A Bird’s Eye View on Pharmacotherapeutic Progress of Indolizine-based Compounds in Context to Modern Scenario

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ABSTRACT

Introduction: Indolizine (INDO) is a bicyclic heteroaromatic compound containing two fused rings (10 pi-electron system); pyridine and pyrrole via bridging N-atom at the centre of both the rings. This scaffold exists very rarely in nature and is an isomeric form of indole. It is analogous of indole (isoelectrically resembles indole system) which has marked potency in the biological activity. The scaffold is also related to the heterocyclic compound purine which is the base of cellular organisms. The structure of INDO is found in many natural products and is important in the pharmaceutical area because of prominent biological properties.

Aims: Highlighting the recent pharmacotherapeutic progress of indolizine-based compounds.

Methodology: In the preparation of this review article, a comprehensive scrutiny of the published literature in diverse pharmaceutical and medical databases such as Google Scholar, PubMed, etc. was successfully conducted and classified accordingly.

Results: The derivatives of INDO have various applications in drug design, biological area, and pharmaceutical research. INDO is a pharmacological active moiety and broadly displays biological activities such as anti-microbial, hypoglycemic, anti-inflammatory, analgesic, anti-oxidant, anti-depressant, anti-cancer activities, etc. The substituents on the INDO nucleus ring exhibit a wide range of biological activities such as anti-cancer, anti-bacterial, anti-fungal, anti-tubercular, anti-histamine, CNS-depressant activity, etc.

Conclusion: This imperative review article broadly highlighted the summary of the diverse pharmacotherapeutic potentials of INDO. This review will be a true inspiration for the medicinal chemists and pharmacologists in designing and screening low-molecular-weight inhibitors of the INDO scaffold.

Key Words: Indolizine, Derivatives, Pharmacology, Therapeutics, Targets, Inhibitors

INTRODUCTION

Indolizine (INDO) is a bicyclic heteroaromatic compound containing two fused rings (10 pi-electron system); pyridine and pyrrole via bridging N-atom at the centre of both the rings (Figure 1). This scaffold exists very rarely in nature and is an isomeric form of indole.¹ It is analogous of indole (isoelectrically resembles indole system) which has marked potency in the biological activity.² The scaffold is also related to the heterocyclic compound purine which is the base of cellular organisms.³ In this structure, various modifications, observations, and investigations have been reported over time.

Figure 1: Structure of Indolizine.

INDO is a pharmacological active moiety and broadly displays biological activities such as anti-microbial⁴, hypoglycemic⁵, anti-inflammatory⁶, analgesic⁷, anti-oxidant⁸, anti-depressant⁹, anti-cancer activities (Figure 2).¹⁰,¹¹ The structure of the INDO is found in many natural products and
is important in the pharmaceutical area because of prominent biological properties. The derivatives of INDO have various applications in drug design, biological area, and pharmaceutical research. Recently, the derivatization of INDO has been a core area of research due to the presence of the heterocyclic structure in several alkaloids extracted from neotropical frogs. Although, some methods have been published such as the racemic form of INDO derivatives, yet limited literature of enantiomeric selective has been reported.  

**Anti-tubercular activity**  
Tuberculosis is one of the dangerous respiratory diseases caused preliminary by *Mycobacterium tuberculosis* and is one of the primary reasons for both disability and death. According to the World Health Organization (WHO), more than 95% of people death is reported in a low and middle-income country. In addition to it, 0.4 million people expired from tuberculosis who are suffering from HIV infections. From the data, it was evidenced that more than 500 thousand people developed resistance against multi-drug and rifampicin drug therapy which required the need for the new anti-TB drugs with better pharmacokinetic attributes. INDO derivatives have been evaluated through in vitro assay for anti-TB properties against H37Rv and multidrug resistance strain. Gundersen et al. synthesized a series of 1-substituted INDO analogues and screened for the mycobacterial inhibitory activity where these compounds demonstrated effective minimum inhibitory activity (MIC, it is the minimal concentration at which the drug substance demonstrates no noticeable microbial growth over the Petri dish) at concentration 6.25 μg/mL.  

**Anti-microbial activity**  
Srikanth et al. synthesized a series of 1-carboxyhydrazide INDO derivatives and screened against *Staphylococcus aureus, Escherichia coli*, and *P. aeruginosa*. The anti-bacterial activity (*Bacillus subtilis, S. aureus, S. faecalis, M. luteus*, and *E. coli*) of the new series of carbonitrile INDO derivative was screened by Hazra et al.  

**Anti-fungal activity**  
The frequency of fungal diseases has augmented significantly in the past 50 years. Fungal diseases have marked themselves differently including mycoses in the skin, hair, nails, but also as systemic mycoses. The last reason, systemic mycoses, remains the major medical issue due to amplification in the immunocompromised patient population. One of the most common fungal infections is candidiasis, caused primarily by *Candida albicans*, a diploid fungus that grows both as yeast and filamentous cells. This fungus can also inflate resistance to anti-mycotic drugs that already subsist in the market, which necessitates a constant search for new drugs and treatments. A newly synthesized series of 3-substituted INDO-1-carbonitrile derivatives have been screened for their antifungal activity and recently been recognized as phosphatase inhibitor.  

**Anti-cancer activity**  
Cancer is constantly rising health risk and mortality rate. About, 25% of patients show a familial history of the disease which causes responsible factors like genes and environment. INDO nucleus has been reported to exhibit potential anti-cancer activity. Recently, novel heterocyclic indozolyl glyoxylamide derivatives have been synthesized and screened against MDR cell lines of cancer where these compounds were found to be active. The researchers have reported derivatives which were effective as anti-cancer through the destabilization of microtubules in the cancer cell. The researchers also studied that these derivatives presented marked effectiveness against multidrug resistance (MDR) cell lines without any neurotoxicity.  

**Anti-histamine and Central Nervous System (CNS) depressant activities**  
Histamine exhibits allergic and hypersensitivity reactions by the action of antigen and antibodies. Depression is referred to an imbalance between neurotransmitters which leads to psychosis and ultimately death. Approximately, 5% of the worldwide populations are suffered from these conditions which emerged the development of newer drug therapy. Recently, synthesized alkyl INDO derivatives have been reported which expressed both anti-depressant and anti-histaminic activities.
**Cellular Apoptosis**

INDO is present in various natural products such as homocrepidine-A\(^48\), tashiromine\(^49\), swainsonine\(^50\), Pandalisines-A and Pandalisines-B\(^51\), Flueggedine\(^52\), etc. which expresses multifarious biological activities such as anti-herpes virus\(^53\), cyclooxygenase and lipoxygenase inhibitors\(^54\), anti-tuberculosis\(^55\), and acetylcholine receptor agonist.\(^56\) p53, a well-known component in apoptosis-inducer and tumor suppressor has been a bird’s eye for modern-day researchers.\(^57\)\(^58\) A recent study indicated that the tumor suppressor (p53) in the C3 cell induces apoptosis with different genotypic profiles like p53HepG2, p53 null Hep3B, and mutant p53 Huh-7.\(^39\) It was initiate that C3 presented a marked anti-proliferation of HepG2 cells as compared with other cell lines and activation of p53 is relate with the amplify of ROS production.\(^60\)\(^61\)

It was found that carboxylated derivatives of INDO have been markedly effective towards the induction of apoptosis through the mitochondria p53 pathway in HepG2 cell.\(^62\)\(^66\)

**Anti-angogenesis effect**

During the last decades, the investigation was carried out for decorated polyfunctional scaffold with fluorescent INDO derivatives bearing various orthogonal groups such as amines, esters, oximes, alkynes, etc. with the anti-angiogenic drug COB223 (ERK1/2 inhibitor) that was structurally similar to the INDO scaffold. This scaffold showed binding with the ribonucleic acid (RNA) protein which effectively inhibited the process of angiogenesis.\(^67\)\(^68\)

**CONCLUSION**

This imperative review article broadly highlighted the summary of the diverse pharmacotherapeutic potentials (hypoglycemic, anti-inflammatory, analgesic, anti-oxidant, anti-depressant, anti-cancer, anti-bacterial, anti-fungal, anti-tubercular, anti-histamine, etc.) of numerous Indolizine derivatives. This interesting reviewed literature content will be a true inspiration for the modern-day medicinal chemists and motivated pharmacologists in rationally designing and in vivo / in vitro screening of low-molecular-weight inhibitors bearing Indolizine scaffold. The comprehensive study opened new avenues of research and application perspectives in identifying the potential leads.

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**Conflict of Interest**

Authors declare no conflict of interest regarding the publication of this article.

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**Authors’ Contribution**

KRD: Physically authored the whole manuscript

PK: Complete literature survey performed

DKM: Made Figures, Wrote Structured Abstract, Drawn Graphical Abstract, Set References

UNM: Final reviewing of this manuscript, provided suggestions, and corrected few errors

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