hypertensive action of reserpine is a result of depleted catecholamines from peripheral sympathetic nerve endings [184]. Hirsutine is an indole alkaloid isolated from Uncaria rhynchophylla have shown to relieve headache and dizziness due to hypertension. It has also reported to possess sedative and anti-arrhythmic pharmacological activities [185].
3.10. Miscellaneous

Various drugs with indole in their architecture have been implicated in various other disorders. Antiarrhythmic drugs ajmaline and vinopocetine having indole in their structures are marketed drugs. Ajmaline (Gilurytmal), an indole alkaloid isolated from the roots of Rauwolfia serpentina as well as Catharanthus roseus is a Class Ia antiarrhythmic agent. The drug has shown to lengthen the refractory period of the heart by blocking sodium ion channels and also interfere with hERG (human-ether-a-go-go-related gene) potassium ion channels. Ajmaline is implicated in the treatment of Wolff-Parkinson-White-Syndrome, which is characterized by arrhythmias with ventricles contracting prematurely resulting in tachycardia and shortened refractory period [186]. Vinopocetine (Cavinton), a semi-synthetic derivative of vinca alkaloid 'vincamine' is marketed for vasodilation and nooptropic for memory impairment and cerebral metabolism. It is also used as an anti-inflammatory agent in the treatment of Parkinson’s disease and Alzheimer’s disease. It acts by selective inhibition of voltage sensitive sodium channels, resulting in decreased extracellular calcium ions in striatal nerve endings [187].

Silodosin (Rapaflor), α1-adrenoceptor antagonist, is indicated in the symptomatic treatment of benign prostatic hyperplasia (BPH) [188]. It received US FDA approval in 2008. Bazedoxifene (Viviant, Pfizer), third generation selective estrogen receptor modulator (SERM), is used in the prevention of post-menopausal osteoporosis. FDA approved the combination of bazedoxifene and premarin (conjugated estrogens) for menopausal osteoporosis and treatment of moderate to severe hot flushes. The drug is under trials for use in dyspareunia (painful sexual intercourse), breast cancer and pancreatic cancer [189]. Fluvastatin (Lescol) belongs to statin class of drugs for hypercholesterolemia and prevention of cardiovascular disease. The drug shows its effect by blocking the HMG-CoA reductase enzyme that catalyzes an important step in cholesterol synthesis. It is also known to exhibit antiviral activity against hepatitis C [190]. Icatibant (Firazyr) is a peptidomimetic orphan drug consisting of 10 amino acids, which is selective and specific antagonist of bradykinin B2 receptors received FDA approval in 2011. It is used in the treatment of acute attacks of hereditary angioedema in the adults with C1-esterase inhibitor deficiency [191]. Zafirlukast (Accolate) is an oral leukotriene receptor antagonist for the maintenance treatment of asthma that acts by blocking the activity of 5-lipoxygenase. It blocks the action of cysteinyl leukotrienes on the CysLT1 receptors, thus reducing the constriction of airways, build-up of mucus in the lungs and inflammation of the breathing passages [192].
4. Perspective

As discussed in the previous sections, indole fits in as “privileged scaffold”, the definition given by Evans as “structures that are able to provide high-affinity ligands for more than one type of receptor” [193]. Thus, this scaffold may be utilized as a versatile building block in drug discovery due to wide spectrum of biological activities possible via varying structural modifications that govern the major interactions with the receptor relevant to develop selective and potent drug candidates with specific pharmacological activity. The nucleus may be further used in scaffold re-education/ refining such as scaffold hopping, multi-target directed ligand designing using computational tools, focused libraries and diversity oriented synthesis [194,195].

5. Conclusion

A large number of drug molecules possessing indole nucleus, whether from natural origin or synthesized in laboratory, have been reported for the treatment of various disease conditions. Many of these molecules have been approved by FDA and are being currently utilized in drug therapies. However, due to the extensive research, the full potential of indole based molecules is yet to be disclosed. There is a lucama regarding the exhaustive knowledge in this research reports explaining the individual pharmacological activity of the indole based molecules, providing thorough insight into the SAR of those compounds. The present review covers all pharmacological aspects of the indole based molecules, along with the chemistry involved in those activities. This review provides information regarding how the indole nucleus can be utilized by a medicinal chemist for the design and development of clinically viable molecules.

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