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# Review on Indole Derivatives and its Pharmacological Applications

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**Abstract-** Indoles are extensively studied heterocyclic ring systems that have a wide range of applications in various pathophysiological conditions, including cancer, microbial and viral infections, inflammation, depression, migraine, emesis, and hypertension. The presence of the indole nucleus in the amino acid tryptophan makes it a significant component in phytoconstituents such as perfumes, neurotransmitters, auxins (plant hormones), and indole alkaloids. The unique molecular structure of indoles makes them promising candidates for drug development. This review article aims to provide an overview of the chemistry, biology, and toxicology of indoles, with a specific focus on their application as drugs. Our objective is to consolidate the available information on natural indole alkaloids, FDA-approved drugs based on indole, and clinical trial candidates with diverse therapeutic uses. This compilation of information can serve as a reference point for modifying existing ligands and designing novel potent molecules with reduced side effects.

**Keywords**: Indole, Synthesis, Reactions, Anti inflammatory.

## Introduction:

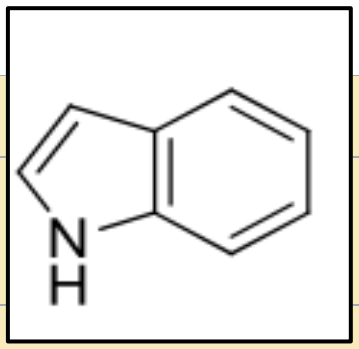
The presence of an indole ring in the nucleus gives rise to a notable scaffold in alkaloids, peptides, and synthetic compounds. The heterocyclic nature of the phytochemicals' nucleus offers extensive possibilities in pharmaceutical applications, including pharmacological activity and synthetic chemistry. Indole and its derivatives serve as a fundamental framework in heterocyclic chemistry, incorporating a nitrogen atom.[1] Indole, with the chemical formula C8 H7 N, consists of a bicyclic structure that combines benzene with a pyrrole moiety. Its derivatives have been found to have diverse applications in medicinal chemistry.[2] The synthesis of indole was achieved through the reduction of oxindole, as proposed by Adolf Von Baeyer in 1866.[3]. In a heteroaromatic planar molecule, indole, there are 10 π electrons that resonate. The π electron system in the indole ring includes the delocalization of a lone pair of a nitrogen atom. This delocalization makes indole a weak base. As a result, the lone pair of electrons on nitrogen does not undergo protonation but instead becomes protonated at the C-3 carbon meta position. This specific position allows for the withholding of aromaticity and provides thermodynamic stability. Due to this property, indole is involved in various chemical synthesis reactions such as cycloaddition, carbon lithiation, oxidation, electrophilic substitution, and organometallic indole anion complexes, among others [4]. The solid form of indole can be found at a temperature of 23-25°C. It is naturally present in human feces, giving it a distinct odor. At lower concentrations, it has a floral scent and is a key component in flower fragrances, coal tar, and perfumes.

Additionally, indole plays a role in various biological reactions in humans. It affects the physiology of bacteria, influencing plasmid stability, spore formation, virulence, biofilm formation, and drug resistance.[5] This characteristic of indole enhances its potential for synthetic manipulation. Indole is a significant constituent in various plant species and is produced by different bacteria. The presence of this nucleus in essential amino acid 'tryptophan' accounts for its natural occurrence. [6]

**Indole:**

Indole, a heterocyclic organic compound with the chemical formula C8H7N, possesses an aromatic nature. Its structure comprises a fused benzene ring with a pyrrole ring, forming a bicyclic structure. Indole is naturally found in various environments and can be synthesized by different bacteria. Acting as a signaling molecule between cells, indole plays a crucial role in regulating multiple aspects of bacterial physiology, such as spore formation, plasmid stability, drug resistance, biofilm formation, and virulence. Tryptophan, an amino acid, serves as an indole derivative and acts as a precursor for the neurotransmitter serotonin.[ 20]

**Structure:**



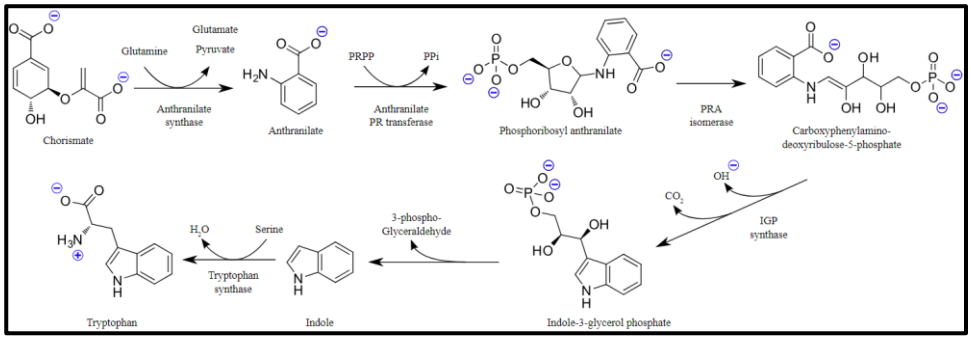

| **Names** | |
|---|---|
| **IUPAC name**<br>**1H-Indole** | |
| **Other name**<br>**2,3-Benzopyrrole, ketole, 1-benzazole** | |
| **Properties** | |
| Chemical formula | $C_8H_7N$ |
| Molar mass | 117.151 g·mol$^{-1}$ |
| Appearance | White solid |
| Odor | Feces or jasmine like |
| Density | 1.1747 g/cm$^3$, solid |
| Melting point | 52 to 54 °C (126 to 129 °F; 325 to 327 K) |

| | |
|---|---|
| Boiling point | 253 to 254 °C (487 to 489 °F; 526 to 527 K) |
| Solubility in water | 0.19 g/100 ml (20 °C)<br>Soluble in hot water |
| Acidity ($pK_a$) | 16.2<br>(21.0 in DMSO) |
| Basicity ($pK_b$) | 17.6 |
| Magnetic susceptibility ($\chi$) | $-85.0 \cdot 10^{-6}$ $cm^3/mol$ |
| **Structure** | |
| Crystal structure | $Pna2_1$ |
| Molecular shape | Planar |
| Dipole moment | 2.11 D in benzene |

**SAR OF INDOLE :**

1. The replacement of the carboxyl group with any other acidic functionalities lead decreases the activity.
2. Acylation of the indole nitrogen with aliphatic carboxylic acid or aryl alkyl carboxylic acids result in the decrease of activity.
3. Amide analogues are inactive.
4. The N-benzoyl derivatives substituted in the p-position with F. CI, CFs groups are the most active.
5. The 5-position of the indole when F, OCH groups was more active than the unsubstituted indole analogue
6. The presence of indole ring nitrogen is not essential for activity because the corresponding 1-benzylidenylindene analogue (Sulindac) was active.

**Synthesis of indole:**



**Indole is produced via anthranilate and reacts further to give the amino acid tryptophan.[21]**

**Pharmacological applications of indole derivative's:**

**Anti-Inflammatory and Analgesic Activity:**

Inflammation is the intricate response of the body to harmful stimuli such as bacteria, damaged cells, and irritants. The presence of inflammation complicates the process of tissue healing. However, when inflammation persists, it can have detrimental effects on the body. To address this, anti-inflammatory drugs are used to reduce swelling and discomfort by treating inflammation. A powerful cyclooxygenase inhibitor called indole has been discovered [7]. In the year 2020, Deepmala and colleagues synthesized 1, 5 – disubstituted derivatives of indole. All the newly synthesized compounds were thoroughly characterized using spectroscopic and analytical methods. The anti-inflammatory activity of these compounds was screened, with the pharmacological screening ranging from 12.12% to 65.51%. Among the synthesized derivatives, compound 1 was found to be more potent than the standard drug indomethacin. Additionally, compounds 4 and 5 exhibited greater activity compared to compounds 1, 2, and indomethacin [8].

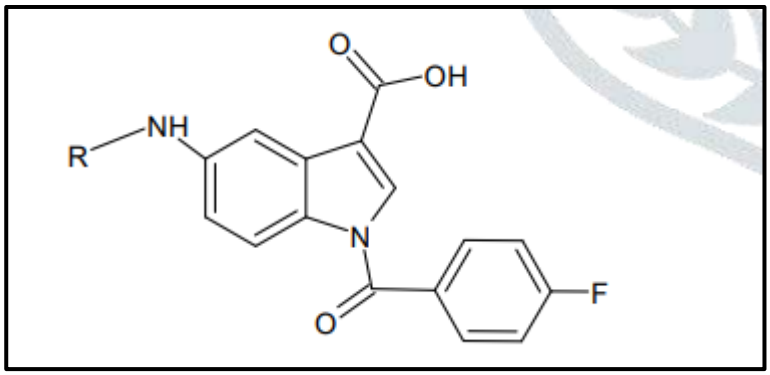



Fig.1 Chemical structure of indole derivatives having anti-inflammatory activity

1= R=CH3CO,

2=R=C6H5CO

3=R=C2H5C6H4CO

4=R=NO2C6H4CO

5=R=BrC6H4CO.

In 2017, Khaled R. A. Abdellatif and his colleague successfully synthesized a new group of (4-substitutedphenyl) (3-((2-(4-substitutedphenyl) hydrazono) methyl)-1H-indol-1-yl) methanone derivatives 13a-f as analogues of the medication indomethacin. This was achieved through the N-benzoylation of indole-3-cabaldehyde with a suitable benzoyl fragment, followed by a reaction with substituted phenyl hydrazine.

Unlike the original indomethacin, all of the synthesized compounds were subjected to in vitro testing for their inhibitory action on COX-1/COX-2 enzymes, as well as in vivo testing for their anti-inflammatory efficacy. Among these compounds, 6a, b, and e, which contained SO2Me or SO2NH2 as a COX-2 pharmacophore, exhibited the highest levels of anti-inflammatory activity and selectivity. Consequently, these compounds were further evaluated

by calculating their ED50 percent dosages and ulcerogenic indices to ensure their safety margin for the stomach, in comparison to indomethacin [9].

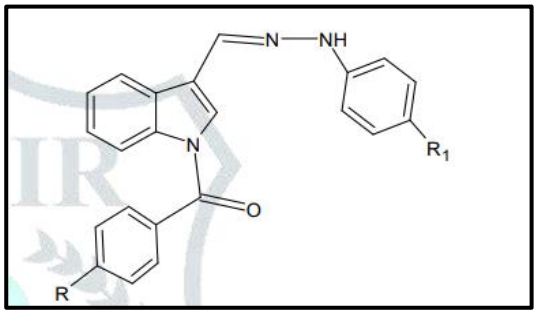



Fig. 2. Chemical structure of indole derivatives having anti-inflammatory activity

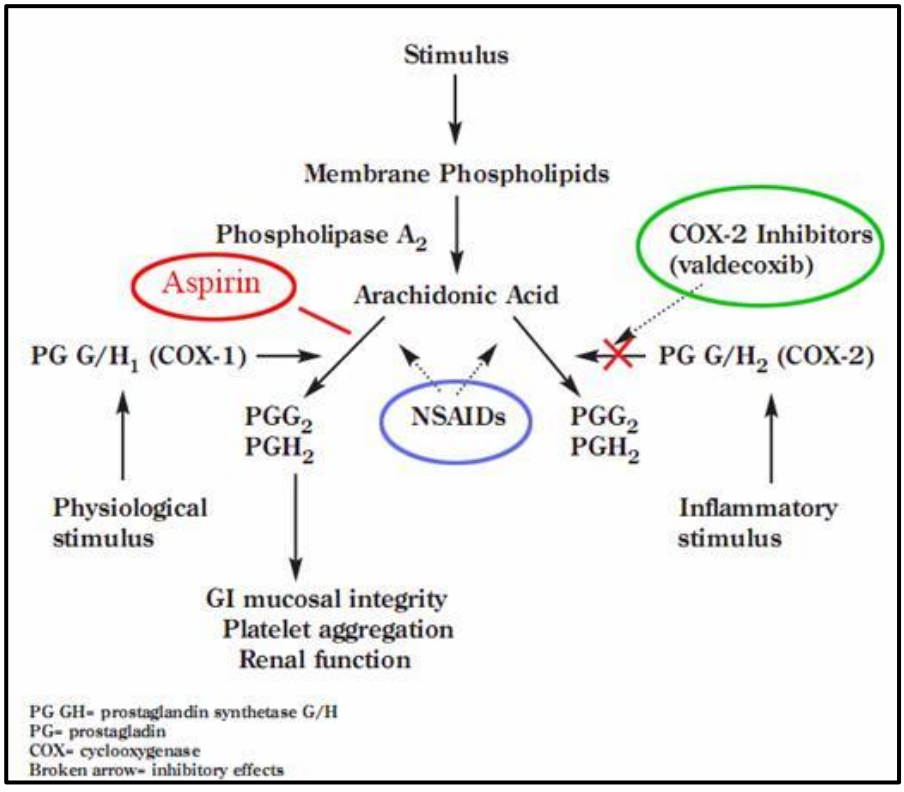
6a, R=H, R1=SO2CH3

6b, R=H, R1=SO2NH2

6d, R=Cl, R1=SO2CH3

6e, R=Cl, R1=SO2NH2

In 2014, Mayura A. Kale and her colleague conducted a study involving the treatment of 3-acetyl indole (1) with various aromatic aldehydes (2). This treatment resulted in the production of 3-chalconylindoles 7a-e, which offered a convenient method for synthesizing novel anti-inflammatory and analgesic medications. By subjecting these 3-chalconylindoles 7a-e to hydrazine hydrate, pyrazoline derivatives 8a-e were obtained. Further reactions of the pyrazoline indoles 8a-e with the diazotized salt of aniline led to the formation of azo derivatives of pyrazoline indoles 9a-e. These newly synthesized compounds were then subjected to testing for their anti-inflammatory and analgesic properties, which yielded promising results [10].



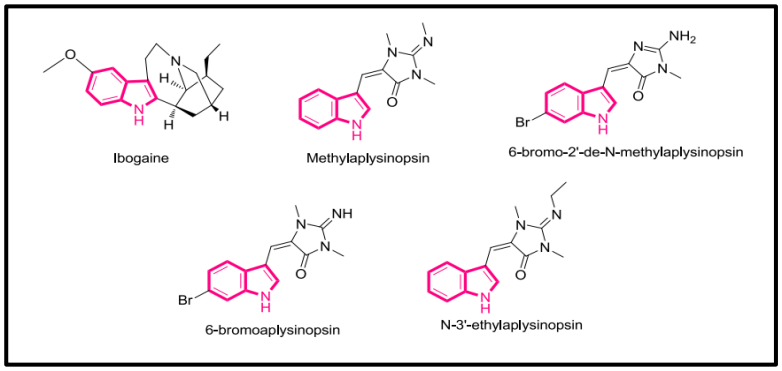
**Antimicrobial activity**:

Since the introduction of the first antimicrobial agents in the 1940s, antimicrobial resistance has become a significant issue in clinical practice. In order to address this problem, it is crucial to preserve the effectiveness of current antimicrobials through their appropriate use, while also focusing on the discovery and development of new agents. The treatment of microbial diseases is becoming increasingly challenging and costly due to the rise in antimicrobial resistance, leading to higher mortality rates. According to the latest survey conducted by the World Health Organization (WHO), approximately 500,000 individuals across 22 countries are suffering from antibiotic resistance in the case of bacterial infections. To tackle this issue, it is essential to develop new indole derivatives that target microorganisms through different mechanisms. Various indole derivatives have been identified and evaluated as potential antimicrobial agents, as discussed by Sanna and colleagues in their synthesis study.

Indole-thiourea hybrids were synthesized and tested against a diverse range of microbes, including both Gram-positive and Gram-negative types. Compound 56 exhibited high potency (MIC < 12.5 µg/mL) compared to the standard drug ciprofloxacin (MIC < 1.0 µg/mL). Thiazolidine, known for its antimicrobial activity, was combined with other compounds to design potent antimicrobial agents. Inspired by this, Abo-Ashour and colleagues designed and synthesized oxindole-thiazolidine conjugates. The synthesized derivatives were evaluated against various microbes, and the SAR study revealed that chloro and methyl substitution favored the activity. Compound 57 showed the highest activity (MIC < 0.98 µg/mL) as both an antimicrobial and antifungal agent, comparable to ciprofloxacin. Pyrazole and imidazole were found to have broad-spectrum antimicrobial activity, possibly due to the presence of a nitrogen atom in their five-membered rings, which inhibit cell wall synthesis or cause DNA damage. To overcome microbial resistance, scientists attached pyrazole and imidazole rings to the indole nucleus. In 2017, Quazi and colleagues synthesized and evaluated various indole-pyrazole derivatives. Compound 62a showed good activity against gram-positive bacteria, while compound 62b exhibited good activity against fungal strains. Additionally, a series of imidazole-based indole derivatives were synthesized and tested against bacterial and fungal strains. [11]

**Anti-depressant activity**:

Antidepressants are a class of medications used to treat major depressive disorder, which is characterized by a pervasive and persistent low mood. The prevalence of depression is increasing at an alarming rate, particularly among young individuals. The literature has reported various antidepressant drugs containing indole, which will be discussed below. Tabernanthe iboga, a perennial rainforest shrub found in Central Africa, acts as a central nervous system stimulant and has a notable ability to reduce drug addiction and dependence. The iboga alkaloids, represented by ibogaine, consist of an indole ring. In the past, several indole-based compounds of marine origin have been utilized to manage anxiety and depression. Methylaplysinopsin, isolated from Aplysinopsis reticulata, inhibits monoamine oxidase (MAO) and displaces serotonin from its receptors. Additionally, 6-bromoaplysinopsin and N-3'-ethylaplysinopsin, isolated from Smenospongia aurea, have been reported to exhibit a high affinity for 5HT2A and 5HT2C receptors. Furthermore, 5,6-dibromo-N, N-dimethyltryptamine demonstrated antidepressant effects in forced swim and tail suspension tests conducted on mice.[12]




In the 1990s, several synthetic antidepressants were developed as reversible inhibitors of monoamine oxidase A (MAO-A). MAO-A is an enzyme responsible for breaking down serotonin, dopamine, and norepinephrine through oxidative deamination. By inhibiting this enzyme, these drugs prevent the breakdown of monoamine neurotransmitters and enhance their availability. Russia synthesized three drugs, namely metralindole (Inkazan), pirlindole (Pyrazidol), and terindole, as inhibitors of monoamine oxidase A. [13].

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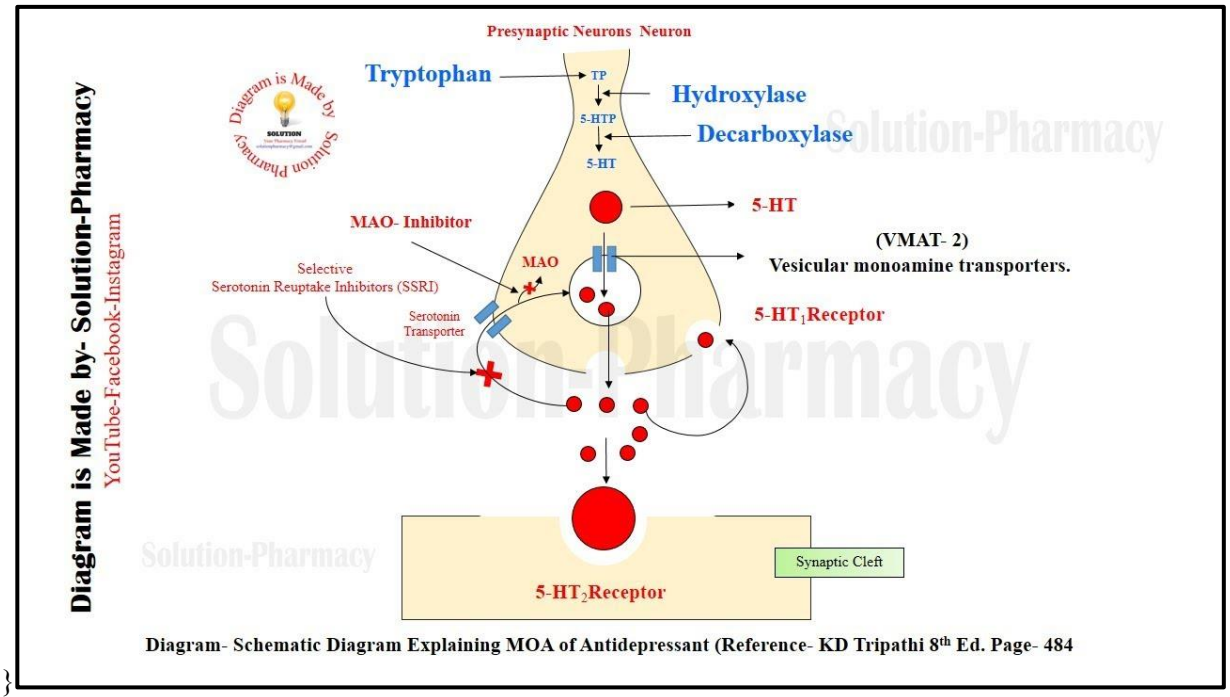


Diagram- Schematic Diagram Explaining MOA of Antidepressant (Reference- KD Tripathi 8th Ed. Page- 484

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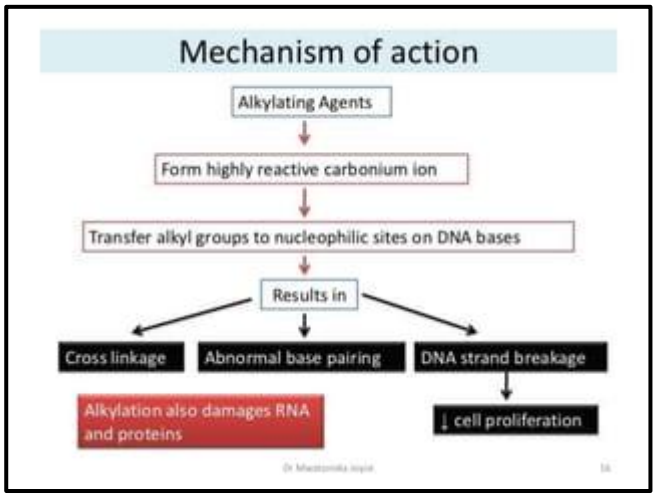
**Anti-tumor activity:**

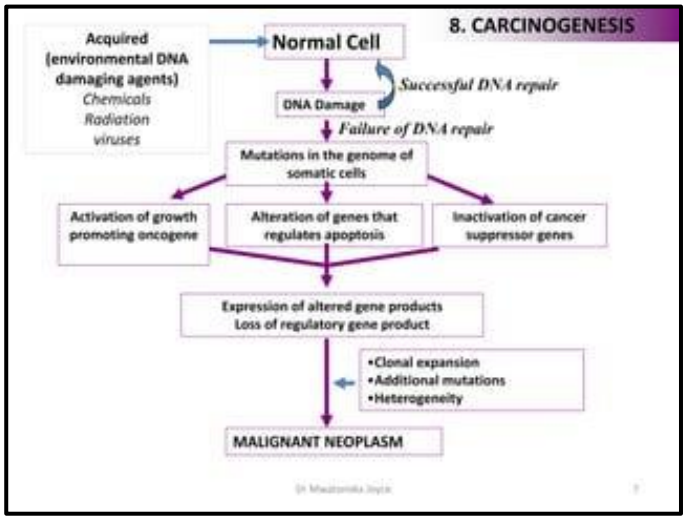
Cancer, a widespread disease that impacts billions of individuals worldwide, is a leading cause of death. Numerous anti-cancer substances have been identified, each functioning through distinct mechanisms. The FDA has approved several molecules containing an indole nucleus, while many others are currently being assessed in clinical trials.[13]




**Anti-cancer activity:**

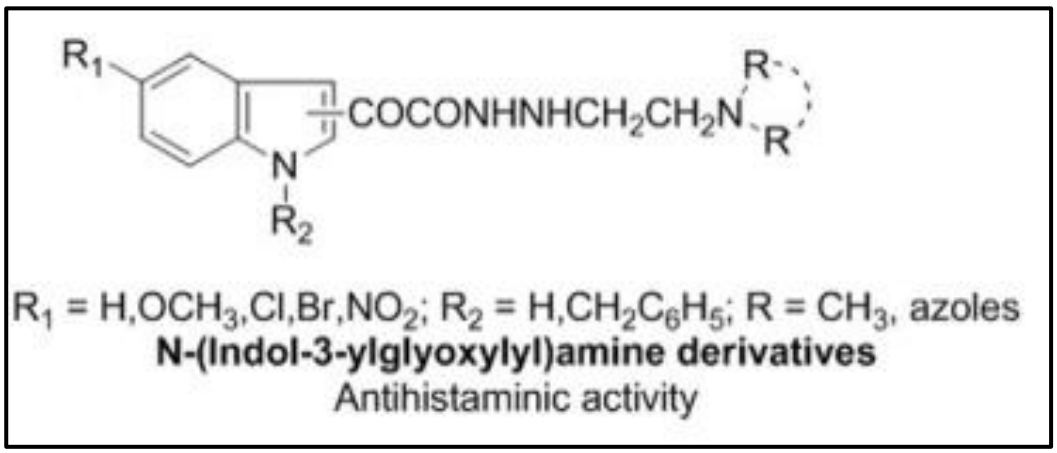
In 1999, Medarde et al. synthesized 2,3-diarylindoles based on the structure of combretastatins and assessed their cytotoxic activity against different cancer cell lines. In 2007, Xu et al. synthesized indolopyrrolemaleimides and evaluated their cytotoxicity against various human cancer cell lines. Among all the derivatives, compounds containing bromo substituent exhibited the most promising activity. In the same year, Kaufmann et al. reported 2-phenylindole-3-carbaldehydes as antitumor agents by suppressing tubulin polymerization, which inhibits the growth of breast cancer cells. Additionally, various other substituted 2-arylindoles have been reported as inhibitors of tubulin polymerization by Gastpeer et al. in 1998 and Medarde et al. in 1999. In 2008, Ulrich et al. In 2008, the design of 3,5-bis(2-indolyl) pyridine and 3-[(2-indolyl)-5-phenyl] pyridine derivatives as CDK inhibitors and anticancer agents were introduced. Wu et al. (2009) conducted a study on the anticancer activity of 3-aroylindoles, which led to the development of improved therapeutics. Hong et al. synthesized a series of tricyclic and tetracyclic indoles and evaluated their anticancer activity. Among these compounds, those containing methoxy and hydroxyl groups exhibited the highest in vitro activity against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC cell lines) (Sharma et al., 2010). Vidhya Lakshmi et al. (2010) successfully synthesized 3-pyranylindole derivatives from 3-cyanoacetyl indole and assessed their antioxidant and anticancer activities. Some of these compounds demonstrated superior anticancer activity against breast cancer cell lines compared to the standard drug. Dalip Kumar et al. (2010) reported the synthesis of 4-(3′-indolyl) oxazoles from 3-acetyl-N-benzenesulfonylindole under microwave conditions, which exhibited promising cytotoxicity against various human cancer cell lines. In 2012, Dalip Kumar et al. investigated the anticancer activity and cytotoxicity of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles against breast cancer cell lines. Meric Koksal et al. (2012) developed a series of indole-based 1,4-disubstituted piperazines that displayed cytotoxicity against human liver and colon cancer cell lines.

MacDonough et al. (2013) made the discovery of 2-aryl-3-aroylindoles and evaluated their cytotoxicity and their ability to inhibit tubulin polymerization. [17].




**Anti-histamine activity:**

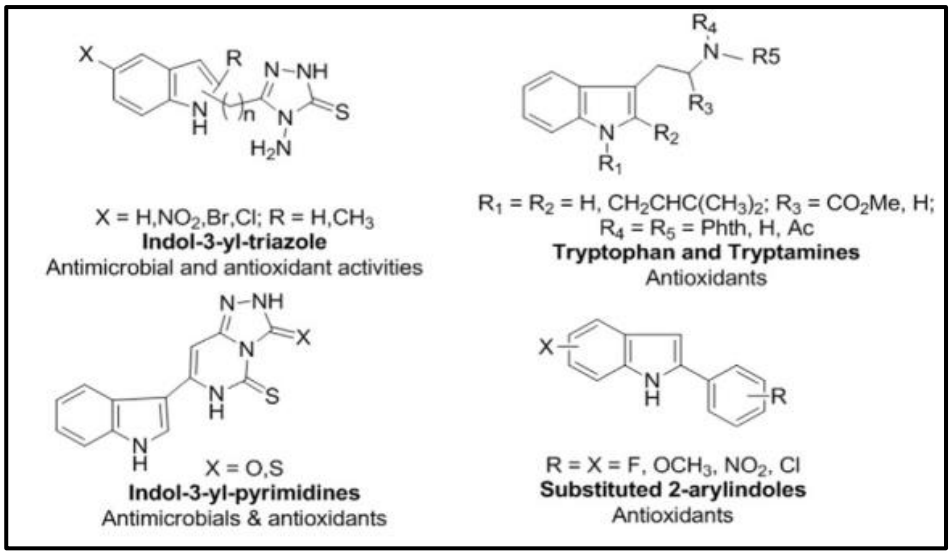
Several indole amide derivatives with a substituted side chain were synthesized and evaluated for their antihistaminic activity. These compounds, unlike traditional antihistamines that contain a benzimidazole nucleus, feature an indole ring. The most potent compounds were further examined in vivo to determine their effectiveness in inhibiting histamine-induced cutaneous vascular permeability in rats [18].



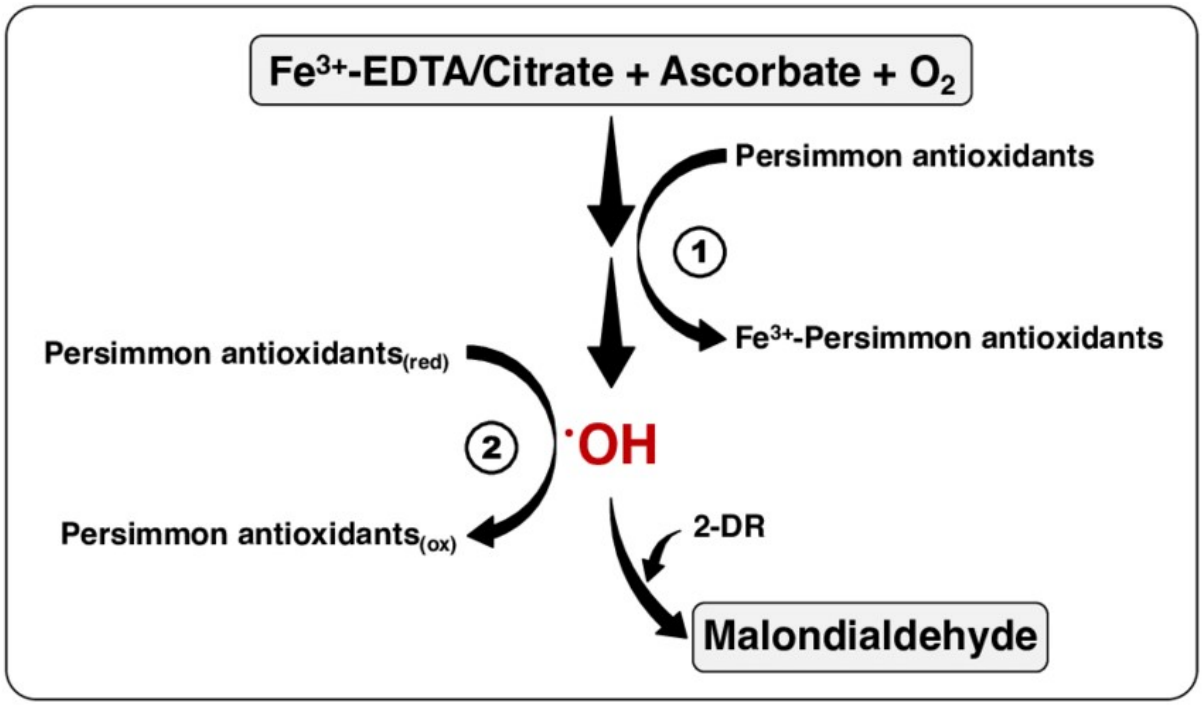

**Anti-oxidant activity:**

Andreadou et al. (2002) published a study in 2002 where they discovered new indole derivatives with a triazole nucleus that showed potential as antioxidants. They also investigated the anti-ischemic properties of these derivatives. Enien et al. conducted a separate study and found that indole-2 and 3-carboxamides exhibited antioxidant properties through chemiluminescence and electron spin resonance spin trapping (Sharma et al., 2010). They further observed that derivatives with unsubstituted phenyl rings had the strongest scavenging effect on OH radicals, effectively quenching N30%. In 2010, Monica Estevao et al. synthesized a novel series of indole-based tryptophan and tryptamine derivatives and discussed their antioxidant activity, which depended on the substituents on the relative positions of the indole nucleus. Mosaad

Sayed Mohamed et al. (2014) synthesized a series of indol-3-ylpyrimidine derivatives in 2013 and tested them for antimicrobial and antioxidant activities. These compounds exhibited significant antimicrobial activity and higher antioxidant activity than ascorbic acid. In the same year, Karaaslan et al. (2013) synthesized a series of substituted 2-arylindoles and evaluated their antioxidant property using the DPPH radical scavenging assay method. The fluoro analogues demonstrated potent activity comparable to the standard.

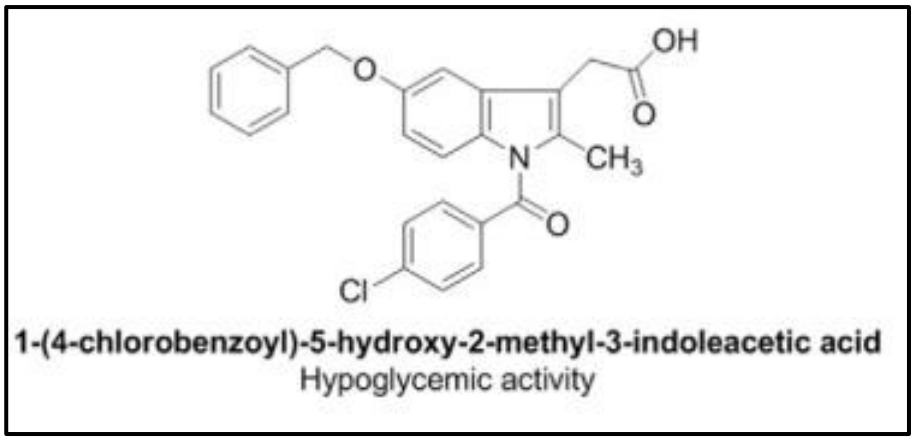


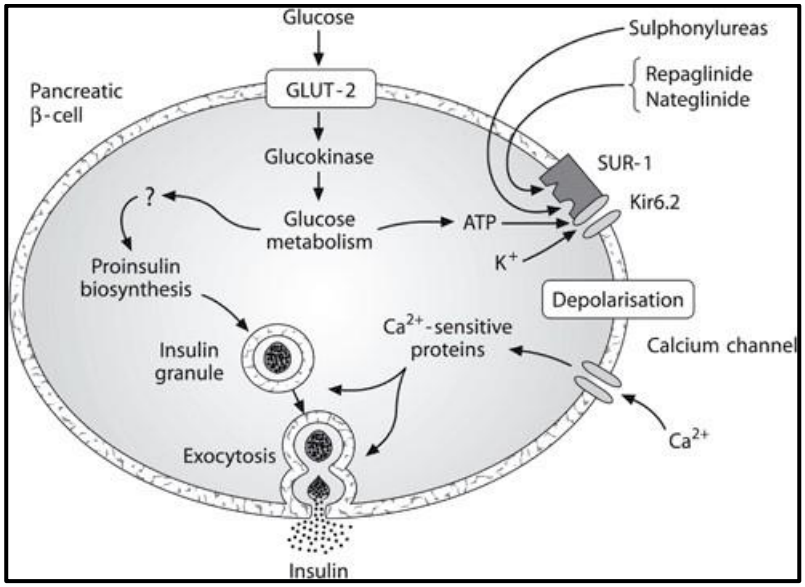

**drug, melatonin (Fig. 9).[17]**



**Anti-diabetic activity:**

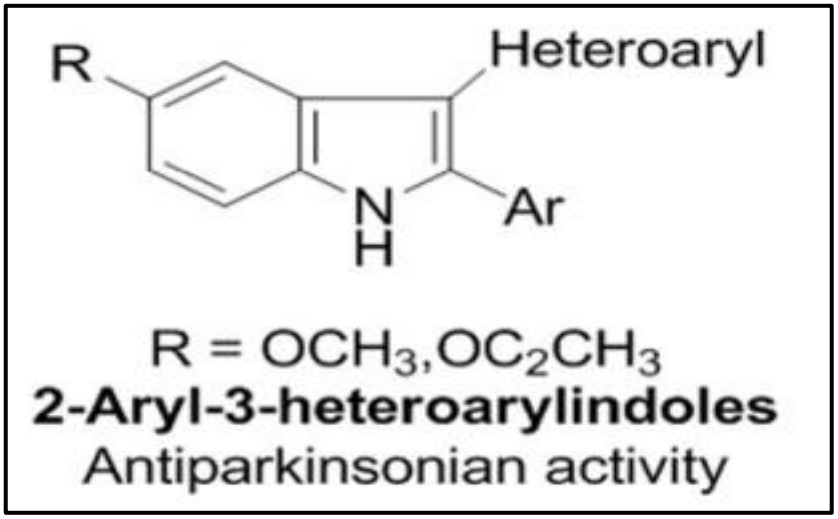
Li et al. (2007) conducted an evaluation of certain indole derivatives to determine their effectiveness in improving insulin sensitivity and reducing glucose levels. Among these derivatives, the one containing a chloro benzoyl group exhibited enhanced activity as a PPARc agent. This increased activity resulted in decreased serum glucose levels, thereby contributing to its potential as an antidiabetic treatment. The derivatives of these indole compounds hold promise as alternative therapies for managing type 2 diabetes and other metabolic disorders (Fig. 11) [17].



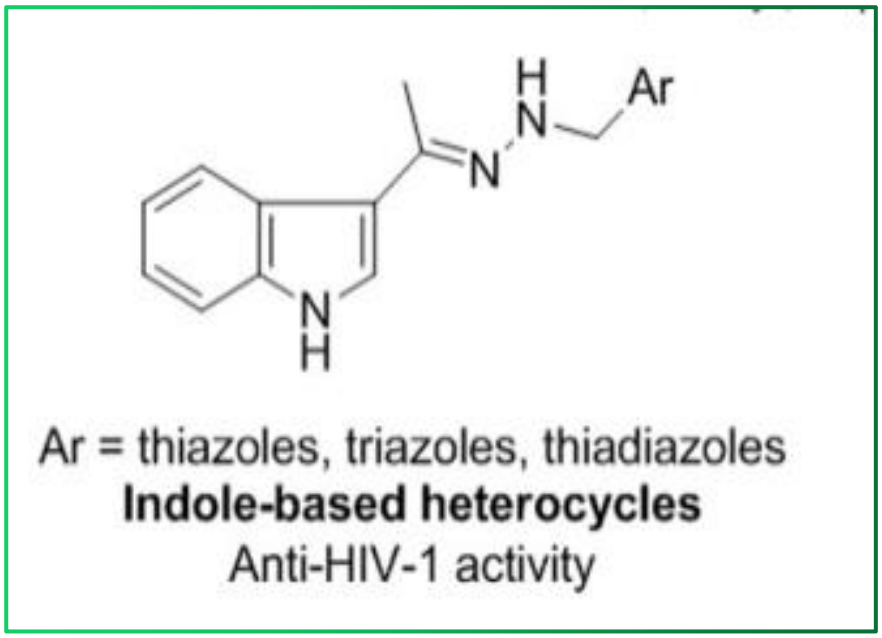

**Anti-parkinsonian activity:**

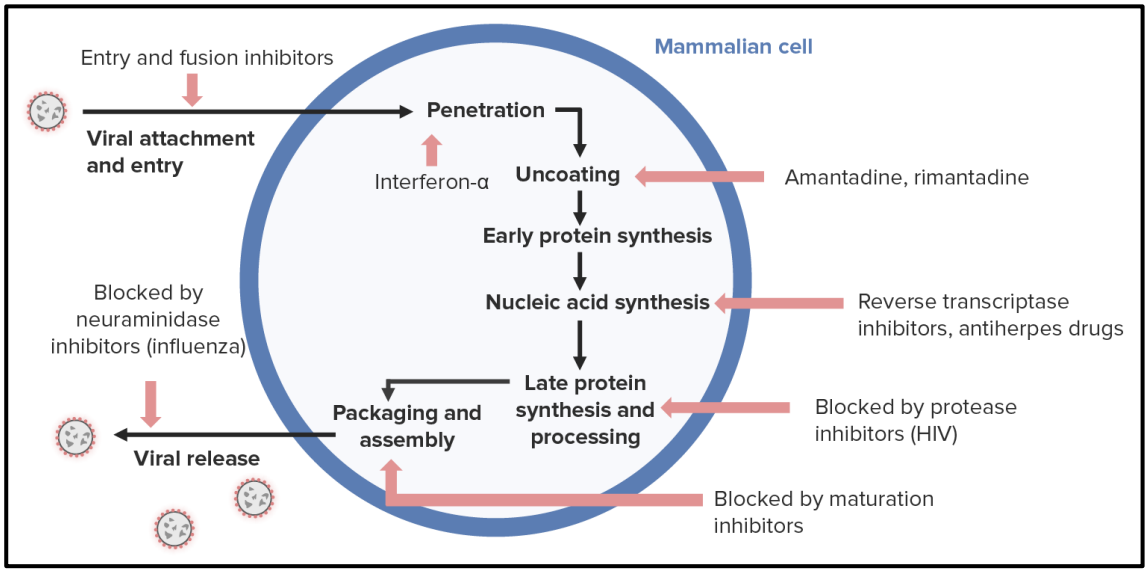
The antiparkinsonian activity of 2-aryl-3-heteroarylindoles, derived from 2-arylindole-3-carbaldehyde, has been investigated. The evaluation revealed that 3-adamantayl-2-(2-(2,5-dihydroxyphenyl)-5-methoxy-1H-indol-3- yl) thiazolidin-4-one (Fig. 12) [1] exhibits strong inhibition against parkinsonian agents.[18]




**Anti-viral activity:**

In their study, Abdel-Gawad et al. (2010) utilized 3-acetylindole as a primary compound to introduce 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine and 1,3-thiazole derivatives into the indole nucleus. These derivatives were identified as effective anti-herpes simplex virus-1 and cytotoxic agents, as depicted in Figure 13 [17].






**Medicinal Importance of indole:**

**List of drugs containing indole:**

| *Drug* | *Application* | *Drug* | *Application* | *Drug* | *Application* |
|---|---|---|---|---|---|
| **Vincristine** | Anticancer | **Vincamine** | Vasodilator | **Roxindole** | Schizophrenia |
| **Vinblastine** | Anticancer | **Reserpine** | Antihypertensive | **Delavirdine** | Anti-HIV |
| **Vinorelbine** | Anticancer | **Peridopril** | Antihypertensive | **Atevirdine** | Anti-HIV |
| **Vindesine** | Anticancer | **Pindolol** | Antihypertensive | **Arbidol** | Antiviral |
| **Mitraphylline** | Anticancer | **Binedaline** | Antidepressant | **Zafirlukast** | Anti-Asthmatic |
| **Cediranib** | Anticancer | **Amedalin** | Antidepressant | **Bucindolol** | β-Blockers |
| **Panobinostat** | Anti-leukamic | **Oxypertine** | Antipsychotic | **Pericine** | Opioid agonist |
| **Apaziquone** | Anticancer | **Siramesine** | Antidepressant | **Mitragynine** | Opioid agonist |
| **Tropisetron** | Antiemetic | **Indalpine** | Antidepressant | **Pravadoline** | Analgesic |
| **Doleasetron** | Antiemetic | **Yohimbine** | Sexual Disorder | **Bufotenidine** | Toxin |
| **Oglufanide** | Immunomodulatory | **Indomethacin** | Anti-inflammatory | **Proamanullin** | Toxin |

**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, despite the extensive research, the full potential of indole based molecules is yet to be disclosed. There is a lacuna regarding the exhaustive knowledge of various research reports explaining the individual pharmacological activity of the indole based molecules, providing a 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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