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Unveiling the Latest Biological Insights of Indole and its Derivatives: A Compact Review

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ABSTRACT:

Indole, a versatile pharmacophore and privileged scaffold exhibits diverse pharmacological activities such as antidiabetic, anticancer, anti-convulsant, antidepressant, antimicrobial, anti-HIV, anti-inflammatory, antimalarial and antifungal effects. Its ability to mimic protein structures makes it invaluable in drug discovery. Recent research (2018–2023) has focused on synthesizing indole derivatives and exploring their therapeutic potential. This review provides a concise overview of these advancements, aiding researchers in developing novel, less toxic indole derivatives with promising pharmacological activities.

1. Introduction

Indole (figure 1), stands out as a remarkable heterocyclic compound renowned for its diverse pharmacological effects stemming from its versatile modes of action. Its adaptability as a pharmacophore and its prevalence as a preferred scaffold contribute significantly to its significance in drug development. Notably, its resemblance to numerous protein structures enhances its utility as a valuable moiety in pharmaceutical research and development.Indole also known as benzo[*b*]pyrrole is an organic compound represented by the chemical formula C_8H_7N. Indole is a compound made up of a fused ring system, with a six-membered benzene ring connected to a five-membered nitrogen-containing pyrrole ring[1]. Indole holds considerable significance in medicinal chemistry, serving as a fundamental building block for numerous pharmaceutical compounds and drug development endeavors.From a chemicalperspective, indole exhibits extremely weak basicity[2].The chemistry of indole originates from the mid19th century driven by intensive investigations into the natural dye indigo. In 1866, the synthesis of indole was achieved through the zinc distillation of oxindole[3].

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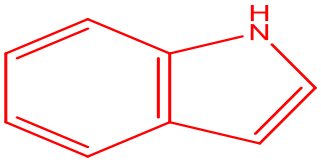

Figure 1. Structure of indole.

Indole derivatives are highly significant in the realm of biology due to their wide-ranging biological propertiesincluding but not limited to antifungal, antimicrobial, anti-HIV, anticonvulsant, anti-inflammatory and anticancer properties. Indoles arguably represent one of the most pivotal classes of heterocyclic compounds in drug discovery. Consequently, the allure of indole derivatives captivates the attention of organic chemists[4]. Tryptophan is one of the essential indole alkaloids that is essential to animal and human nutrition [5]. While reserpine is used as a blood pressure lowering agent and a tranquillizer, serotonin is an essential neurotransmitter in animals [6]. Chemotherapy for cancer frequently uses mitomycin and its byproducts [7]. Moreover, the field of indole chemistry benefits from indole-3-acetic acid, which functions as a heteroauxin or plant growth hormone. The production of indoles synthetically and isolated from natural sources has increased significantly[1].The pharmacological potential of natural indole derivatives has spurred extensive research into the synthesis of synthetic compounds incorporating indole. Medicinal chemists are leveraging various heterocyclic nuclei combined with indole to target a range of diseases. Several commercially available indole derivatives have been developed including Pindolol, introduced by Novartis in 1982 for the treatment of hypertension and Indapamide, developed by Servier for heart failure and hypertension[8,9]. Other significant examples include perindopril, trandolapril, carvedilol and delavirdine, all approved by the US FDA for the treatment of HIV-1[10]. Additionally, Indomethacin exhibits promise as an anti-inflammatory and analgesic medication[11], while Yohimbine has shown efficacy against sexual dysfunction and may reduce the risk of type 2 diabetes[12].These are just a few examples, as numerous other indole derivatives are also on the market. Analysis from FDA databases underscores the importance of nitrogen-containing heterocycles in drug designwith indole and its derivatives ranking ninth among the top 25 molecules involved in synthesizing fundamental FDA-approved drugs in 2015[13]. In recent years, this class of heterocyclic compounds has gained significant importance due to their diverse pharmacological activities.Attracting considerable attention for their wide range of biological and clinical applications, this review focuses on summarizing some recent advances (2018–2023) in the effective chemical synthesis of indole derivatives. Additionally, it aims to highlight the significant pharmacological activities associated with these derivatives.

2. Pharmacological Properties of Indole Derivatives

Given the versatile characteristics inherent to indole, this compound has garnered significant favor among both organic and medicinal chemists alike. Numerous pharmaceutical compounds featuring the indole nucleus have been identified for their efficacy in treating a spectrum of diseasesincluding but not limited to cancer, malaria, tuberculosis and HIV infection.

2.1 Anti-Alzheimer

Alzheimer's disease, also referred to as dementia is a neurological condition impacting numerous individuals characterized by a range of symptoms including behavioral disturbances, cognitive decline, various neuropsychiatric issues and challenges in daily activities due to its complex neurodegenerative nature[14]. Elevated blood pressure and high cholesterol levels, common risk factors for cardiovascular health, are closely associated with Alzheimer's disease[15]. Typically manifesting in individuals aged 56 and above, Alzheimer's is commonly perceived as an age-related ailment leading to dementia in older populations. In developing countries, Alzheimer's ranks as the second leading cause of mortality, following incidents involving the brain, cancer and cardiovascular diseases. Presently affecting 35 million individuals globally, projections indicate a surge to 107 million cases by 2050[16]. One of the neurotransmitters affected in Alzheimer's disease is acetylcholine, which plays a crucial role in memory and learning processes. Anticholinesterase medications work by blocking the activity of acetylcholinesterase, the enzyme responsible for breaking down acetylcholine in the synaptic cleft. By inhibiting this enzyme, these drugs elevate acetylcholine levels, thereby augmenting cholinergic neurotransmission in the brain. The rationale for utilizing anticholinesterase

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drugs in Alzheimer's disease is to mitigate cognitive symptoms by boosting cholinergic activity in the brain.While these drugs do not halt the progression of the disease, they can temporarily improve cognitive function and quality of life in some individuals with Alzheimer's disease[17].In 2018, Prochnow et al. synthesized 2-substituted-N-alkynylindoles and investigated their potential as anticholinesterase agents. Among these compounds, 1 and 2 were identified as promising inhibitors of cholinesterase activity[18].In the same year, Denya and colleagues explored a range of urea and carbamate derivatives of indole to assess their potential for inhibiting human monoamine oxidase-A (hMAO-A), human monoamine oxidase-B (hMAO-B), acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE).Molecular modeling studies revealed significant interactions with the active sites of these enzymes. Among the compounds studied,3 exhibited the highest potency[19].In 2019, Bingül et al. synthesized novel derivatives of 4,6-dimethoxyindole-7-thiosemicarbazone and examined these derivatives for their anticholinesterase properties. Compound 4showedinhibition of both acetylcholinesterase and butyrylcholinesterase enzymes[20].In 2020, Bingul et al. prepared a new series of hydrazide hydrazones derived from 4,6-dimethoxyindole and examined their effectiveness in inhibiting cholinesterase enzymes (AChE and BuChE). Among these compounds, 5 demonstrated the highest level of activity[21].In their 2020 study, Purgatorio and colleagues synthesized 36 novel compounds, primarily consisting of 3-(2-phenylhydrazono) isatins and related 1H-indole-3-carbaldehyde derivatives aiming to investigate their potential as inhibitors of beta amyloid (Aβ) aggregation, a crucial aspect in Alzheimer's disease development. Compound 6 demonstrated potent inhibition against both MAO A and MAO B with IC_{50} values of 0.34 μM and 0.23 μM respectively and also displayed significant suppression of Aβ aggregation with an IC_{50} value of 8.4 μM[22]. Lamie and colleagues (2022) synthesized a range of indole-based compounds and assessed their capabilities as anti-Alzheimer's and anti-neuroinflammatory agents. The study revealed that compounds 7, 8, 9 and 10 exhibited dual inhibitory activity against both AChE and BuChE, with IC_{50} values ranging from 27.54 to 89.12 nM and 36.85 to 80.44 nM respectively at nanomolar concentrations[23]. In their 2022 research, Nadeem and colleagues synthesized and assessed 2-arylidine derivatives of thiazolopyrimidine for their potential in treating Alzheimer's disease. The compounds showed significant inhibition of MAO-B with considerable specificity over MAO-A. Particularly, compounds 11 and 12 emerged as the most potent MAO-B inhibitors among the synthesized compounds, with IC_{50} values of 0.13 μM and 0.10 μM, respectively[24].Angelova et al. (2023) devised and synthesized two innovative series of hybrid molecules incorporating melatonin and donepezil, integrating hydrazone or sulfonyl hydrazone fragments. These compounds were meticulously evaluated as multifunctional ligands targeting the neurodegenerative mechanisms associated with Alzheimer's disease employing both *in silico* and *in vitro* methodologies. The findings highlighted compounds 13and 14 as noteworthy prototypes in the pursuit of novel compounds aimed at addressing Alzheimer's disease linked neurodegeneration accompanied by oxidative stress[25].Figure 2 displays the structures of indole derivatives (1–14) with demonstrated anti-Alzheimer's activities.

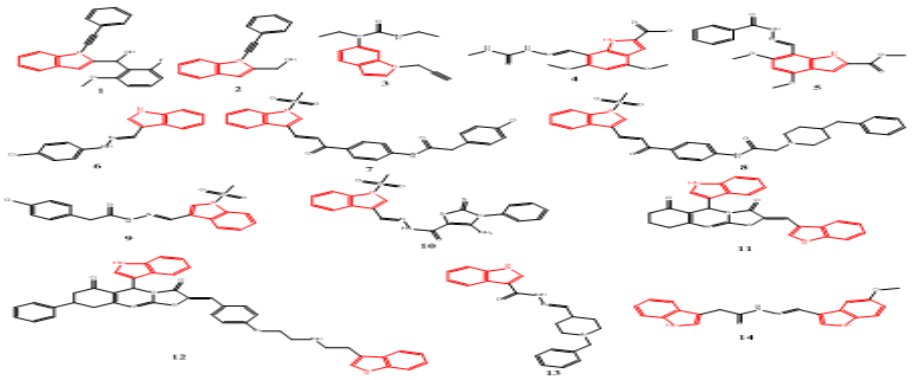

Figure 2. The structures of indole (1–14)derivatives exhibited anti-alzheimer activity

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2.2 Anticancer activity

Cancer characterized by abnormal cell growth and spread, presents a significant health challenge in modern society. Its mortality rate exceeds that of AIDS, malaria and tuberculosis combined, highlighting its severity. Globally, cancer is a major health concern with nearly 20 million new cases reported annually. In 2020, the World Health Organization (WHO) recorded approximately 10 million cancer-related deaths. Projections suggest that by 2040, the number of cancer cases will double with an estimated 29-37 million new cases diagnosed. Importantly, the most significant increase in cases is expected in low and middle-income countries[26].The limits of existing anticancer treatments highlight the pressing need for new drug development to address societal requirements. A wide spectrum of anticancer actions have been demonstrated by indole and its analogues, indicating its promise in the battle against this severe illness[27].An experiment by Parkash et al. (2018) sought to create indole derivatives and evaluate their potential as therapeutic agents for cervical cancer. With IC_{50} values of 13.41 μM and 14.67 μM, respectively, compounds 15 and 16 demonstrated exceptional potency among the synthesized compounds. Significantly, the activity of the common medication cisplatin, which has an IC_{50} of 13.20 μM, is comparable to these results.This suggests that compounds 15 and 16 have promising potential as anticancer agents[28].In 2018, Romagnoli and co-researchers conducted a study focusing on the synthesis and screening of a range of 3-substituted-2-oxindole hybrid derivatives. Among these derivatives, Compound 17 demonstrated high activity with an IC_{50} value of less than 5500 μM against HL-60 cells indicating Compound 17 could be a promising candidate for further development as an anticancer agent offering potential advantages over existing standard drugs[29].In 2018, Corigliano and colleagues designed and synthesized a variety of indole derivatives substituted with 2,4-thiazolidinedione. These compounds were assessed against two cell lines: MCF-7 (human breast cancer cells) and PC3 (human prostate cancer cells). Compound 18 demonstrated notable potency, with an IC_{50} value of 5 μM. [30].A range of thiosemicarbazone derivatives of indole were synthesised by Bakherad and colleagues, who then evaluated their effectiveness against the cancer cell lines MCF-7 (breast cancer), A-549 (lung cancer) and Hep-G2 (liver cancer). Comparing Compound 19 to conventional medications such as etoposide (IC_{50} = 38.23 ± 1.89 μM; Hep-G2, IC_{50} = 33.17 ± 3.19 μM) and colchicine (IC_{50} = 1.9 ± 0.23 μM; Hep-G2, IC_{50} = 6 ± 0.49 μM), Compound 19 showed substantial potency against the A-549 (IC_{50} = 12.5 μM) and Hep-G2 (IC_{50} = 56 ± 6.30 μM)[31].El-Sharief and colleagues synthesized isoindole derivatives and assessed their impact on three cancer cell lines. Compound 20 displayed significant potency (IC_{50}< 6.67 ± 0.36 μM), as did compound 21 (IC_{50}=6.34 ± 0.21 μM), when compared to standard drugs like isatin (IC50 < 41.83 μM) and doxorubicin (IC50 < 7.03 μM)[32].In 2019, Kaur et al. developed diazenyl derivatives hybridized with indole and investigated their cytotoxic effects on various human cell lines using the MTT assay. Compounds 22 and 23 exhibited promise specifically against the breast cancer cell line (MDAMB231)[33].In 2019, Yousif and colleagues synthesized various derivatives of 2-phenylindole and subsequently evaluated the anticancer efficacy of these compounds against liver carcinoma, prostate cancer, colorectal carcinoma and breast adenocarcinoma. Compounds24 and 25 exhibited notable cytotoxic effects against the tested cancer types[34].In 2020, Karadayi et al. developed new ethylsulfonyl indole-benzimidazole derivatives by modifying positions $1^{st}$and $5^{th}$of benzimidazole and indole groupsrespectively. These compounds were evaluated for their anticancer potential by assessing their cytotoxicity, interaction with potential targets such as Estrogen Receptor negative (ER) and their impact on molecular pathways associated with anticancer effects. Compound 26 showed promising efficacy against MCF-7 cells[35].In 2022, Hawash and colleagues introduced a series of innovative trans-indolyl-3-acrylamide derivatives designed to serve as tubulin polymerization inhibitors, targeting the colchicine site with precise binding. These newly developed compounds showed moderate efficacy in inhibiting the proliferation of diverse cancer cell lines. Particularly noteworthy was compound 27, which displayed the most potent antiproliferative activity, with an IC_{50} value of 5 μM in Huh7 cells, comparable to sorafenib[36].Figure 3 illustrates the structures of indole derivatives (15–27) exhibiting anticancer activities.

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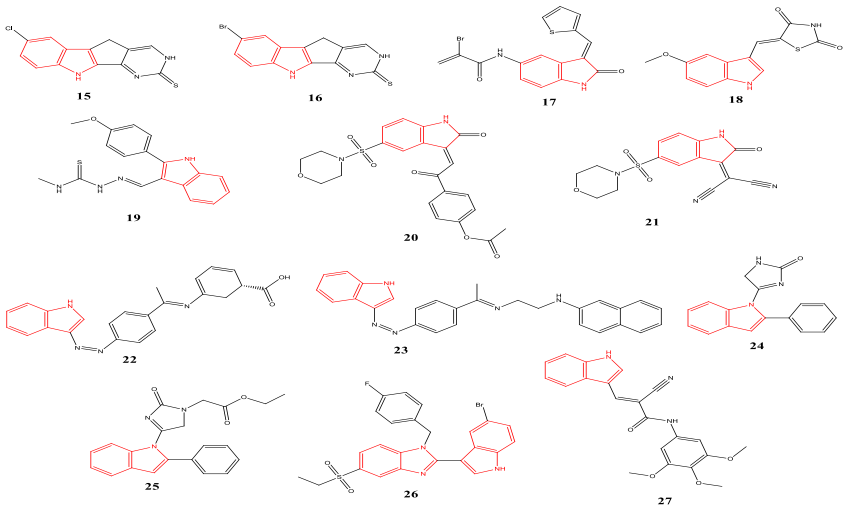

Figure 3. The structures of indole (15–27) derivatives exhibited anti-cancer activity.

2.3 Anti-convulsant activity

Epilepsy is a condition affecting the central nervous system, marked by recurrent and unprovoked seizures. It can manifest in various ways, affecting physical, mental and behavioralfunctions[37]. According to collaborative efforts by the World Health Organization (WHO), the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE), approximately 1% of the global population, or roughly 50 million people are affected by epilepsy at any given time. Around 2.4 million new cases are reported each year. WHO predicts that by 2024, epilepsy will become the second leading cause of death due to complications arising from stress and cardiovascular problems[38].

In 2021, Fayed et al. conducted a study to investigate the biological significance newly synthesized isatin derivatives containing thiazole components. These derivatives were screened *in vivo* for their anticonvulsant effects against pentylenetetrazole-induced convulsions in mice, with phenobarbitone sodium used as the standard anticonvulsant drug for comparison[39]. The majority of the tested compounds showed anticonvulsant activity, with potency ranging from 0.02 to 0.2 compared to phenobarbitone. Notably, compounds 28, 29, 30 and 31 were among the most active derivatives tested[40].In their 2022 study, Tchekalarova and colleagues synthesized a range of new indole compounds featuring aroylhydrazone components and assessed their anticonvulsant effects in mice. Their investigation revealed that compound 32 displayed effectiveness in combating kainate (KA)-induced status epilepticus (SE) and associated oxidative stress in a mouse model[41].Figure 4 depicts the structures of the indole derivatives (28–32) that exhibited anticonvulsant properties.

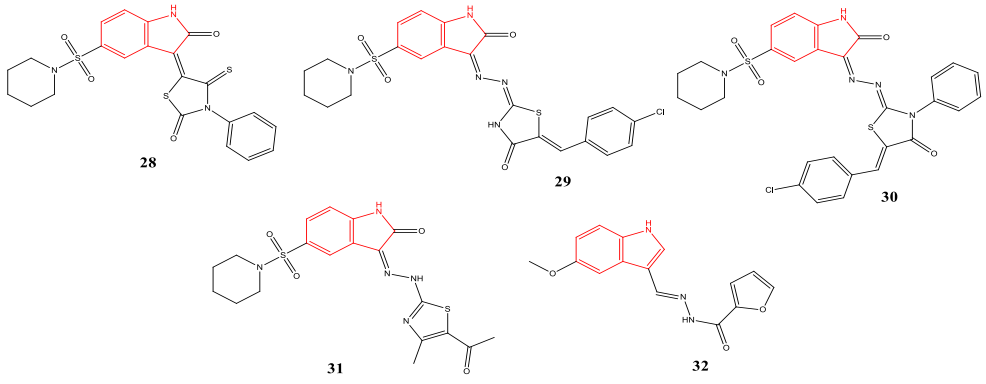

Figure 4. The structures of indole (28–32) derivatives exhibited anti-convulsant activity.

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2.4 Anti-diabetic activity

Diabetes mellitus comprises a range of metabolic conditions marked by elevated blood sugar levels due to deficiencies in insulin secretion, function or both. It is a non-communicable disease associated with significant mortality rates and substantial healthcare expenses[42].According to the International Diabetes Federation (IDF), approximately 8.8% of the adult population worldwide has diabetes, with men experiencing slightly higher prevalence rates compared to women.India's diabetes population was anticipated to be 77 million in 2019 and is expected to rise to over 134 million by 2045[43].

In 2021, Khan et al. synthesized several Indole-3-acetamides and evaluated their potential antihyperglycemic effects. They found that all compounds demonstrated good to moderate inhibition against the α-amylase enzyme, with IC_{50} values ranging from 1.09 ± 0.11 to 2.84 ± 0.1 µM, compared to the standard acarbose (IC_{50} = 0.92 ± 0.4 µM). Compound 33 (IC_{50} = 1.09 ± 0.11 µM) showed the most promising activity displaying strong inhibition against α-amylase[44]. In the same year Solangi et al. synthesized indole acrylonitriles and assessed their potential as α-glucosidase inhibitors. Their evaluation involved comparing the activity of these compounds to the standard acarbose (IC_{50} = 2.91 ± 0.02 µM). Remarkably, Compound 34 (IC_{50} = 0.53 ± 0.01 µM) displayed the most promising inhibition, surpassing the standard by several folds. [45].Alomari and colleagues (2021) created and examined a set of nineteen compounds derived from indole-thiadiazole to determine their capacity to impede the activity of α-glucosidase. Compared to the standard acarbose (IC_{50} = 1.70 ± 0.10 µM), the compounds showed different degrees of inhibition with IC_{50} values ranging from 0.95 ± 0.05 to 13.60 ± 0.30 µM. Compound 35 demonstrated the strongest inhibitory effect of α-glucosidase, with an IC_{50} value of 0.95 ± 0.05 µM[46].In 2022, Khan et al. conducted the synthesis of thiazolidinone-based indole derivatives and examined their efficacy in inhibiting α-amylase and α-glucosidase. Analogs36 (1.80 ± 0.70 and 2.70 ± 0.70) and 37 (1.50 ± 0.05 and 2.40 ± 0.10), displayed markedly superior inhibitory activity compared to the standard drug acarbose with IC_{50} values of 10.20 ± 0.10 and 11.70 ± 0.10 µM, respectively[47].Figure 5 illustrates the structures of indole derivatives (33–37) exhibiting antidiabetic activities.

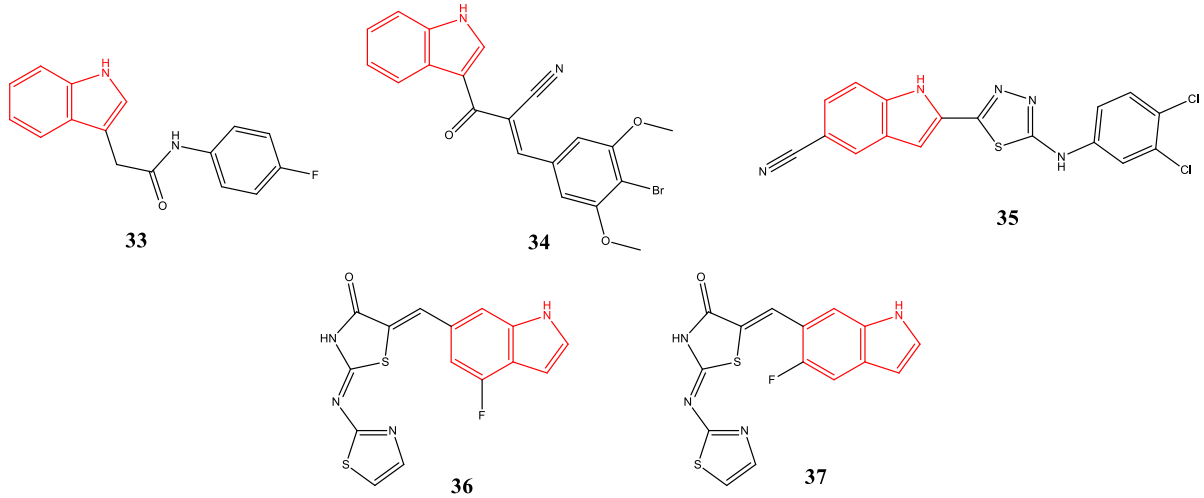

Figure 5. The structures of indole (33–37) derivatives exhibited anti-diabetic activity.

2.5 Antidepressant

Depression, clinically referred to as depressive disorder is a mood disorder characterized by distressing symptoms that typically impact emotions, thoughts, and daily functioning such as sleep, appetite and work.Depression often coexists with other significant health conditions such as cancer, Parkinson's disease, diabetes and heart disease. This mutual relationship can exacerbate both depression and the primary illness. Additionally, medications prescribed for treating these conditions may sometimes trigger side effects that

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contribute to depressive symptoms[48]. Acknowledging the interconnectedness of physical and mental health, the World Health Organization (WHO) emphasizes the equal importance of both. Depression is projected to affect 5.7% of individuals over 60 and 5% of adults worldwide, impacting 3.8% of the global population.Over 700,000 lives are lost to suicide each year, making depression the fourth largest cause of death for those aged 15 to 29 globally. Suicide affects over 280 million people[49].In 2019, Wróbel et al. synthesised a variety of new 3-(1H-indol-3-yl)pyrrolidine-2,5-dione derivatives and evaluated their affinity for serotonin reuptake inhibition and 5-HT_{1A}/D_2/5-HT_{2A}/5-HT_6/5-HT_7receptors. The forced swim test (FST) was used to assess the antidepressant potential of certain drugs *in vivo*. The results showed that compound 38, which functions as an agonist of the pre- and postsynaptic 5-HT_{1A}receptor, had antidepressant-like effects in the FST model and showed promising affinities for 5-HT_{1A}/D_2/5-HT_{2A}/5-HT_6/5-HT_7receptors[50].Kerzare et al. (2020) synthesized a series of 3-{2-[1-acetyl-5-(substitutedphenyl)-4,5-dihydropyrazol-3-yl]hydrazinylidene}-1,3-dihydro-2H-indol-2-ones using an appropriate synthetic route. The maximum electroshock test was used to experimentally assess these drug's antidepressant and antianxiety properties. Among them, compound 39 demonstrated noteworthy action in comparison to the reference medication diazepam, with an ED_{50} of 13.19 mmol/kg and TD_{50} of 43.49 mmol/kg, with a high protective index of 3.29. In 2022, Mesripour et al. synthesized a novel series of Schiff bases containing N-alkyl and N-benzyl isatin derivatives and investigated their antidepressant effects in mice. Results indicated that compound40 emerged as a promising candidate. Compared to the control group, compound 40 administration at dosages of 25 mg/kg and 50 mg/kg resulted in a substantial reduction in immobility time during the forced swimming test (127.3±7.1 sec)[51]. In 2024, Sahu et al. synthesized derivatives of 1-ethyl acetate-2-phenylindole and examined their antidepressant properties using the forced swim test (FST) and tail suspension test (TST). Notably, compounds 41 and 42 were observed to effectively decrease mouse immobility in the TST while enhancing swimming frequency[52].Figure 6 displays the structures of indole derivatives (39–42) that exhibited anti-Alzheimer's activity.

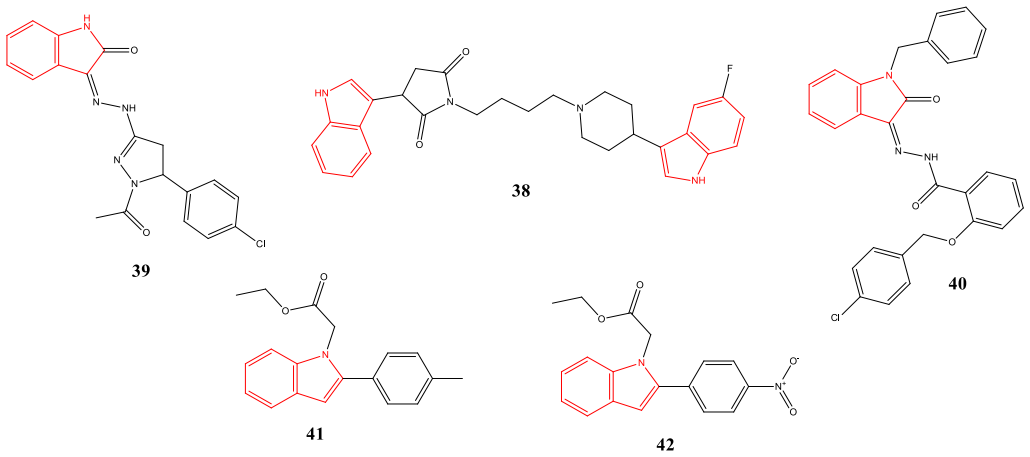

Figure 6. The structures of indole (39–42) derivatives exhibited anti-depressant activity.

2.6 Anti-HIV

A group of diseases known as acquired immunodeficiency syndromes (AIDS) are characterised by T cell immune insufficiency brought on by HIV infection[53]. Since the initial AIDS case report in 1981, around 40 million individuals worldwide have succumbed to the disease[54]. The widespread and fast transmission of AIDS along with its high mortality rate, pose significant risks to public health and social development. HIV comprises two strains: HIV-1, the primary pathogen and HIV-2 which has been identified globally and is associated with an increasing risk of infection[55,56].

The 3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one nucleus served as the basis for the design and synthesis of twenty-two compounds by Chander et al. (2019).

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With T lymphocyte cells, these compounds were next tested *in vitro* utilizing the syncytia formation assay for their anti-HIV-1 efficacy against the wild strain HIV-1IIIB. Among them, compounds 43, 44 and 45 exhibited promising potency at concentrations ranging from low micromolar to nanomolar levels[57].El-Hussieny et al. (2020) synthesized and assessed new 2-(thiophen-2-yl)-1H-indole derivatives for their ability to inhibit the HIV-1 reverse transcriptase (RT) enzyme. During the evaluation of HIV-1 reverse transcriptase enzyme inhibition, compound 46 demonstrated exceptional potency with an IC_{50} value of 2.93 nM. Notably, the inhibitory potency of compound 46 was approximately three times greater than that of Efavirenz, which exhibited an IC_{50} value of 6.03 nM[58].In research published in 2022, Xu et al. synthesised and assessed the antiviral activity of twenty piperazinone phenylalanine derivatives with a terminal indole. The synthesised compounds were very active against HIV-2. Compound 47, for example had an EC_{50} value of 4.52 μM, which was similar to the lead compound PF74's EC_{50} value of 4.16 μM. PF74 consists of a phenylalanine core, an indole substituent and a linker between them[59].Figure 7 illustrates the structures of indole derivatives (43–47) exhibiting anti-HIV activities.

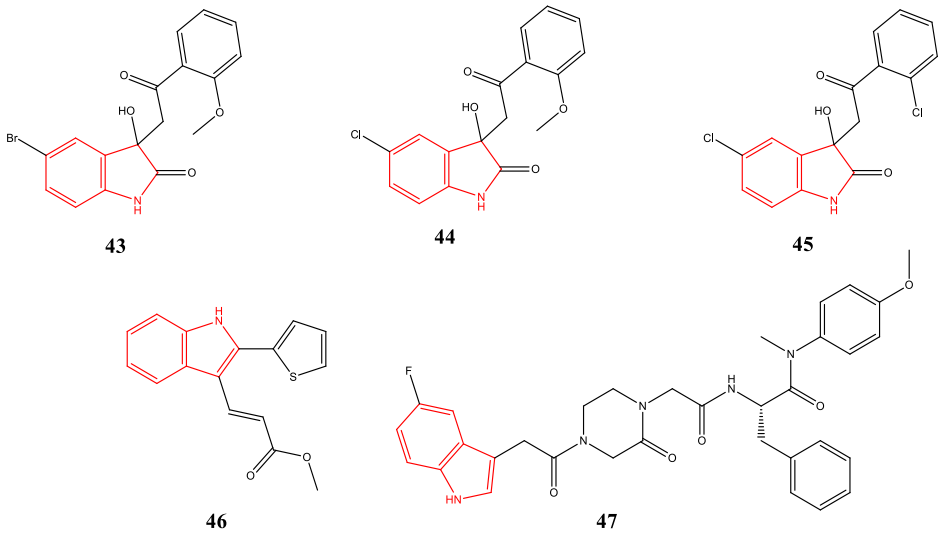

Figure 7. The structures of indole (43–47) derivatives exhibited anti-HIV activity.

2.7 Anti-inflammatory

The inflammatory response is crucial for restoring homeostasis following tissue injury and infection[60]. However, when inflammation becomes uncontrolled leading to chronic inflammation, it can result in tissue damage and various inflammation-related diseases such as cancer, diabetes,rheumatoid arthritis, asthma, inflammatory bowel disease and neurodegenerative diseases[61-63]. Non-steroidal anti-inflammatory medicines (NSAIDs) are often used in therapeutic therapies for chronic inflammation; nevertheless, prolonged use of NSAIDs can have serious adverse effects, such as cardiovascular toxicity and gastrointestinal damage. As a result, scientists are working to create new anti-inflammatory medications with fewer adverse effects[64]. In 2018, Bhat et al. introduced a new series of derivatives named 2-(5-methoxy-2-methyl-1H-indol-3-yl)-N0-[(E)-(substituted phenyl) methylidene] acetohydrazides as potential anti-inflammatory agents. Using the carrageenan-induced paw edema method, the compounds were evaluated. Compound 48 exhibited 61.99% inhibition after 2 hours and 61.20% inhibition after 3 hours. In comparison, the reference drug indomethacin showed 77.23% inhibition after 2 hours and 76.89% inhibition after 3 hours. This study identifies compound 48 as a promising lead compound with potential as an anti-inflammatory agent[65].Kumar et al. created and examined 12 compounds of oxadiazole and pyrazole functionalized with indole in 2021 for their anti-inflammatory properties utilizing the carrageenan-induced paw edema technique. Compound 49 exhibited noteworthy efficacy, demonstrating a 74.07% edema reduction percentage.

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This is in line with indomethacin's 92.59% reduction percentage and outperforms the other compounds examined[66].In 2018, Jacob et al. synthesized and assessed a series of novel thiosemicarbazone derivatives containing indole for their anti-inflammatory effects using the Carrageenan-induced paw edema test in Swiss mice. Compound 50 demonstrated significant inhibition, reaching 100% inhibition of edema at doses of 30 and 50 mg kg−1 after 4 hours, compared to indomethacin's inhibition of 84.81% at the same time[67].Figure 8 illustrates the structures of indole derivatives (48-50) exhibiting anti-inflammatory activities.

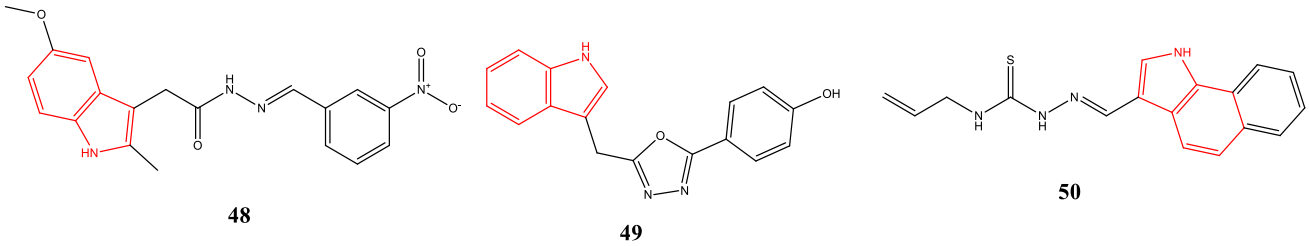

Figure 8. The structures of indole (48–50) derivatives exhibited anti-inflammatory activity.

2.8 Antimicrobial

Infectious diseases pose significant challenges to global health, particularly for immunocompromised individuals and those with conditions such as tuberculosis, AIDS or cancer[68]. They contribute to high mortality and morbidity rates, leading to prolonged hospitalization and increased healthcare costs. Fungal and bacterial infections account for a substantial portion of infectious diseases, causing approximately 1.5 million deaths worldwide each year[69]. Despite the availability of antimicrobial drugs, challenges such as microbial resistance, drug specificity issuesand narrow spectrum hinder effective microbial therapy[70]. Predictions indicate that by 2050, microbial illnesses may result in 10 million fatalities yearly due to the increasing prevalence of antibiotic resistance[71].

In 2018, Shirinzadeh et al. synthesized novel indole derivatives containing 1,2,4-triazole, 1,3,4-thiadiazole and carbothioamide. They assessed the efficacy of these compounds against various bacterial and fungal strains including MRSA, *Candida albicans*,*Escherichiacoli*,*Candidakrusei*,*Bacillus subtilis*and*Staphylococcus aureus*. Among the tested compounds, 51

(indole-thiadiazole) and 52 (indole-triazole) exhibited the most potent antimicrobial activity, both exhibited an MIC value of 6.25 µg/mL[72].In 2018, Sayed et al. synthesized and screened novel indolyl chalcone derivatives for antimicrobial activity. Compound 53exhibited the highest antibacterial activity against all bacterial strains, surpassing the corresponding reference antibiotics (ciprofloxacin and levofloxacin)[73].In 2019, Kaur et al. synthesized indole hybridized diazenyl derivatives and evaluated their antimicrobial activity against various pathogenic bacterial and fungal strains using the tube dilution method. Most derivatives exhibited strong activity against Gram-negative bacteria particularly*K. pneumonia* and *E. coli* with MIC ranges of 1.95–7.81 µg/ml, comparable to standard drugs like ciprofloxacin and cefotaxime. Notably, derivative 54 demonstrated the highest activity against *K. pneumoniaE. coli*, and*S. enterica* with MIC values of 1.95–3.90 µg/ml[74].In 2020, Shaker et al. developed and synthesized three sets of 2-(4-methylsulfonylphenyl) indole derivatives, which were tested for their antimicrobial efficacy. Compound 55 exhibited the highest potency as an antibacterial agent against MRSA, *K. pneumoniae*, *E. coli*,*P. aeruginosa* and *A. baumannii*strainscorrespondingly, while maintaining a safe therapeutic dosage[75].In 2020, Tiwari et al. conducted the synthesis of N-substituted indole derivatives, followed by their evaluation for antimicrobial efficacy against*PseudomonasputidaEscherichiacoli*,*Candidavis wanathii*and*Bacillus subtilis*. Notably, compounds 56IC_{50} value 0.19 ± 0.03 µM,compounds 57IC_{50} value 0.14 ± 0.02 µM and compound 58IC_{50} value 0.16 ± 0.06

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μMdisplayed noteworthy activity respectively, against *B. subtilis*. These values were comparable to the IC_{50} of chloramphenicol (0.25 ± 0.03 μM)[76].Figure 9 depicts the structures of indole derivatives (51–58) exhibiting antimicrobial activities.

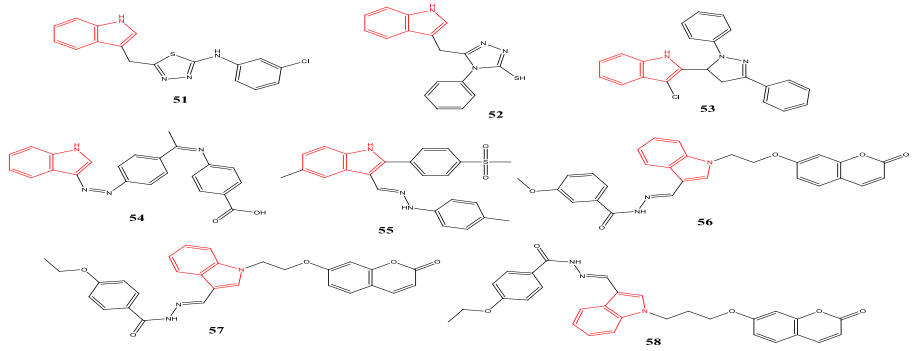

Figure9. The structures of indole (51–58) derivativesexhibited anti-microbialactivity.

2.9 Anti-malarial

Malaria, an often-fatal disease caused by Plasmodium parasites transmitted through bites of infected female Anopheles mosquitoes, disproportionately affects children and vulnerable populations in tropical and subtropical regions. With an annual death toll estimated between 0.8 to 1.2 million globally, it remains a significant public health challenge[77]. In India, diverse geographic and ecological landscapes are home to nine species of Anopheline mosquitoes responsible for malaria transmission. Despite approximately 2 million confirmed cases and 1,000 deaths reported yearly, WHO's South East Asia Regional Office projects a much higher burden estimating around 15 million cases and 20,000 deaths annually[78].Luthra et al. (2019) developed antimalarial substances derived from indo that target the melatonin pathway. Their research demonstrated that some of these compounds effectively hindered parasite survival, with compound 59 standing out for its ability to halt parasite growth during the trophozoite stage[79].In the same year, Jyoti et al. conducted research involving the synthesis of indolyl chalcone derivatives and assessed their effectiveness against *Plasmodium falciparum*. Among the compounds tested, 60 demonstrated the highest activity exhibiting an IC_{50} value of 2.1 mM/L[80].Elshemy et al. (2020) synthesized pyridyl-indole derivatives as antimalarials, effective against bothsensitive to chloroquine and resistant strains of *P. falciparum*. Notably, compounds 61, 62 and 63 showed the highest selectivity index, with indices ranging from 3.8 to 10[81].In 2021, Pingaew et al. conducted investigations on the antimalarial activities of indole-sulfonamide derivatives. These derivatives were evaluated for their effectiveness against *P. falciparum*. The most potent antimalarial agent identified 64 with an IC_{50} value of 2.79 μM[82].Figure 10 illustrates the structures of indole derivatives (59–64) exhibiting antimalarial activities.

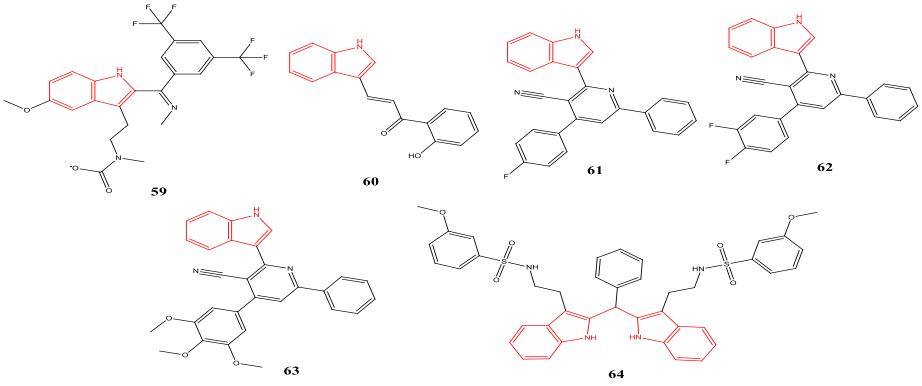

Figure 10. The structures of indole (59–64) derivatives exhibited anti-malarial activity

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3.0 Antileishmanial

Leishmaniasis, caused by intracellular protozoan parasites of the *Leishmania spp*., is one of the most neglected tropical diseases. Leishmaniasis is widespread, affecting nearly 98 countries worldwide with around 2 million cases reported annually and approximately 350 million individuals at risk[83]. The disease presents in four main forms: cutaneous, visceral, kala-azar dermal leishmaniasisandmucocutaneous. Visceral leishmaniasis is prevalent in India, Bangladesh, Nepal, East Africa and Brazil impacting about 90% of their populations. Primary treatment options rely on pentavalent antimonial compounds, but their efficacy is limited, with drug resistance occurring in roughly 60% of cases[84-85]. Ashok et al. (2019) assessed the anti-leishmanial activity of a 9-methyl-1-phenyl-9H-pyrido[3,4-b]indole derivatives against *Leishmania donovani*and*Leishmania infantum*. In the assay targeting *Leishmaniainfantum* compounds 65, 66 and 67 showed significant inhibition of both promastigotes and amastigotes, with EC_{50} values of 1.59 µM, 1.47 µM, and 3.73 µM for promastigotes and 1.4 µM, 1.9 µM, and 2.6 µM for amastigotes respectively[86].In the same year, Taha et al. synthesized a new series of bisindoleanalogs with potent anti-leishmanial activity. Compound68 showed the highest potency with an IC_{50} value of 0.7 ± 0.01 µM, compared to the standard pentamidine (IC_{50} value of 7.20 ± 0.20 µM)[87].Tiwari et al. (2020) synthesized N-substituted indole derivatives and tested their eifficacy against *Leishmania donovani* promastigotes for antileishmanial activity using the MTT assay. Among the compounds, 69 demonstrated notable antileishmanial activity with an IC_{50} of 21.5 ± 2.12 µM[88].Figure 11 illustrates the structures of indole derivatives (65–69) exhibiting antileishmanial activities.

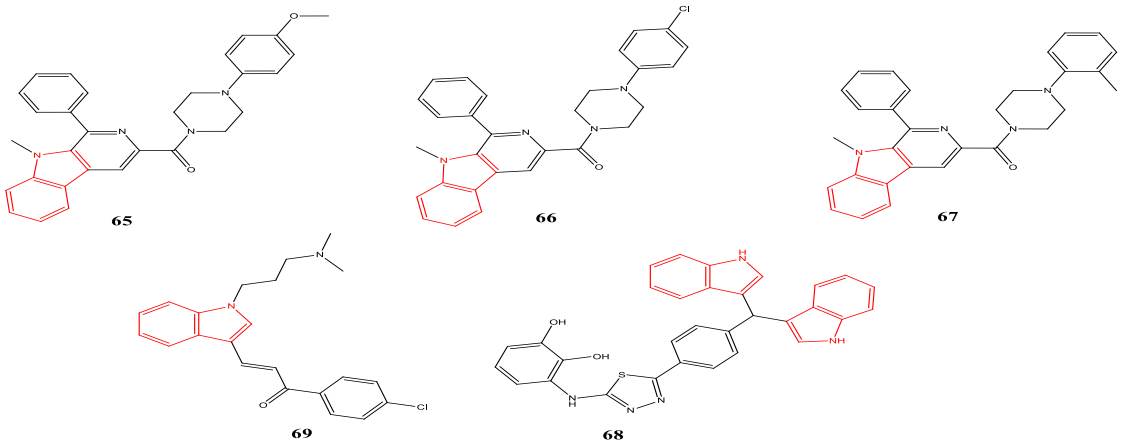

Figure 11. The structures of indole (65–68) derivatives exhibited anti-leishmanial activity

3.1 Antifungal

Fungal diseases in food crops have become a significant concern in global agriculture, leading to reduced yields and quality, resulting in substantial economic losses for farmers worldwide[89]. Moreover, some pathogenic fungi can produce toxins and metabolites that are harmful to both humans and livestock[90].

Wang et al. (2022) synthesizednovel indole base derivatives with a 1,3,4-thiadiazole scaffold modified by a thioether group. These derivatives were tested for antifungal activity against various fungi, including *Fusarium graminearum*, *Fusarium oxysporum*, *Fusarium moniliforme* and *Phytophthora parasitica var. nicotiana*, using the mycelium growth rate method. Compound 70 displayed the highest inhibition rates achieving 76.5%, 89%, 95.7% and 100% inhibition at 500 µg/mL against*P. p. var. nicotianae*,*F.moniliforme*, *F. oxysporum*, and *F. graminearum*. respectively[91].The structures of indole derivative (70) displayed antifungal activity is shown in Figure 11.

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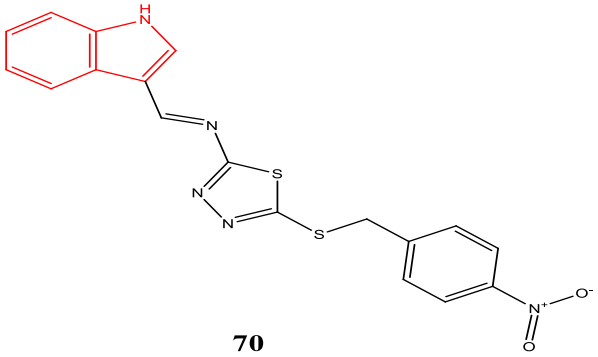

70

Figure 12. The structures of indole (70 derivative exhibited anti-fungal activity**.**

3. Conclusion

The indole component is widely found in compounds with diverse biomedical uses. It serves as a key structural element in synthetic drugs, aiding their attachment to target binding sites. Indole derivatives display a broad spectrum of biological properties including anticancer,antidiabetic, antimicrobial, antimalarialanti-HIVandanti-inflammatory effects. Researchers are actively exploring indole's potential for discovering new chemical entities to develop safer and more effective drugs. While existing literature provides valuable insights for new researchers, further investigation is necessary to fully understand indole's therapeutic potential. This research gap highlights the need for more preclinical and clinical data on newly synthesized indole derivatives to confirm their therapeutic efficacy.

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