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Review Article

Indole Beyond Tradition- A Next Generation Pharmacological Scaffold

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ABSTRACT

The unique structure of indole makes it very useful in drug development. It is a nitrogen containing heterocycle, having resemble peptide structure and it reversibly bind to many enzymes which are building blocks of numerous physiologically active compounds. This review, highlight the researches from the recent years on indole derivatives showing the activities like antibacterial, antifungal, anti-HIV, anti-inflammatory, anticancer, anti-migraine, antimalarial, anti-dengue, anti-diabetic, antioxidant, anti-Herpes Simplex Virus.

INTRODUCTION

Nitrogen-containing heterocycles, such as Indole was widely used for various diseases. Indole, also referred to as “Benzopyrrole” which is an aromatic compound with a benzenoid nucleus and 10 π-electrons (two from a lone pair on nitrogen and eight from double bonds). Like the benzene ring, indole undergoes electrophilic substitution quickly because of excessive π-electrons delocalisation. Indole is an essential heterocyclic compound which gives strychnine, lysergic acid diethylamide (LSD), and alkaloids derived from plants their structural compounds1.Indole nucleus derivatives having various pharmacological activities like physostigmine (anticholinergic)2, carprofen (nonsteroidal)3, pindolol (anticancer)4, oglufenadine (antineoplastic)5, tropisteron (serotonin receptor antagonist)6, harmine (anti HSV)7.

* Various pharmacological activities of indole nucleus derivatives:

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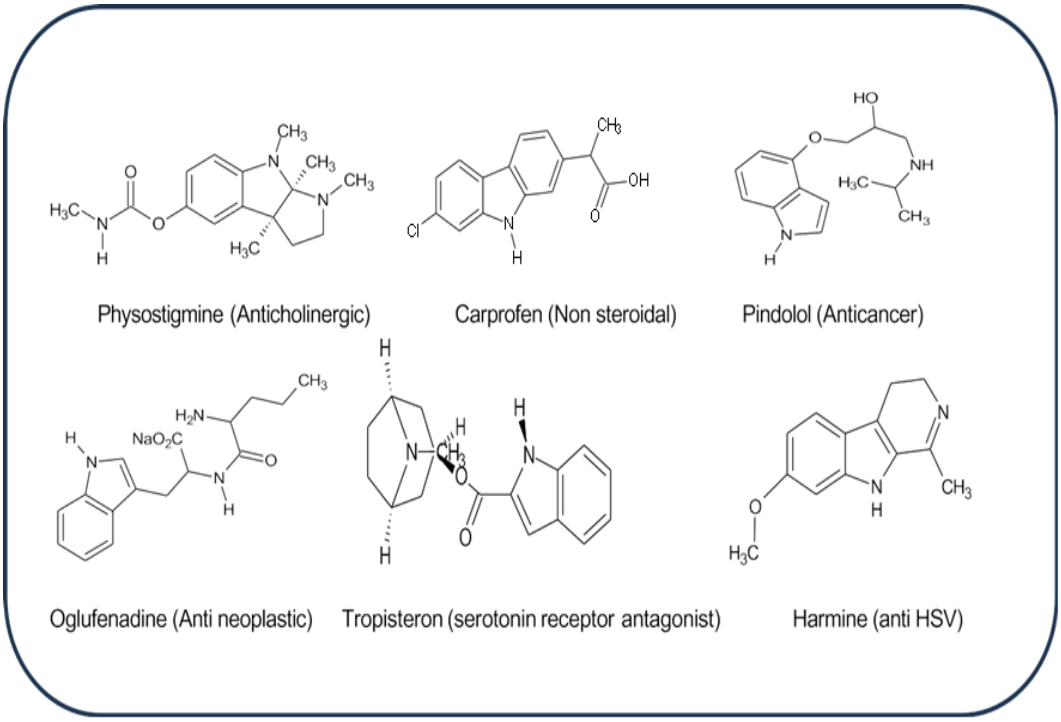

***Pharmacological activities:**

Anti-Bacterial activity:

The antibacterial activity of Klebsiella oxytoca selectively inhibits *Pseudomonas solanacearum* without affecting E. coli. Indole fully inhibits *Pseudomonas solanacearum* at >100 µg/mL, which is largely depend on its nitrogen and aromatic ring. Erchinines A and B strongly inhibit *Bacillus subtilis* in In-vitro with Minimum Inhibitory Concentration (MIC = 0.78 µg/mL) [8].

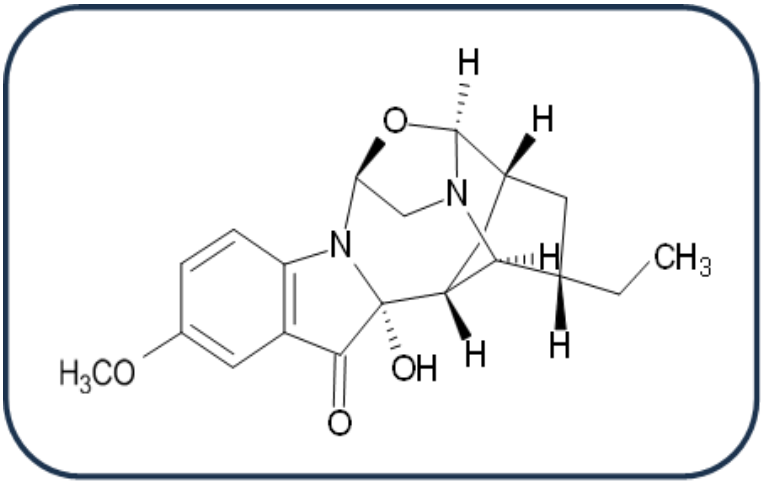

Figure 1: Antibacterial activity of indole derivative

Anti-Fungal activity:

Zhang et al. explained the streptochlorin activity profile and mode of action is associated with disruption of fungal sporulation and inhibition of mycelia growth. Erchinines A and B strongly inhibit Trichophyton in In-vitro with Minimum

Inhibitory Concentration of 12.5 µg/mL and 6.25 µg/mL, respectively[9].

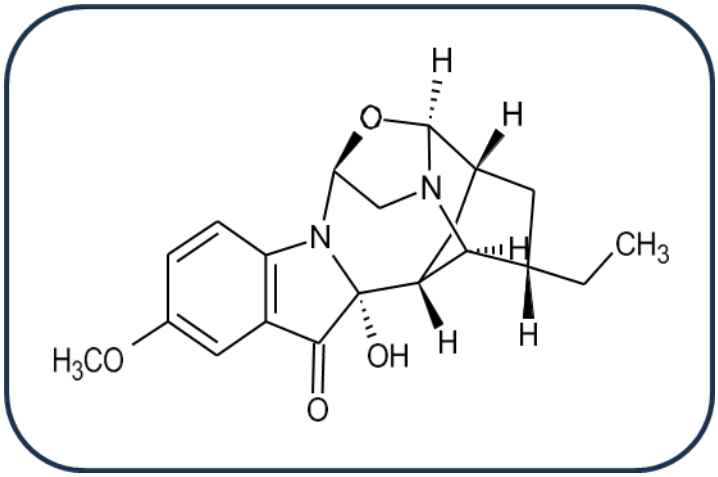

Figure 2: Antifungal activity of indole derivative

Anti-Inflammatory activity:

Classical NSAIDs inhibit COX-1 and COX-2 by blocking prostaglandin synthesis which reduce inflammation and pain. Substitution at the indole 3-position enhances potency. Indomethacin inhibits COX-1 by modifying the indole, it can affect COX-2 activity.

Strictosamide was tested for anti-inflammatory effects in mice with ear swelling caused by Tissue Plasminogen Activator (TPA) when given at doses of 20 and 40mg per kg of body weight[10].

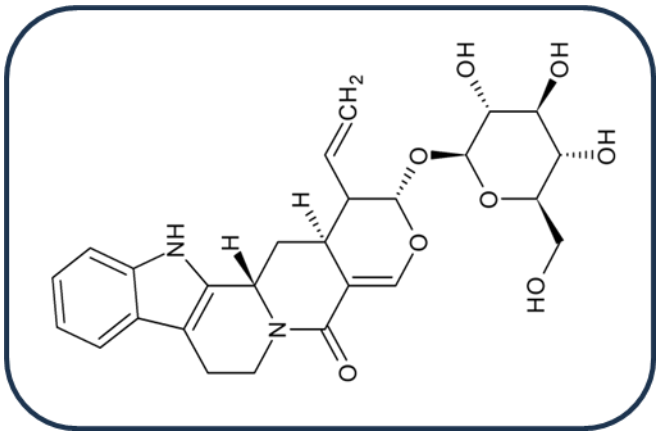

Figure 3: Anti-inflammatory activity of indole derivative

Anti-Cancer activity:

Indole derivatives induce apoptosis via the p53 pathway, mitochondrial cytochrome-c release.

Vallesiachotamine and iso-vallesiachotamine showed strong activity against lung cancer cells (IC_{50} = 4.24 µM and 3.79 µM11.

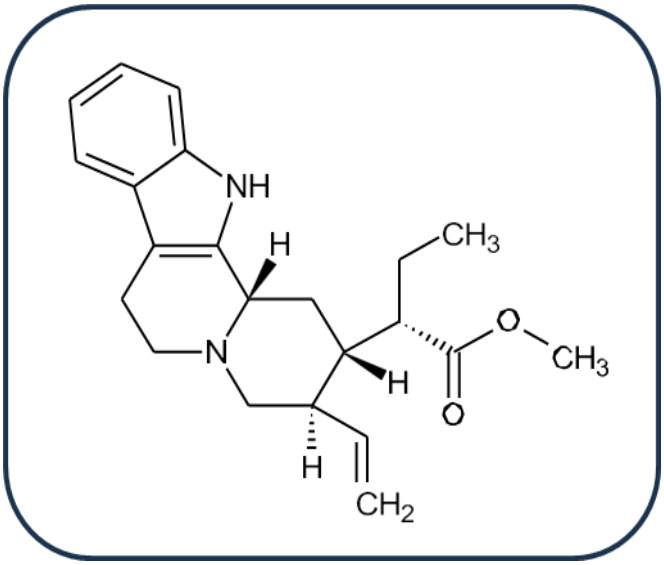

Figure 4: Anticancer activity of indole derivative

Anti-Migraine activity:

Indole derivative like triptansacts on 5-hydroxytryptamine1B receptor (5-HT1B) /5- hydroxy tryptamine 1D receptor (5-HT1D) which cause vasoconstriction of dilated cranial Blood Vessels and prevent release of neuropeptides (substance P, neurokinin A, Calcitonin gene-related peptide). These actions relieve migraines by suppressing pain pathways and inflammation. Dihydroergotamine was administered intravenously into anesthetized pigs. The doses ranging from 3– 100 µg12.

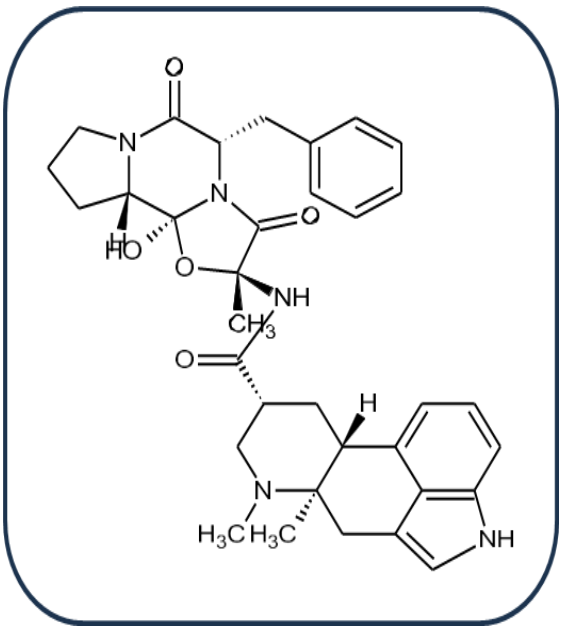

Figure 5: Anti-migraine activity of indole derivative

Anti-Malarial activity:

Melatonin regulates Plasmodium replication by affecting their development stages (ring,

trophozoite, and schizont) via Protein kinase an activation, proteases, increase Ca^{2+}, and increase cAMP levels. Infected mice is treated with melatonin by intraperitoneally at doses of 5–10 mg/kg for 4 days. It showed the protective effects like reducing brain swelling, blood–brain barrier protection, less inflammation, and helped the mice to live longer13.

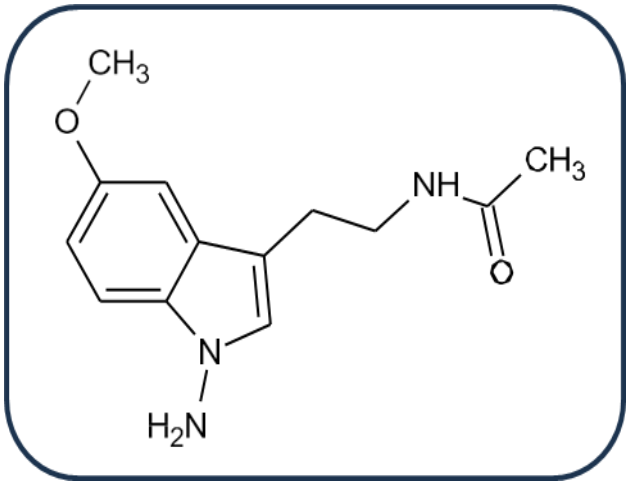

Figure 6: Antimalarial activity of indole derivative

Anti-Dengue activity:

Indole-based nucleoside derivatives act as RNA-dependent RNA polymerase (RdRp) inhibitors. Which prevent the synthesis of viral RNA. Hirsutine is a potent anti-DENV compound in cell culture. They report EC_{50}=1.97µM (antiviral potency) and CC_{50} > 10 µM (low cytotoxicity) [14].

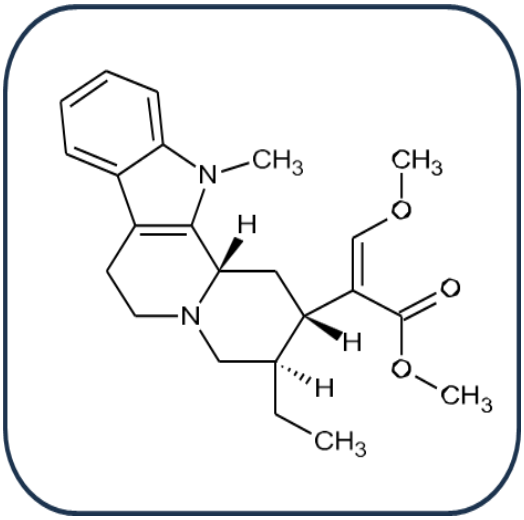

Figure 7: Dengue activity of indole derivative

Anti-Diabetic activity:

Indole–triazole derivatives act via α-glycosidase inhibition. Sprague-Dawely rats and spontaneously diabetic torii rats are used and they were fasted for 16 hours before test. Glucose (2 g/kg BW), L-tryptophan or D-tryptophan (62.5 mg/kg BW) orally was given. Which Results: L-

tryptophan reduced the rise in blood sugar at 30 to 60 min. D-tryptophan also lowers the glucose levels but less effective than L-tryptophan. Finally, L-tryptophan shows stronger anti- hyperglycemic effect during glucose load.

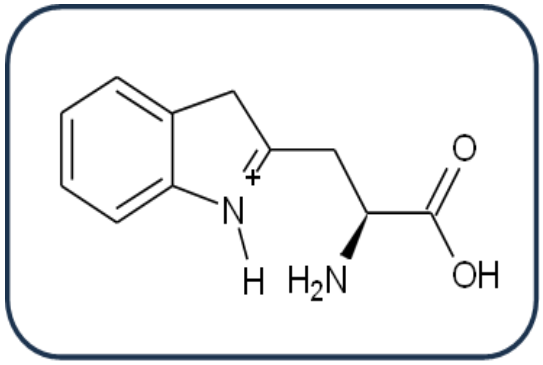

Figure 8: Anti diabetic activity of indole derivative

Anti-HSV activity:

Organic extracts of *Peganum harmala* seeds and their alkaloids show anti-HSV-2 activity in In-Vitro by inhibiting viral replication. Harmaline acts against HSV-1 by interfering with early replication in Vero cells, without blocking entry. Harmine showed potent anti-HSV-2 activity with $EC_{50} \approx 1.47$ µM and a wide safety margin ($CC_{50} \approx$ 337 µM), indicating low host cell toxicity at effective doses[15].

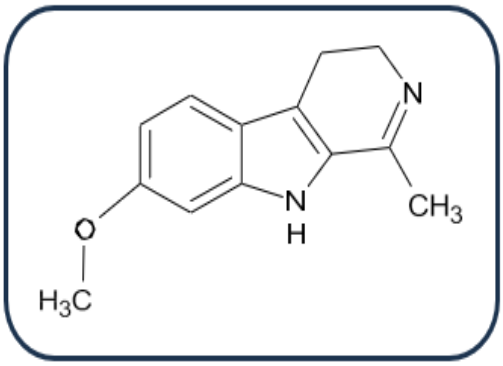

Figure 9: Anti-HSV activity of indole derivative

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