IJPSR (2020), Volume 11, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 February 2020; received in revised form, 27 April 2020; accepted, 08 May 2020; published 01 November 2020

THERAPEUTIC SIGNIFICANCE OF INDOLE SCAFFOLD IN MEDICINAL CHEMISTRY

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Keywords:

Indole, Biological activity, Drug discovery, *In-vitro* antimicrobial, Molecular derivatives

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ABSTRACT: Discovery of New Chemical Entities (NCEs) is the result of a series of high throughput screening process after the successful design and synthesis scheme. The indole nucleus is an important heterocyclic compound containing nitrogen, and it has been a source of vital therapeutic agents. It is noteworthy in recent advances of synthetic, medicinal chemistry; the last decade has been witnessed with a multitude of reports on several indole derivatives corroborating these chemical entities to be an eminent target for the discovery of new drugs. Global research investigations published has outstanding impact attention for the scientists working on indole derivatives which transformed into various commercially approved indole candidate in the commercial market and there are several in the pipeline. This review highlighted recent achievements of indole lead molecules in biological, chemical, and pharmacological activity having diverse perspectives on how this indole moiety as a privileged structure may be browbeaten for elucidating salubrious biological activities.

INTRODUCTION: Indole is a notable privileged lead scaffold that arises in several natural products such as alkaloids, peptides, and various synthetic compounds [1]. Heterocyclic renders chemistry with a broad scope of pharmaceutical applications playing a pivotal part in synthetic chemistry and pharmacological activity. Indole and its derivatives have been employed as an exclusive platform in heterocyclic chemistry containing a nitrogen atom and it is an aromatic heterocyclic organic compound having a formula of C_8H_7N in which a bicyclic structure comprised of a benzene skeleton is merged with pyrrole moiety with derivatives possess various biological applications in medicinal chemistry [1, 2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(11).5441-60

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(11).5441-60

Indole is a hetero-atomic planar lead molecule [3]. The chemistry of indole up to dates to the mid 19th century is due to wide-ranging research on a natural violet-blue dye named indigo through leads to the preparation of indole **Fig. 1A** in 1866 by zinc distillation of oxindole [4, 5, 6]. Therefore, in this review, we emphasized the various synthetic route of the indole-based scaffold and their biological activity. This moiety is an important bioactive molecule which is an essential component of

pharmacologically active natural products such as plant growth hormone, indole-3-acetic acid (IAA) (antibacterial), indole alkaloids like tryptophan (essential amino acid), reserpine, alstonine, ergo-tamine, vincristine and vinblastine and 5-hydroxy-tryptamine (serotonin), melatonin are generally known as the neurotransmitter, anti-psychotic, migraine, hypertension, cancer chemo-therapy and lowering blood pressure, correspondingly [7-12]. Biological evaluation of indole-3-carbinol (I3C) along with 3, 30-di-indolylmethane (DIM), (a natural derivatives consequent commencing the digestion of I3C) are under research because of their anti-cancer, antioxidant as well as anti-atherogenic activity [13, 14, 15, 16]. In addition, some of the important pharmaceutical lead-containing indole rings are roxindole, indalpine, ondansetron, tadalafil and fluvastatin, perindopril, reserpine, pindolol introduced by Novartis is an application intended in management of hypertension since 1982 [17]. Indapamide marketed by Servier, used in the treatment of heart failure and hypertension [18]. Delavirdine and ateviridine are approved by the US FDA against HIV-1 [19].

Indomethacin containing the most important promising lead drug molecule for anti-inflammatory and analgesic effects.20 Along with this, various other marketed indole derivatives such as apaziquone (anti-cancer), abridol (anti-cancer), zafirlukast (antihistaminic), indoleamine (antibiotic) and strychnine has been shown in **Table 1** [21-25].

TABLE 1: BIOACTIVE MOLECULE CONTAINING THE INDOLE FRAMEWORK:

S. no.	Name	Chemical Structure	Indication	References
1	Delavirdine		Antiviral	19
2	Ateviridine		Antiviral	19
3	Abridol		Antiviral	22
4	Indole -3-Acidic acid		Antibacterial	29
5	Sumatriptan		Antimigrain	10
6	Serotonin		Antipsychotric	11
7	Apaziquone		Anticancer	21

8	Zafirlukast	Antihistaminic	23
9	Indomethacin	Anti-inflammatory	20
10	Indolmycin	Antibiotic	24
11	Pindolol	Antihypertensive	17
12	Reserpine	Antihypertensive	09
13	Strychnine	Antidot	25
14	Indapamide	Antihypertensive	18
15	Alstonine	Antipsychotic	02
16	Ergotamine	Migraine and uterine muscle Contraction	10
17	Vincristine	Anticancer	02

18	Roxindole ((EMD-49,980)	Schizophrenia	02
19	Indalpine	Antidepressant	[02]
20	Ondansetron	Anti-nausea and vomiting	02
21	Tadalafil	To improve erectile dysfunction	02
22	Fluvastatin	Anti-hyperlipidemia	02

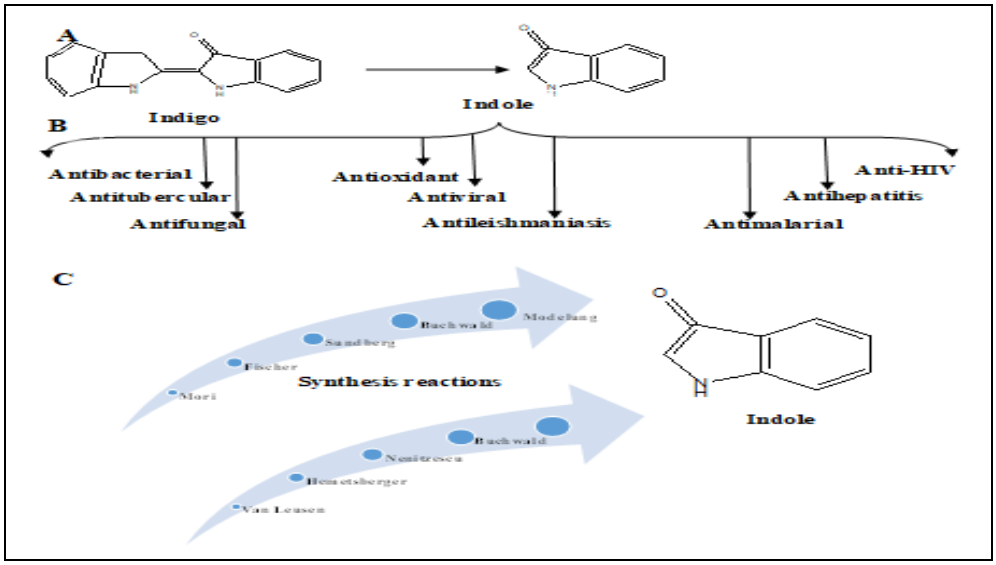

FIG. 1: (A) DISCOVERY OF INDOLE, (B) PHARMACOLOGICAL PROFILE OF INDOLE NUCLEUS AND (C) DIFFERENT TYPES OF CONVENTIONAL INDOLE SYNTHESIS

In medical science, indole based therapeutic drugs possess valuable biologic activities such as anti-HIV (Human immunodeficiency virus), anti-microbial, anti-malarial, antiviral, anti-fungal, anti-leishmanial, anti-oxidant, and anti-tubercular **Fig. 1B** [26-33]. Indole is a principal structural molecule which is explained as a privileged scaffold. Evans and co-workers introduced and define indole scaffolds that are proficient in performing as ligand meant for receptors diversity [34-36].

They have the special property of mimicking the structure of proteins and inversely binding with enzymes that offer great opportunities to discover novel drugs with a proliferation mode of action. Many of the marketed drugs containing indole (synthesized) have been reported as the "Best Retail" by USA[37-41]. In this review, an attempt has been made to summarize recent advances in the moiety with diverse biological and therapeutic functionality in the health care domain.

We designed to accumulate the details of synthetic form, *in-vitro*, *in-silico,* and *in-vivo* evaluation had been completely done on diverse indole molecules through collecting the different research articles survey during literature search from different scientific portals area. There are also a number of accepted indole based drug molecules in the market along with lead molecule presently obtainable through diverse clinical phases.

Chemical Synthesis of the Indole Ring: Conventional synthesis of the indole nucleus by various methods have been reported in the literature. It involves a number of starting materials and different strategies as mentioned in **scheme** 1 which includes: Mori indole synthesis, Buchwald indole synthesis, Sundberg indole synthesis, Hemetsberger indole synthesis, Kanematsu indole synthesis, Van Leusen indole synthesis, Nenitzescu indole synthesis, Modeling indole synthesis, and Fischser indole synthesis **Fig. 1C** [42-50].

Pharmacological Evaluation of Indole Compounds: Due to the universal nature of indole derivatives, it has gained vast recognition among the organic and medicinal chemists.

Many lead drug molecules containing indole moiety are found to be under investigation and research to control various disease conditions such as bacterial, malaria, fungal, viral, tubercular, and HIV infections.

Antimicrobial Activity: In general, antibacterial action of clinically approved drugs and newly reported moiety are based on bactericidal or bacteriostatic mode of action. Antibiotic acts either acting directly on bacterial cell wall or enzyme based hacked systems. Bacterial cell wall is composed of complex polysaccharides which is targeted by antibiotics and caused cell wall degradation or fragmentation and thereby causing cytoplasmic content to be oozed or released. This may be a potential mechanism of bacteria death. Another aspect is enzyme mediated or nuclear mechanism. There are several enzymes responsible for a cell physiological normal process. However, bacterial cells are differentiated from mammalian cells in several terms which seek an attention for the drug discovery scientist. This was a basis new drug development such as rifampicin which primarily acts on bacterial mRNA dependent DNA polymerase.

Rapid development of drug resistance has emerged as a serious challenge since the entry of the first agent into the clinical market in the 1940s. To curtail the development and spread of antimicrobial resistance, it requires the preservation of current antimicrobials through their appropriate use, besides the drug development and discovery of new lead molecules. A higher rate of mortality and cost are observed in the management of microbial disease and further is amplified to enhance its antimicrobial resistance [51].

The WHO's (World Health Organization) latest survey revealed that 0.5 million people are antibiotic-resistant across 22 countries [52]. To combat the problem of anti-microbial resistance new indole derivatives targeting microorganism through different mechanism should be developed. Various indole derivatives are identified and evaluated as anti-microbial agents. Sanna and his colleagues mentioned the synthesis of indole-thiourea hybrids and evaluated it against a pool of microbes containing both Gram-positive and Gram-negative types. Compound (1) (minimum inhibitory concentration as MIC (minimum inhibitory concentration) < 12.5 μg/mL) was establish to be extremely potent as compared with standard drug ciprofloxacin (MIC < 1.0 μg/mL) [53].

Thiazolidine is also known for its activity as an antimicrobial agent and therefore researchers are trying to combine thiazolidine moiety with others to design potent antimicrobial agents [54]. Abo-Ashour and coworker synthesized oxindole-thiazolidine conjugates. All the synthesized derivatives were evaluated against *S. aureus*, *P. aerugenosa*, *E. coli*, *M. tuberculosis*, *A. fumigates* and *C. albicans*. SAR (structural activity relationship) study concluded that chloro and methyl substitution are favorable for the activity. Compound (2) (MIC < 0.98 μg/mL) was established to be nearly all active with equal potency both as antifungal and as antimicrobial relative to ciprofloxacin (MIC < 3.90 μg/mL) and amphotericin B (MIC < 1.95 μg/mL), respectively [55]. Recently, synthesized and evaluated various indole derivatives containing heterocyclic nucleus were explored as antimicrobial agents. The

presence of thiophene and imidazole rings improved the antimicrobial evaluation of prepared new compounds. It was observed that compound (3) (MIC < 8 μg/mL) showed high antibacterial activity, whereas compound (4) (MIC < 6 μg/mL) showed high antifungal activity [56]. Various 5-hydroxy-indole moieties were prepared and measured next to *C. albicans, A. niger, E. coli* and *B. cirroflagellosus*. Compounds (5) (zone of inhibition = 28 mm) showed maximum potency as compared with standard drug griseofulvin (zone of inhibition ~ 30 mm) [57].

Mane *et al.,* 2016 evaluated and prepared various indole-2-carboxamide derivatives having research that various ester derivatives and amide moieties of indole-2-carboxylic acid was found to be potent antioxidant and antibacterial properties. New synthesized derivatives were assessed against *K. pneumonia, E. coli, P. aeruginosa, S. typhi, C. albicans, C. neoformans, A. fumigatus* and *C. parapsilosis*. SAR studies suggested that the alkyl and halogen-substituted phenyl and cyclohexyl carboxamide derivatives are favorable for the activity. Compound (6) (MIC < 6.25 μg/mL) exhibited maximum antimicrobial activity compared with standard drug gentamicin (MIC < 3.0 μg/mL) [58].

It is found that pyrazole and imidazole have the wide spectrum of antimicrobial evaluation owing to because the existence of nitrogen atom in five-membered rings which acts by inhibiting cell wall synthesis or DNA (Deoxyribose nucleic acid) damage [59-61]. The antimicrobial activity of these heterocyclics attracted various scientists to attach pyrazole and imidazole rings with the indole nucleus to prevent the problem of microbial resistance. In 2017, Quazi *et al.,* prepared and assessed different indole-pyrazole derivatives.

All the new derivatives, (7) (zone of inhibition < 0.5 cm) showed good activity against Gram-positive bacteria and compound (zone of inhibition < 0.1 cm), has good activity against fungal strain Macrophominaphaseolina and Sclerotiumrolfsii [62]. A new class of imidazole-based indole moities were prepared and evaluated against bacterial strains *S. aureus, S. pyogenes, Shigella flexneri, Proteus mirabilis, Vibrio cholera* and on fungal strains such as *Candida albicans, C. glubrate,* and *C. crusei* **Fig. 2A**.

Considering another context, density functional theory, computational method, X-ray crystallo-graphic analysis and molecular docking study were also used to evaluate indole compounds and its derivative for physicochemical properties by several authors. Compound (8) (MIC < 12.5 μg/mL) showed good chemical stability, reactivity and bond parameters due to the presence of negative charges on oxygen and nitrogen atoms as compared to methicillin standard drug (MIC < 6.25 μg/mL) [63]. In the same year, Yadav *et al.,* 2016, reported the role antibacterial activity of 1, 2, 3, 5 substituted indole derivatives and evaluated against *S. aureus, S. pyogenes, E. coli,* and *P. aerugenosa*. Compounds (9) (MIC = 37.5 μg/mL) was establish to be active [64].

Choppara *et al.,* 2015, have designed and synthesized bis-indole derivatives and evaluated against *B. subtilis, E. coli, K. pneumonia,* and *P. aerugenosa*. SAR study concluded the role of prenyl system for the activity. Compound (10) (zone inhibition < 24 mm), (zone of inhibition < 21 mm) (8) (zone of inhibition < 20 mm) were establish to be the main active as compared to reference ciprofloxacin (zone of inhibition < 27 mm) [65]. Gali *et al.,* 2015 investigated the synthesis of thiazolylcoumarins substituted indole derivatives and further evaluated against *B. subtilis* and *E. coli*. SAR highlighted that the occurrence of unsubstituted thiazolylcoumarins was favorable for the evaluation. Compound (11) (zone inhibition < 18 mm) was initiate highly potent as compared to reference drug streptomycin (zone of inhibition < 30 mm) [66].

Hydrazone is another moiety having immense antimicrobial activity due to inhibition of microbial cell wall synthesis described in a large literature data [67-68]. Based on this, Shirinzadeh *et al.,* synthesized and evaluated various indole-hydrazone derivatives to cope with the problem of multidrug-resistant bacteria. SAR studies suggested that activity increased with the introduction of halogen atoms into the phenyl ring especially at the ortho position. (12) (3, 5-difluoro) (MIC < 100 μg/mL), showed the highest activity when compared to standard drugs sultamicillin (MIC < 25 μg/mL), ampicillin (MIC < 50 μg/mL), fluconazole (MIC < 0.78 μg/ml) and ciprofloxacin (MIC < 0.19 μg/mL) [69]. Nassar *et al.,* 2010, also

prepared pyrazoline, pyridine, pyrimidine substituted indole compounds as antibacterial agents. All the new prepared compounds were assessed against *S. aureus*, *E. coli*, *P. aerugenosa*, Fusarium *A. niger*, and *C. albicans*. SAR study indicated the role of methoxyphenyl substitution. Compound (13) (zone inhibition < 34 mm) showed promising antimicrobial potency when compared to reference drug ciprofloxacin (zone of inhibition < 44 mm) and nystatin (zone of inhibition < 44 mm) **Fig. 2B** [70-71].

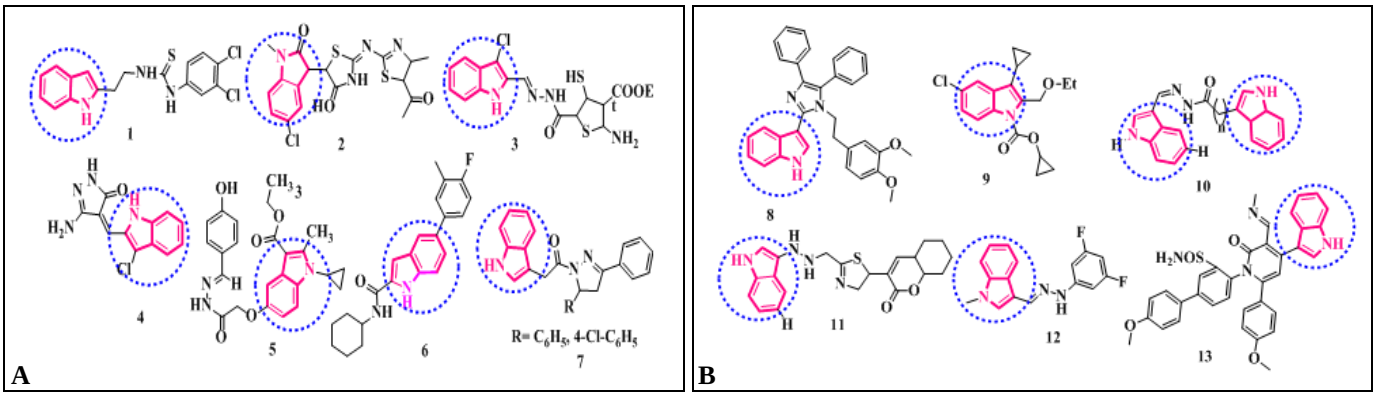

FIG. 2: ANTIMICROBIAL ACTIVITY OF INDOLE DERIVATIVES (A) AND (B)

El-Sayed, *et al.*, 2015, bisindolyl-substituted cycloalkane-anneallated indoles as a new series of antibacterial activity. The new active derivatives (14) was containing cyclohexane indole moiety when evaluated against *S. aureus* and MRSA (methicillin resistance *S. aureus*) [72]. Choppara, *et al.*, 2015, synthesized two classes of new analogues bis (indole) and selected for their antimicrobial, antitumor activities, and the SAR. Compound (15) N (-((5-bromo-1H-indol-3-yl) methylene)-2-(1H-indol-3-yl) acetohydrazide) was establish to be active potent.

Shi *et al.*, 2015, reported the new synthesis and antibacterial evaluation of new indole containing 1, 2, 4-triazole, and 1, 3, 4-oxadiazole moieties during ultrasound irradiation. In the present series two optimized drugs (16) 3-(1H-indol-3-yl)-5-[[2-[[5-(4-methoxy-phenyl)-1, 3, 4-oxadiazol -2-yl]thio] ethyl]thio]-4H-1, 2, 4-triazol-4amine and (17) 3-(1H-indol-3-yl)-5-[[2-[[5-(4-aminophenyl)-1, 3, 4-oxadiazol-2-yl] thio] ethyl]t hio] -4H-1, 2, 4-triazol-4-amine exhibited tremendous intrinsic effectiveness **Fig. 3A** [73].

Anti-tubercular Activity: Tuberculosis is global and deadly air borne infectious disease caused by Mycobacterium tuberculosis affecting lungs as well as other parts of the body [74]. According to WHO report 2019, 10 million new cases of TB were estimated globally [75]. Tuberculosis is considered the most life-threatening disease that causes about 100 million deaths worldwide [76].

A number of indole derivatives are mentioned here having advanced anti-tubercular activity [77]. In 2018, Abo-Ashour *et al.*, 2018, synthesized and evaluated various oxindole-thiazolidine conjugates active against M. tuberculosis bacterial strain RCMB 010126. The methoxy, ethoxy, and alkyl groups were found to be favorable for the activity. Compounds (18) (MIC = 0.39 µg/mL) were more and equally potent compared to standard drug isoniazid, (MIC = 0.78 µg/mL) [78].

Various indole derivatives were synthesized using Knoevenagel and Michael reaction mechanism, and in-*vitro* activity was conducted to assess the anti-tubercular activity against M. tuberculosis bacterial strain (MTCC 300). Docking study was also performed to further detect the affinity between the synthesized compound and enoyl-acyl carrier protein reductase using Auto Dock-Vina software (Los Angeles, USA).79 SAR studies concluded that chloro and nitro substituent at the para and ortho positions of phenyl ring were favorable for the activity. Compound, (19) has comparable activity (MIC = 40 µg/mL) to standard drug isoniazid (MIC = 10 µg/mL) and good binding affinity (-11.6) with the target protein [80]. Based on reported literature, piperazine is also goog anti-tubercular agents [81-82]. Naidu *et al.*, 2016, reported various indole-piperazine derivatives and evaluated against Mycobacterium tuberculosis (H37 Rv). The introduction of electron-withdrawing groups such as Br, CF3 leads to an increase in anti-tubercular

activity. Compounds, (20) (MIC = 6.16 μM) showed highly potent anti-tubercular activity compared to standard drug isonicotinic acid hydrazide (MIC = 91.14 μM) [83.] In the same year, Stec J *et al.,* designed and synthesized various indole-carboxamide derivatives targeting MmpL3 protein and were further evaluated for anti-tubercular activity by conducting *in-vivo* and *in-vitro* studies.

Lipophilic compounds exhibited higher activity compared to hydrophilic derivatives. The compound, (21) was of potential activity (MIC = 0.012 μM) against multidrug-resistant and extensively drug-resistant M. tuberculosis strains. Apart from this, docking studies were also conducted, showing the maximum binding of 21 (MIC = 0.29 μM) with MmpL3 protein [84].

Some new pyridine and indole based 1, 3, 4-oxadiazole derivatives having anti-tubercular activity was reported. The *in-vitro* studies were conducted to evaluate the anti-tubercular activity against M. tuberculosis H37 Ra and M. bovis BCG. However, the anti-proliferative activities of synthesized derivatives were also evaluated using three cell lines- HeLa, A549, and PANC-1. According to SAR, the substitution pattern at the phenyl ring of chalcone significantly modulates the activity. At the 2nd position of the phenyl ring, –OH and $–NO_2$ functional group is favorable for the activity. Compound, (22) were recognized as the better active derivatives amid MIC ranging with 0.94 to 5.17 μg/mL compared to isoniazid (MIC = 0.037 μg/mL) and rifampicin (MIC = 0.017 μg/mL). Docking studies were also conducted using Grid-Based Ligand Docking [85].

Compounds (23) exhibited maximum docking in the active area of mycobacterial enoyl reductase (InhA) [86]. Khan *et al,* 2016 have synthesized novel 3-alkylated indole derivatives using mp CuO as a heterogeneous catalyst having high catalytic efficiency, maximum surface area, and recyclability. Among all the synthesized compounds, (24) (MIC = 15 μg/mL) containing p-methoxy phenyl derivative at the 3rd position of indole exhibited significant anti-tubercular activity against M. tuberculosis bacterial strain (MTCC 300) in comparison to the isoniazid taken as a standard drug (MIC = 10 μg/mL). Docking studies were also conducted using enoyl-acyl carrier protein reductase and the binding score was calculated for each derivative. Among all the synthesized derivatives, 24 showed maximum binding score [87].

Various organic moieties containing a hetero atom, the double bond between carbon and nitrogen, are found to be the most potent inhibitor of DNA gyrase enzyme causing the bacterial death. Hydrazone and thiazolidinones falling under this category are found to be potent anti-tubercular agents [88-90].

Because of this, Ustundag *et al.,* 2016 investigated and designed indole-based hydrazide-hydrazone, 4-thiazolidinones and evaluated for anti-tubercular evaluation against *M. tuberculosis* H37 Rv. SAR studies concluded that substitutions on the phenyl ring have a major impact on the activity. Substitution with F, CN, NO_2, CF_3 and $COOCH_3$ at the para position were favorable for the activity. Compound, (25) (MIC = 25 μg/mL) demonstrated notable anti-TB activity ranging from 6.25 to 25 mg/mL compared to rifampicin as standard drug (MIC = 25 μg/mL). However, anticancer activity is also evaluated using the colon cancer cell line COLO 205 [91].

Various indole-2-carboxamide derivatives were also established. SAR studies revealed that -Cl, -F, -CN substituents at the 4th and 6th position of indole and methyl substitution on phenyl ring attached with indole leads to increase in potency. All the synthesized derivatives were tested against M. tuberculosis H37 Rv strain. The compound (MIC_{50} = 0.23 μM) was found to be highly effective as compared to the reference isoniazid drug (MIC_{50} = 0.33 μM) [92].

Later in 2014, Tehrania and colleagues synthesized and evaluated various Schiff' base based indole derivatives. All the synthesized compounds are further evaluated using a microtitre plate on the Gram-positive and Gram-negative strain. SAR studies concluded that urea-based derivatives were highly potent. Compounds (26) (MIC = 3.91 μg/mL) exhibited maximum potency as compared with standard drug ethambutol (MIC = 0.75 μg/mL) **Fig. 3B** [93].

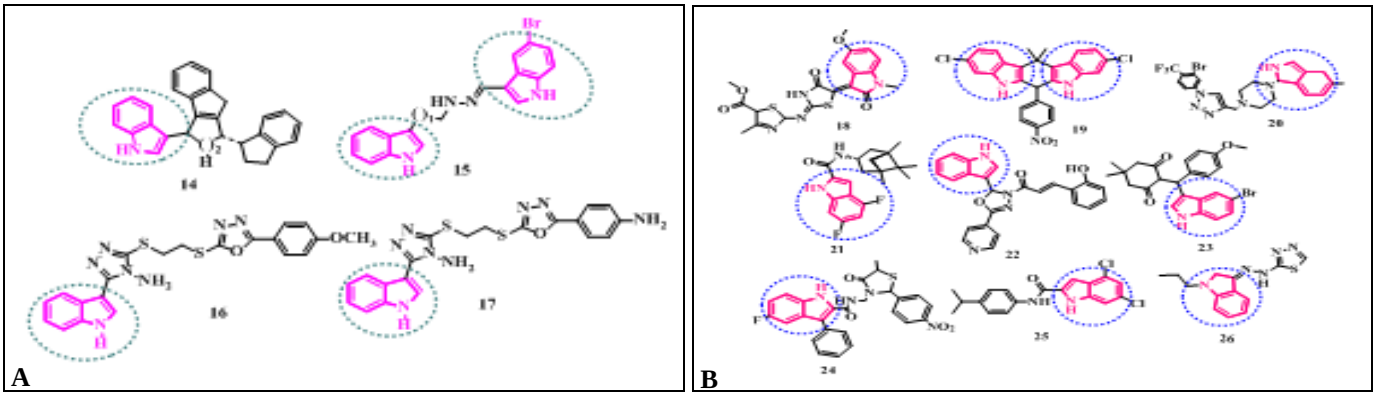

FIG. 3: ANTIMICROBIAL ACTIVITY OF INDOLE DERIVATIVES (A) AND ANTI-TUBERCULAR ACTIVITY OF INDOLE DERIVATIVES (B)

Anti-malarial Activity: Malaria is the most infectious ailment infected by Plasmodium parasite. Malaria is a chronic disease that leads to thousands of deaths annually [94]. As per WHO 2016 report, among the 216 million reported cases of malaria, 731000 patients died worldwide. Maximum cases were reported from African [95]. It is required to develop anti-malarial drugs at a fast pace to combat this problem. A few of indole derivatives as antimalarial agents are discussed below that have shown potential to encounter malaria. Yadav *et al.*, 2016, synthesized and evaluated various novel indole derivatives and evaluated against *P. falciparum*.

SAR studies explained that alkyl substitution with carboxylate at 1st and 2nd position and aryl at the 3rd position of indole was favorable for the activity. Compounds (27) showed high potency, having MIC value not more than 0.70 µg/mL on comparing to the standard drugs quinine (MIC = 0.270 µg/mL) and chloroquine (MIC = 0.02 µg/mL) [96]. Various indole-based piperidine derivatives were prepared, and *in-vitro* studies were conducted in P. falciparum culture, and activity was measured in terms of EC_{50}. Lipophilicity was also calculated in terms of the partition coefficient (logP), to further assess the activity of synthesized derivatives.

Piperidinyl moiety was found to be critical for the activity. Compound (28) was obtained having selectivity for malaria parasites without drug resistance and better activity (EC_{50} ~ 3 µM, cLogP = 2.42 and MW = 305) as compared to most of the standard drugs such as chloroquine, atovaquone, amodiaquine and artesunate with EC_{50} value of 285 ± 58 µM, 0.35 ± 0.14 µM, 12.30 ± 4.21 µM and 1.97 ± 0.43 µM, respectively [97]. Melatonin is an indole-derived hormone secreted by the pineal gland. It is involved in various signaling pathways involving the Plasmodium cell cycle and a major role in the replication of Plasmodium. Inhibition of this hormone can be used to inhibit the growth of Plasmodium. Keeping this in mind, Schuck and coworkers have investigated various melatonin-based indole derivatives.

They synthesized derivatives having an inhibitory effect on the cell cycle of *P. falciparum*. The *in-vitro* studies were conducted in *P. falciparum* culture, and a flow cytometer was used for activity calculation. SAR studies explained that carbo-xamide at the C-3 position of indole was decisive for the activity. Compounds (29) (IC_{50} = 2.93 µM) exhibited maximum antimalarial activity. Alkyl and aryl substitution with carboxamide at the C-3 and methoxy group at the C-5 gave maximum potency [98]. Amongst the entire major heterocyclic nucleus, quinoline derivatives are the well known antimalarial agents acting through the inhibition of DNA synthesis of microorganism [99].

Assuming it to be a wonderful idea to combine this moiety with indole. Teguh *et al.*, 2013 to synthesized various quinoline-indole conjugates and tested against *P. falciparum* using K1 strain. SAR studies concluded that the amino group and alkyl-substituted amino group were favorable for the activity. Compound (30) (IC_{50} < 0.4 ± 0.2 µg/mL) demonstrated promising antimalarial activity [100]. Meridianin G, is an indole alkaloid obtained from marine invertebrate Aplidium meridianum. It is found to be the inhibitor of cyclin-dependent protein kinase, involved in the progression of malaria. Based on this fact, Bharate

et al., 2013 reported various meridianin G-based indole derivatives and evaluated against chloroquine-sensitive and resistant clones of *P. falciparum* through plasmodial LDH (lactate dehydrogenase) activity. Compound, (31) (IC_{50} < 4.01 µM) was found to be most effective as compared to standard drug artemisin (IC_{50} < 0.09 µM) and chloroquine (IC_{50} < 0.72 µM) [101]. Santos *et al.*, 2015, reported, in their project a class of 3-piperidin-4-yl-1H-indoles containing on a hit with an HTS whole-cells evaluates against Plasmodium falciparum and assess for anti-parasitic evaluation. SAR report was done which exhibited that 3-piperidin-4-yl-1H-indole is prejudiced to new N-piperidinyl modifications. New compounds (32) (4-(1H-indol-3-yl) piperidin-1-yl) (pyridin-3-yl) methanone showed prospective anti-malarial activity [102]. Schuck *et al.*, 2014 have reported two series of melatonin analogues compounds which were evaluated in *P. falciparum* culture and their anti-malarial potencies were studies new technique flow cytometry. Among the melatonin analogue, derivative (33) was able to inhibit the *P. falciparum* development and thereby found be active **Fig. 4** [103].

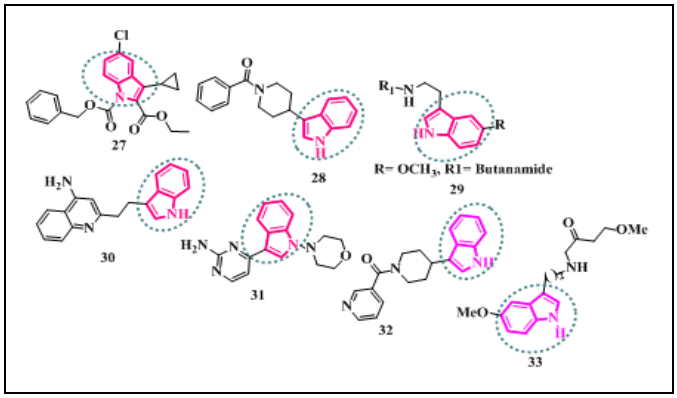

FIG. 4: ANTI-MALARIAL ACTIVITY OF INDOLE DERIVATIVES

Antiviral Activity: A viral infection spreads by pathogenic viruses and infectious virus particles when enters inside the body. Various antiviral drugs are available in the market against HIV, Herpes viruses, hepatitis B and C viruses. Among all the infections, viral infection is the fastest spreading, creating about 60% illness in developed countries [104]. Due to the fast replication rate, it is required to design safe and efficacious antiviral drugs. Researchers are working to design novel antiviral drugs with a wide range of activities [105]. Scuotto *et al.*, 2016 designed a new class of novel multi-target indole-3-carboxylate analogues as antiviral activity. All the new synthesized derivatives were evaluated against Chikungunya virus in vero cell culture through a CPE reduction method. SAR studies reported that the hydroxyl group at the 5th position is found to be most favorable. Compounds, (34) was active compounds (EC_{50} = 6.5 ± 1) which is 10-times more active as compared to the reference drug arbidol. Further docking studies were also performed by using the crystal structure of CHIKV glycoprotein complex. Maximum derivatives inserted into the lateral sites of the active site indole got deeply inserted into the cavity and thiophenol ring occupy solvent-exposed portions showing maximum bonding. The antiviral effect is due to the inhibition of an earlier viral life cycle [106].

Spiroindolines, like indole, has the property to inhibit the viral protein synthesis, nucleic acid synthesis and receptor recognition. With these diversified mechanisms, spiroindoline and indole combination can be the best strategy to control viral action [107]. Based on these facts, Chen *et al.*, 2017, designed synthesized and evaluated fused indoles and spiroindolines. All the synthesized compounds were further evaluated by in-*vivo* and *in-vitro* method against Tobacco mosaic virus. SAR studies concluded that in the case of fused indole derivatives, phenylsulfonyl, 4-tert-butylsulphonyl, 4-chlorophenylsulphonyl groups are favorable for the activity whereas C ring is crucial for the activity. In the case of spiroindolines, electron-withdrawing groups such as -Cl, -CN and -CF_3 on quinolone phenyl ring were vital for activity.

Derivatives (35) (% inhibition = 56 ± 2%) exhibited maximum potency as compared to reference drug ribavirin (% inhibition = 36 ± 1%) and harmin (% inhibition = 45 ± 1%) at the 500 µg/mL concentration [108]. Musella *et al.*, 2016 reported the synthesis of amide substituted indole derivatives and tested against human Varicella zoster virus (VZV). SAR studies concluded that substitution of biphenyl ethyl moiety and acetylation at the amino group of tryptamine is required for the activity against VZV. Compound, (36) (CC_{50} =39 µM) was found to be highly potent as compared to standard drug acyclovir (CC_{50} = 191 µM) and biuvudin (CC_{50} = 160 µM) [109]. Naphthalene derivatives are also observed against a variety of viral disease conditions. Inhibition of

viral replication is the main mechanism used by these derivatives [110]. Prompted by these, Giampieri *et al.,* 2009 fused the indole with naphthalene nucleus to form indole-naphthyl derivatives. All the synthesized derivatives were screened against a variety of viruses *i.e.,* HIV-1 (human immune-deficiency virus-1), BVDV (bovine viral diarrhea virus), YFV (yellow fever virus), CVB-2 (coxsackievirus B-2 strain). The presence of carboxylate, indole and naphthol were found to be imperative for the antiviral activity. Compound (37) (CC_{50} = >57 μM, SI = <5) was quite active among all the compounds and compared to the standard drugs acyclovir, mycophenolic acid, ribavirin, 6-azauridine (CC_{50} = > 100, SI = < 50) [111]. AIDS is a very dreadful disease occurring due to the infection by human immunodeficiency virus (HIV) [112].

According to 2016 Census, 36.7 million people are diagnosed with HIV worldwide [113]. Thus, the advancement of anti-HIV drugs should emphasize on the favorable structural modifications and its mechanism of action. Some novel indole derivatives as anti-HIV agents are mentioned here. In 2018, Sanna *et al.,* mentioned the synthesis of novel indole-thiourea hybrids and evaluated against HIV-1. SAR studies reported the importance of 4-bromophenyl moiety. All the compounds, (38) (EC_{50} = 8.7 ± 0.4 μM) was found to be highly potent as compared to standard drug efavirenz (EC_{50} = 0.002 ± 0.0002 μM) [114]. In 2016, Doussan *et al.,* reported synthesis and evaluation of various indole derivatives for anti-HIV activity. Compounds, (39) (EC_{50} < 0.011 μM) was found to be highly potent as compared 115.

Various indole-7-carboxamide analogue were also showed by Ravichandran *et al.,* [116]. Computational techniques were used to screen the synthesized derivatives, thereby calculated various properties to evaluate the indole-7-carboxamide analogues *i.e.,* electrostatic, steric physicochemical and hydro-phobic properties. SAR studies revealed that bulky and electronegative groups were favorable at the 3rd position of indole-7-carboxamide groups present on benzamido and pyrazine nucleus contribute hydrogen acceptance property which facilitates binding with HIV-1. Compound (40) was highly potent [116]. Ashok *et al.,* 2015, reported the synthesis and evaluation of various indole-pyrido derivatives. *In-vitro* study was conducted on HIV-1 infected cells and molecular properties were also calculated to further screen the synthesized analogues. SAR studies were conducted on the basis of substitutions present on the phenyl ring attached to piperazine, which is further attached with indole. The studies concluded that ortho and para directing substitutions on 4th position of phenyl ring lead to no anti-HIV activity. Whereas, the 2-3rd position of phenyl favors the activity. Replacement of phenyl with benzyl moiety leads to increase impotency.

The compound (41) (EC_{50} = 0.53 μM) was found to be highly potent, whereas others have moderate activity compared to reference drug zidovudine (EC_{50} = 0.002 μM).117 In the same year, trifluoromethyl-indole derivatives having improved drug resistance with anti-HIV-1 NNRTIs were reported by Jiang and coworkers. All the synthesized derivatives were screened against WT (wild-type) HIV-1 strain. SAR studies revealed that the presence of Cl or Br at C-5 improved the activity and presence of nitro at C-7 reduced the activity. Substitution of alkyl chain substituted with halogen at C-3 leads to potent compound (42) (EC_{50} < 133.33 μM) on the basis of the comparison with standard drug nevirapine (EC_{50} = 0.4 μM) and efavirenz (EC_{50} = 0.08 μM).

Further docking analysis gave the idea about the binding mode of various derivatives with HIV reverse transcriptase enzyme [118.] Ferro *et al.,* 2014 designed, synthesized and evaluated indole derivatives by performing the docking study with HIV-1integrase. Docking studies concluded that bulkier substituent on the benzyl group, *i.e.* tert-butyl, trifluoromethyl group, is favourable for the interaction with HIV-1 integrase protein. Compound, (43) (IC_{50} = 0.4 mM) was highly potent [119]. Hassam and coworkers report and assessed cylopropyl indole analogue as HIV non-nucleoside reverse transcriptase analogue. All the new derivatives were evaluated by using HIV-1 retroviral vector system. SAR studies concluded that the C-1 position of propanoic acid and amides were favourable for the activity. At the C-2 position, cyclic groups, *i.e.,* phenyl and thiophene enhance the activity and finally, at the C-3 position, Cl and Br groups are favorable. Compound (44) (IC_{50} = 0.065 μM) were highly potent on the basis

of the comparison with standard drug nevirapine (IC_{50} = 0.087 µM). Docking studies were also conducted to further evaluate the activity using HIV non-nucleoside reverse transcriptase enzyme which confirmed that compound (45) well accommodated within the active site [120].

Various indole-piperazine derivatives were also synthesized and screened using various molecular computational techniques, *i.e.,* combined docking, molecular dynamics and 3D-QSAR study. SAR studies suggested that small bulky substituents were required for the activity and also smaller substituents having balanced steric and electrostatic properties are highly desirable at 7 positions of the indole ring. However, activity reduced in the order of primary>secondary>tertiary amine. Compounds (45) (EC_{50} = 0.005 nM) were found to be highly potent, having good binding affinity with receptor [121]. In the same year, indole-7-carboxamide derivatives were synthesized by Yeung and coworkers.

All the new derivatives were assessed by cell-based assay against a pseudotype virus expressing a JRFL envelope. SAR studies concluded that 4-fluoro substitution is favourable for the activity. All the new compounds, (46) (EC_{50} = 0.29 nM) was found to be highly potent [122]. Regina *et al.*, 2012 synthesized and evaluated nitrogen-containing indole 2-carboxamide derivatives. All the synthesized derivatives were evaluated against mutant Y181C, Y188L, K103N, K101Q, IRLL98 and G190A HIV-1 strain.

SAR studies concluded that pyridine-4-yl methyl substituent is favourable for the activity. Compound (47) (EC_{50} = 2.0 ± 0.2 nM), as compared with standard drug zidovudine (EC_{50} = 2.0 ± 0.2 nM) and efavirenz (EC_{50} = 6.3 ± 3.2 nM) was found to be highly potent [123]. Regina *et al.*, 2011 reported synthesized and evaluated indole 2-carboxamide derivatives with different substitutions.

All the synthesized compounds were further evaluated against mutant L100I and K103N RT HIV-1 strains. SAR studies concluded that nitro and pyrrole substituted carboxamide is favourable for the activity. Compound (48) (EC_{50} = 1.3 ± 0.0 nM) was found to be highly potent than standards, nevirapine (EC_{50} = 19.2 ± 0.2 nM) and efavirenz (EC_{50} = 1.5 ± 0.3 nM) [124]. Tichy *et al.,* 2012 was report some new indole-2-carboxylate analogue which was evaluated for antiviral agents. Their relation with potency was done through SAR report and performed to get the pharmacological activity. Compound (49) 2-(6-chloro-4-(furan-2-yl)-9H-pyrimido [4, 5-b] indol-9-yl)-5-(hydroxymethyl) tetrahydrofuran-3, 4-diol exhibited good inhibitory activity [125].

Xue *et al.,* 2014, reported a series of new indole-2-carboxylate analog and were evaluated to determine their *in-vitro* wide spectrum antiviral potencies. SAR report was also conducted 126. Compounds tested against influenza A virus was analog (50) methyl 6-amino-1H-indole-2-carboxylate exhibiting good potent inhibitory effect **Fig. 5**.

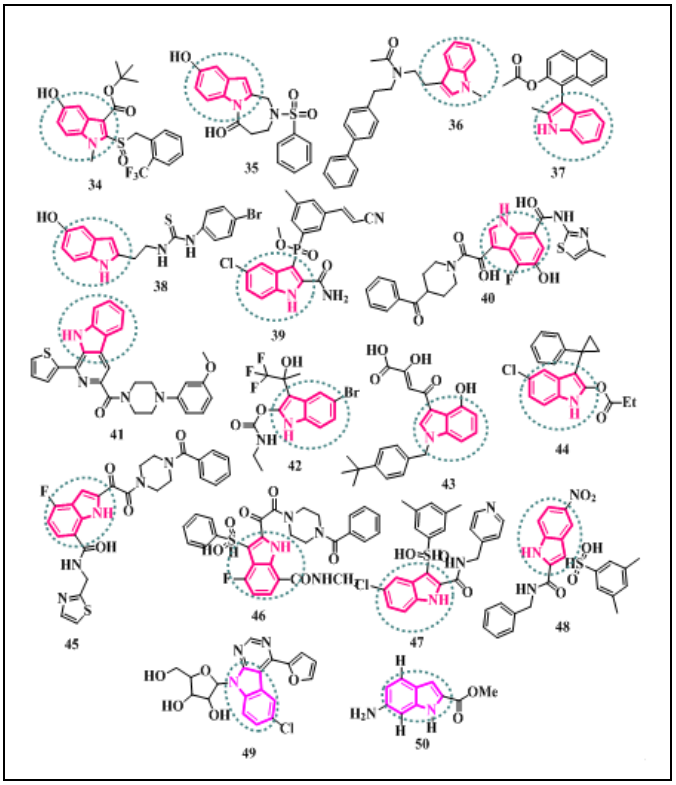

FIG. 5: ANTIVIRAL ACTIVITY OF INDOLE DERIVATIVES

Hepatitis C Virus Activity: Zhang *et al.,* 2005 reported and prepared a new series of 2-(4-sulfonamidophenyl) -indole 3-carboxamides derivatives and evaluated against the HCV genotype 1b replicon. Compound (51) 6-(difluoromethoxy)-2-(4-(1,1-dimethyl ethyl sulfonamido) phenyl)-5-fluoro-1-hexyl-1H-indole-3-carboxamide exhibit good potency **Fig. 6** [127].

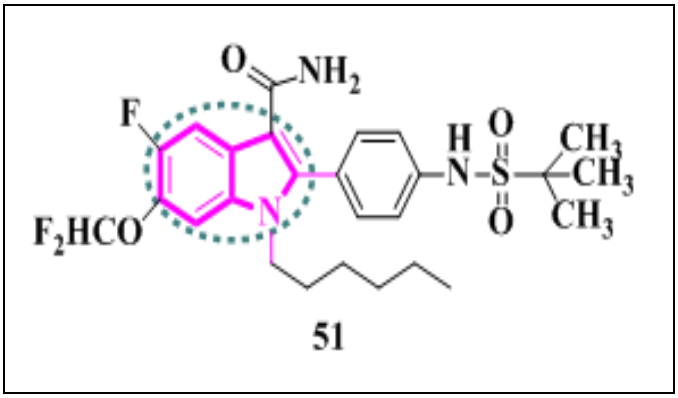

FIG. 6: HEPATITIS C VIRUS GENOTYPE ACTIVITY OF INDOLE DERIVATIVES

Anti-leishmanial Agents: Leishmaniasis is a parasitic disease spread by female sand-fly belonging to genus Leishmania, which can appear in the visceral, cutaneous, diffuse and mucocutaneous form [128]. According to the recent data by WHO, nearly 88 developing and developed countries are affected by leishmaniasis. Every year, nearly 1.5-2.0 million new cases are reported [129]. Leishmania causes a wide range of health problems, it is imperative to develop effective drugs. Recently, Porwal *et al.,* 2017 synthesized and evaluated gem-dithioacetylated indole derivatives.

All the new derivatives were evaluated through *in-vivo* study against Leishmania donovani. SAR report showed that the presence of H2S at the C-3 and p-cyanophenoxy, N-phenyl, pentyl chain at nitrogen atom and dimethyl-sulphoxide at 3rd position of indole was most important for the activity. Compound, (52) (% inhibition = 96-99 %) showed maximum activity [130]. Felix *et al.,* 2016, also reported the synthesis of thiophene-indole hybrids and evaluation against L. donovani. SAR study concluded the role of 5-cyano, 5-methyl were found to be favorable for the activity.

Compounds (53) (IC_{50} = 3.2 µg/mL, SI >124.6) was good potent with as compared to reference drug amphotericin B (IC_{50} = 0.2 µg/mL, SI >124.5) [131]. In 2014, Sharma *et al.,* reported triazino indole-quinoline hybrid analogue were prepared and assessed. All the reported analogue were evaluated through *in-vitro* study against L. donovani. SAR studies suggested that at the nitrogen atom of indole hydrogen, methyl, ethyl, isopropyl, isobutyl, allyl and benzyl were favorable for the activity. Alkyl chain length connecting triazino indole andquinoline should contain a maximum of two carbons. Compounds, (54) (IC_{50} = 0.36 µM) were found to be highly potent as compared with standard drug miltefosine (IC_{50} = 8.10 µM) [132]. The anti-leishmanial activity of 3, 3-diindolylmethane was investigated by Bharat and coworkers. All the synthesized compounds were screened through *in-vitro* study against L. donovani. Pharmacophore model was also developed for diindolyl methane derivatives (55) showed excellent statistical parameters.

SAR studies concluded that 4-nitroaryl substitution was favorable for the activity. Compound (56) (IC_{50} < 8.37 µM) was found to be highly potent as compared with pentamidine (IC_{50} <8.39 µM) and amphotericin B (IC_{50} < 0.17 µM) [133]. Leishmania cysteine protease is essential for the growth, differentiation, and multiplication of parasite. Azetidine derivatives are one of the prominent inhibitors of this enzyme. Based on this fact, Singh *et al.,* synthesized and evaluated azetidine-indole derivatives and screened them through an in-*vitro* study using Leishmania major promastigotes.

SAR studies concluded that methyl substitution to the imine attached to the indole enhanced the activity. Conversion of imine intoazetidin-2-one resulted in a drastic increase in the activity. Compound (57) (0.56 ± 0.06 µg/mL) was found to be highly potent as compared with standard drug amphotericin B amongst them (0.56 ± 0.001 µg/mL) **Fig. 7** [134].

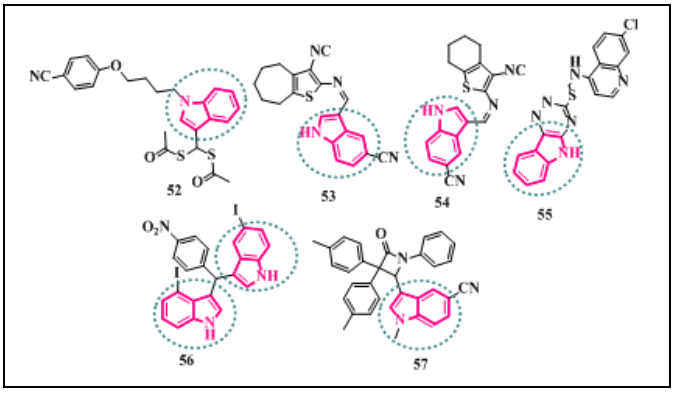

FIG. 7: ANTI-LEISHMANIAL ACTIVITY OF INDOLE DERIVATIVES

Anti-fungal Activity: Recently, indole subunits have gained wide-spread concern due to their remarkable role as antifungal agents. In this perspective, Zhang *et al.,* 2012 have reported

noticeable work in the area of antifungal drug development. In 2012, analogues of pimpirinine, an indole alkaloid obtained from streptomyces species, were synthesized and bioassay was conducted on Pythium dissimile, Alternaria solani, Botyyotinia fuckeliana and Gibberellazeae by Zhang *et al.*, 2012. SAR study concluded that bromo and acetyl chloride substitutions were favorable for the activity. All of them were found to be highly potent [135]. Furthermore, Zhang *et al.*, 2013 synthesized and studied the oxadiazole derivatives of indole.

All the newly prepared compounds were tested against Pythium dissimile, Septoriatritici and Uromyces viciaefabae and compared with pimpirine alkaloid. SAR study concluded that halogen substitution is favorable for the activity. Compounds (58) were found to be potent [136]. Motivated by the promising results, this study was further extended with streptochlor in an indole alkaloid obtained from marine actinomycetes. Synthesized streptochlor in analogs were evaluated against Pythium dissimile, Alternaria-solani, Uromycesviciaefabae, Gibberel-lazeae, Alternariasolani, Phyto-phthorainfestans, Zymo-septoriatritici and A. Solani.

The introduction of chloro and bromo substitution at the 4th position of oxazole ring increases the activity. Compounds (59) were found to be highly potent analogues showing 81-100% control of the disease [137]. Similarly, novel derivatives of streptochlorin were synthesized with more active heterocycles having improved antifungal activity. All analogues were studied against Pythium dissimile, Alternariasolani, Uromycesviciae-fabae, Gibberellazeae, Alternariasolani, Phytophth-orainfestans, Zymoseptoriatritici. The compound was found to be highly potent on Alternaria solani.

SAR study marked the importance of indole moiety in streptochlorin. Due to the high potency of streptochlorin as an antibiotic, extensive study on the derivatization of streptochlorin was also conducted by other researchers. Recently, Jia *et al.*, 2018 also conducted the study on streptochlorin, natural antifungal constituents extracted from marine streptomyces species. Evaluation of analogues was conducted on *Pythium dissimile*, Alternariasolani, Gibberellazeae, *Botrytis cinerea*, Rhizoctorziasolani, Alternaria blotch, and Collecteri chumcapsica. Chloro and bromo substitution were favorable for the activity. Compounds (60) were establishing highly potent [138-139]. 1H-Indole-4, 7-diones were reported and evaluated for *in-vitro* antifungal activity. The analogue 1Hindole-4, 7-diones generally exhibit good antifungal activity against Candida krusei, Cryptococcus neoformans, and Aspergillus niger. The results commented that 1H-indole-4, 7-diones would be better potent antifungal activity.

The modification of lead compounds that were recognized as highly effective in the back report could significantly improve the pharmacological activity of the resulting analog. While targeting lanosterol 14-α demethylase, the molecular modeling technique persuaded that the addition of the phenyl moiety of new derivatives deep into the hydrophobic pocket of the enzyme might raise the enzyme-ligand linked and hence get better the anti-fungal outline of the new molecules. As a result, the recently designed new compounds (61) were prepared and tested for their anti-microbial activity and these compounds were found to display considerably good activity than the previous compounds.

Some of the analogues in this class showed MIC90 16 μg mL^{-1} and 32 μg mL^{-1} against Candida albicans and Aspergillus Niger, respectively, at 312 μg mL^{-1} for analogue [140]. A class of new indole [1, 2-c]-1, 2, 4-benzotriazine analogue was prepared by a Sandmeyer reaction in the presence of tert-butylnitrite (t-BuONO). As a result of hymexazol, a commercial agricultural fungicide, at the concentration of 50 mg/mL, two indoles [1, 2-c]-1,2,4-benzotriazines, (62) showed the more promising lead and prominent antifungal efficacy in *in-vitro* against five phytopathogenic fungi.

It clearly confirmed that the beginning of appropriate substituent on the indolyl moiety of indole [1,2-c]-1,2,4-benzotriazine (63) would lead to the large potent analogues [141]. On the basis of the principle of combination of new structural rings, a bespoke and proficient synthetic technique for three class of new indole-based 1, 3, 4-oxadiazoles (64) was explained. Biological assay conducted at Syngenta exhibited that more than a few of the prepared compounds exhibit good antifungal activity than pimprinine, the natural compounds

which stimulated this synthesis. Two main structural modifications were found to make wider the spectrum of biological activity in most belongings [142]. 2-(Indole-3-yl)-thiochroman-4-ones (65) were prepared *via* ionic liquid and evaluated for *in-vitro* antifungal profile. The contribution of ionic liquid to Michael addition reaction is noteworthy. Structures of whole compounds are optimized by 1H NMR, 13C NMR and HRMS. Most of this analogue gives better antifungal profile than fluconazole drugs. The output of 2-(indole-3-yl) -thiochroman-4-ones would be proficient antifungal activity [143]. Song *et al.*, 2015 reported and prepared 2-(Indole-3-yl)-thiochroman-4-ones and assessed them for *in-vitro* antifungal profile.

The analog showed the best activity than fluconazole. Compound (66) 6-chloro-2-(5- chloro-1H-indol -3-yl) thiochroman-4-one exhibit potent antifungal activity [144]. Pooja *et al.*, 2014 reported the synthesis of amino acid appended indoles moiety and evaluated against *Candida albicans* with their MIC80 in µg/ml assortment. Compound (68) (2R)-2-(2-(1-(4- ((3-(2-((S)-1-carboxy-2- (1H-indol-3-yl) ethylamino)-2-oxoacetyl)-2, 7a-dihydro- 1H-indol-1-yl) methyl) benzyl)-1H -indol-3-yl)-2-oxoacetamido) -3-(3a, 7a-dihydro-1H -indol-3-yl) propanoic acid exhibit best activity [145].

Zhang *et al.*, 2013, report class of new indole-based 1, 3, 4-oxadiazolesand the bioassays of majority of these particular analogue showed higher antifungal profile than pimprinine. Analogue (69) 2-(1H-indol-3-yl)-5- (trifluoromethyl)-2, b-dihydro-1, 3, 4-oxadiazole the most active on the pharmacologic assays **Fig. 8** [146].

A comprehensive mechanistic view of anti-microbial action metallic nanoparticles as drug delivery has been summarized and reviewed by few authors wherein they covered several microbial pathogens including fungal strains [147].

FUTURE PERSPECTIVE: Indole compounds are possessing various pharmacological and chemotherapeutic effects. There are several novel compounds to be reported for several activities. However, the challenging task for a scientist is to provide safety concern for any drug. Despite having potential antimicrobial and physiological action, clinical efficacy and regulatory importance are limited. Secondly, new developed indole compound are commonly hydrophobic which is a challenge for a formulation scientist working in formulation based project. Considering in vivo performance, it is prerequisite to collect enough preclinical pharmacokinetic data in a suitable animal model. These data become a basis for clinical trial of newly developed molecule. In current scenario, covid-19 pandemic attack challenged global healthcare system which provided a new window of understanding for mechanistic pathogenesis of virus in human body. Therefore, there is need to translate laboratory data to clinical bed using sound preclinical data and clinical history of indole drugs. Moreover, recent advances in nanotechnology played a versatile role to improve clinical efficacy and patient compliance. Herbal drugs are new option for the formulation scientist owing to safety aspects and wonderful benefits such as taxol, doxorubicin, amphotericin B, *etc*.

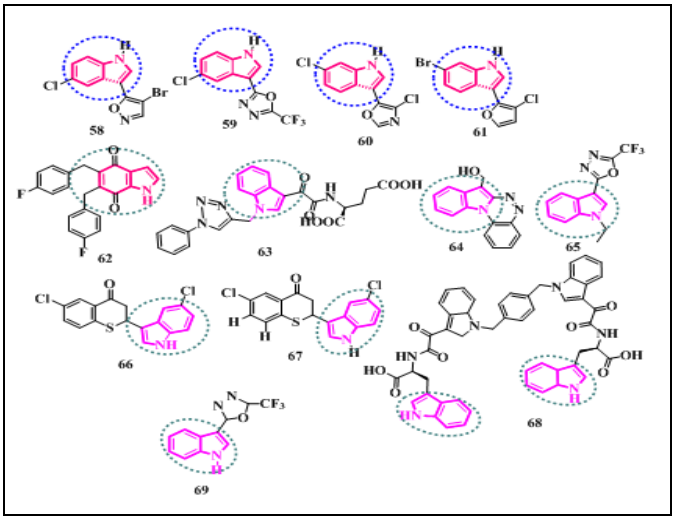

FIG. 8: ANTI-FUNGAL ACTIVITY OF INDOLE DERIVATIVES

CONCLUSION: Several drugs are available possessing the indole nucleus and are involved in the treatment of various diseased conditions varying from acute to the chronic state. This analog can be traced in many commercially available marketed drugs approved by the US FDA for therapeutic purposes. A number of drugs bearing indole nucleus obtained from natural origin and synthetic processes are also under clinical trial. Moreover, researchers and chemists are still working together on indole containing novel

compounds intended for several ailments diseased conditions, including infection and cancer.

However, minimum side effects and improving the biological activity still remained the major challenge. Data obtained from the extensive literature survey concluded that indole is a versatile nucleus touching almost all the disease conditions. A lot of intensive research needs to be carried out, looking at the potential of indole with other chemical entities. It is important to know that various potential indole derivatives need to be confirmed for its pharmacodynamics profile using suitable animal models in preclinical data. There is a scarcity of preclinical and clinical data of newly synthesized indole derivative with anticipated diverse therapeutic activity and potent antimicrobial efficacy.

ACKNOWLEDGEMENT: Authors would like to thank the Head, School of Pharmacy, Glocal University, India, for valuable scientific suggestions in writing the manuscript.

CONFLICTS OF INTEREST: The authors confirm that this article content has no conflicts of interest.

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How to cite this article:
Hussain K, Alam MJ, Hussain A and Siddique NA: Therapeutic significance of indole scaffold in medicinal chemistry. Int J Pharm Sci & Res 2020; 11(11): 5441-60. doi: 10.13040/IJPSR.0975-8232.11(11).5441-60.