Natural Resources for Human Health

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Review

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Received 27 March 2024
Revised 02 May 2024
Accepted 19 May 2024
Available online 23 June 2024

Edited by Ricardo Diego de Albuquerque

KEYWORDS:
Indole derivatives
Synthesis
Phytochemicals
Pharmacological activities
Inflammation and Anticancer activity

Natr Resour Human Health 2024; 4 (3): 308-317
https://doi.org/10.53365/nrfhh/188891
eISSN: 2583-1194

Phytochemical and Pharmacological Intervention of Indole and their Derivatives: A Comprehensive Review

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ABSTRACT: Indole and its derivatives have garnered significant attention in recent years due to their diverse phytochemical compositions and pharmacological properties. This comprehensive review explores the phytochemical diversity and pharmacological interventions associated with indole derivatives, encompassing a wide array of medicinal plants and their bioactive compounds. Highlighting the versatility of these compounds, we discuss their roles in traditional medicine systems, as well as their potential applications in modern drug discovery and development. The review covers the structural diversity of indole derivatives and their mechanisms of action in various biological pathways, including anticancer, antimicrobial, anti-inflammatory, and neuroprotective activities. Additionally, we delve into the potential synergistic effects of indole derivatives in combination therapies and the challenges associated with their utilization, such as bioavailability and toxicity concerns. Overall, this review provides valuable insights into the current understanding of indole-derived compounds and their promising avenues for future research and therapeutic applications.

1. INTRODUCTION

Indole and its derivatives constitute a diverse group of phytochemicals found in various plant species. These compounds have garnered significant attention due to their wide-ranging pharmacological activities, including anticancer, antimicrobial, anti-inflammatory, and antioxidant properties. The structural versatility of indole derivatives enables them to interact with diverse molecular targets within biological systems, making them promising candidates for drug development. This comprehensive review aims to explore the phytochemical diversity of indole derivatives, their pharmacological interventions, and the underlying mechanisms of action, thereby providing insights into their potential therapeutic applications. Indole derivatives are a class of organic compounds containing the indole ring structure, which consists of a benzene ring fused to a pyrrole ring. These derivatives are widely distributed in nature and play a crucial role in various biological processes. In the context of herbal plants, indole derivatives are often associated with secondary metabolites that contribute to the plant's defense mechanisms, growth regulation, and adaptation to environmental stressors. Here, we'll explore methods of indole derivative synthesis and their biological importance in the context of herbal plants. Many herbal plants contain indole derivatives, and these compounds play a significant role in the plants' biological functions. Also it will be discussed the methods of synthesis of indole derivatives and their biological importance in herbal plants (Kornicka et al., 2021).

To date, a wide range of pyrrole ring antibiotics and phytotoxins have been discovered. These substances or their derivatives served as valuable agrochemicals and medicines that were necessary for day-to-day living. Synthesised heterocyclic chemicals also come from natural items, marine products, insects, and so on. Heterocyclic compounds are essential for sustaining life. The elements required for life include haemoglobin, purines, pyrimidenes, amino acids, carbohydrates, vitamins, alkaloids, antibiotics, and nucleic acids (DNA and RNA) (Mondal et al., 2020).

The convoluted natural response of vascular tissues to possibly harming improvements, like microbes, harmed cells, or aggravations, called inflammation. Inflammation can cause discomfort, swelling, a reddened area, and even loss of function or mobility. Arachidonic acid, a 20-carbon unsaturated fatty acid produced from membrane phospholipids, is one of the powerful mediators of inflammation. We now know the mechanism by which numerous medications can reduce inflammation thanks to the clarification of the function of

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inflammatory cytokines. IL-la, IL-ip, and TNF-a are three of these anti-inflammatory cytokines whose interactions with NSAIDs need to be studied (Bariwal et al., 2018). To create an effective treatment, it is important to understand how these cytokines can be impacted by NSAIDs as they suppress the generation of prostaglandins. The use of NSAIDs is constrained by their widespread adverse effects, particularly its propensity to raise the incidence of gastroduodenal ulcers. NSAID use and thrombotic events, notably myocardial infarction and strokes, are currently receiving a lot of attention (Kumar, 2020).

A dual inhibitor of the LOX/COX enzymatic pathways is widely regarded as a sensible strategy for the improvement of additional powerful calming prescriptions with a preferable security profile over ulcerogenic nonsteroidal anti-inflammatory drugs (NSAIDs). Rheumatoid joints have been found to have a large number of cytokines. TNF-a has distinguished itself as a key molecular target for therapy and a preeminent pro-mediator among these. In this study, it has been explored that explore the mechanisms of action of various pharmaceutical products derived from the indole type of the phytochemicals of synthesis based components used as active pharmaceutical agent or their derived products abundantly used in preventing inflammation, cancer, microbial infection, oxidative stress, etc. Furthermore, it gives an overview of the most widely used indole derivatives for acute and chronic ailments. (Karaaslan & Suzen, 2011). In this review, the comprehensive study is explored to understand the role of natural indole derivatives for treatment of Inflammation and study the biological activity of natural indole derivatives as well as survey the strategies for synthesis of various indole derivatives.

2. NATURAL INDOLE DERIVATIVES AND THEIR DERIVATIVES

2.1. Phytochemicals based indole moiety

Even during the Neanderthal era, plants had a significant role in the ancient cultures of India, China, and Egypt as a source of medicine. The discovery of cinchona in the 17th century, followed by the discovery of digitalis, morphine, and other drugs, as well as the advent of aspirin, a plant-based drug derivative, forced people to believe in the marvels of a rich variety of floral diversity in today's globe (Palmisano et al., 2010).

Plants have been the primary source of primitive drugs used to treat or lessen human illness for many millennia. Plants are now equally significant to the discovery and development of drag in the age of modern medicine engineering. A wide range of biological effects, including anti-viral, anti-inflammatory, anti-fungal, anti-oxidant, anti-cancer, anti-bacterial, and anti-tubercular, have been documented for indole, the potent basic pharmacodynamic nucleus.

Indole, a heterocyclic aromatic compound, is widely distributed in nature and serves as a structural motif for numerous phytochemicals with diverse biological activities. Found abundantly in plants, indole-derived compounds play crucial roles in plant defense mechanisms, signaling pathways, and interactions with other organisms. In this section, we delve into the diverse array of naturally occurring indole compounds, their sources, and their pharmacological significance.

Vinca rosea (*Catharanthus roseus*) produces the Vinca alkaloids vincristine and vinblastine. These are chemotherapeutic drugs for cancer that impede mitosis. The primary active component of a traditional Chinese medicine is indurabin, which inhibits glycogen synthase kinase and cyclin dependent kinase (Palmisano et al., 2010). Indole compounds are ubiquitous in the plant kingdom, exhibiting remarkable structural diversity and biological activities. They can be classified into several categories based on their biosynthetic origins and chemical structures.

These nitrogen-containing compounds are derived from the amino acid tryptophan and are found in various plant families such as Apocynaceae, Rubiaceae, and Loganiaceae. Examples include vincristine and vinblastine from Catharanthus roseus, ergot alkaloids from *Claviceps purpurea*, and yohimbine from *Pausinystalia yohimbe*. Indole glycosides are conjugates of indole moieties with sugar molecules. They are often found in cruciferous vegetables like broccoli and cabbage, as well as in medicinal plants such as *Withania somnifera*. Examples include glucobrassicin from Brassica vegetables and withanosides from *Withania somnifera*. Indole phytoalexins are secondary metabolites produced by plants in response to stress or pathogen attack. These compounds possess antimicrobial and antioxidant properties and contribute to plant defense mechanisms. Examples include camalexin from *Arabidopsis thaliana* and gramine from barley. Some essential oils contain indole derivatives, which contribute to their characteristic aroma and flavor. For example, jasmine essential oil contains indole and its derivatives, which impart a floral scent. Indole-3-acetic acid (IAA) is a naturally occurring plant hormone involved in various physiological processes such as cell elongation, root development, and fruit ripening. It is synthesized from tryptophan via the indole-3-pyruvic acid pathway.

The sources of naturally occurring indole compounds are diverse, ranging from medicinal plants and aromatic herbs to microorganisms and marine organisms. Table 1 gives a detailed table highlighting some examples of indole compounds and their natural sources.

Brassica crops like broccoli, Brussels sprouts, kale, and cabbage contain the phytochemical indole-3-carbinol, which has been linked to anticancer and cancer chemopreventive effects of vegetable consumption (Kumar, 2020). A significant metabolite of indole-3-carbinol that spontaneously forms under intragastric acid conditions and has anti-cancer properties is 3,3-diindolymethane. Three NSADDs, indomethacin, etodolac, and tenidap, have been demonstrated to have anti-inflammatory properties. Melatonin is a naturally occurring chemical that can be found in humans, animals, plants, and microorganisms. It has strong antioxidant properties.

Table 1
Resources of naturally occurring indole compounds.

S. No	Compound Name	Natural Source
1.	Vincristine	*Catharanthus roseus* (Madagascar periwinkle)
2.	Vinblastine	*Catharanthus roseus* (Madagascar periwinkle)
3.	Ergot Alkaloids	*Claviceps purpurea* (ergot fungus)
4.	Yohimbine	*Pausinystalia yohimbe* (yohimbe tree)
5.	Glucobrassicin	*Brassica vegetables* (e.g., broccoli, cabbage)
6.	Withanosides	*Withania somnifera* (ashwagandha)
7.	Camalexin	*Arabidopsis thaliana* (thale cress)
8.	Gramine	Barley (*Hordeum vulgare*)
9.	Indole Essential Oils	Jasmine, ylang-ylang, patchouli
10.	Indole-3-Acetic Acid (IAA)	Various plant species (endogenous plant hormone)

Moreover, naturally occurring indole compounds are a diverse and pharmacologically significant group of phytochemicals found in various plant sources. Their structural versatility and biological activities make them valuable targets for drug discovery and development. By exploring the sources and pharmacological properties of indole compounds, researchers can uncover novel therapeutic agents with potential applications in medicine, agriculture, and beyond. Some of the naturally occurring indole phytochemicals exhibits anti-cancer and anti-inflammatory activity are represented in the Figure 1.

2.2. Synthesis of indole derivatives

Fused indoles are a desirable target for the creation of novel pharmacological lead compounds due to their distinctive structural characteristics and wide range of biological activity. The biological activities of indole alkaloids are diverse and include cytotoxic, anticancer, antiviral, antibacterial, antiparasitic, anti-serotonin, and anti-inflammatory effects (Zhang et al., 2015). Some of the known dimeric indole alkaloids had anticancer activity and had a fused six-, seven, or eight-membered ring between two indole rings. The six-membered bis-annelated indolo [3,2-a]carbazole 3 exhibited anticancer characteristics. Ellipticine and olivacine are more instances of bioactive indole fused alkaloids. Two compounds with pyrido[4,3-b]carbazole nuclei, ellipticine and olivacine exhibit exceptional antitumor properties. The human nasopharyngeal cancer (HONE-1) and gastric adeno carcinoma (NUGC-3) cell lines were discovered to exhibit in vitro activity against the tetracyclic indoles. In vitro cytotoxic activity was demonstrated by the pyrrolo[2,3-e]indole derivative F2.6 in the PC-3(prostate) cell line (Figure 2) (Huo et al., 2022).

It was discovered that the fused indole EX-527 exhibited inhibitory effects against sirtuins (Figure 1). The class III histone deacetylases (HDACs) include the silent information regulator Sir2 and Sir2-like proteins (SIRT1–7, sirtuins). Some cancers and the ageing process have been linked to their function. The sirtuins are regarded as prospective targets for cancer therapies since they are known to be up-regulated in a variety of cancer

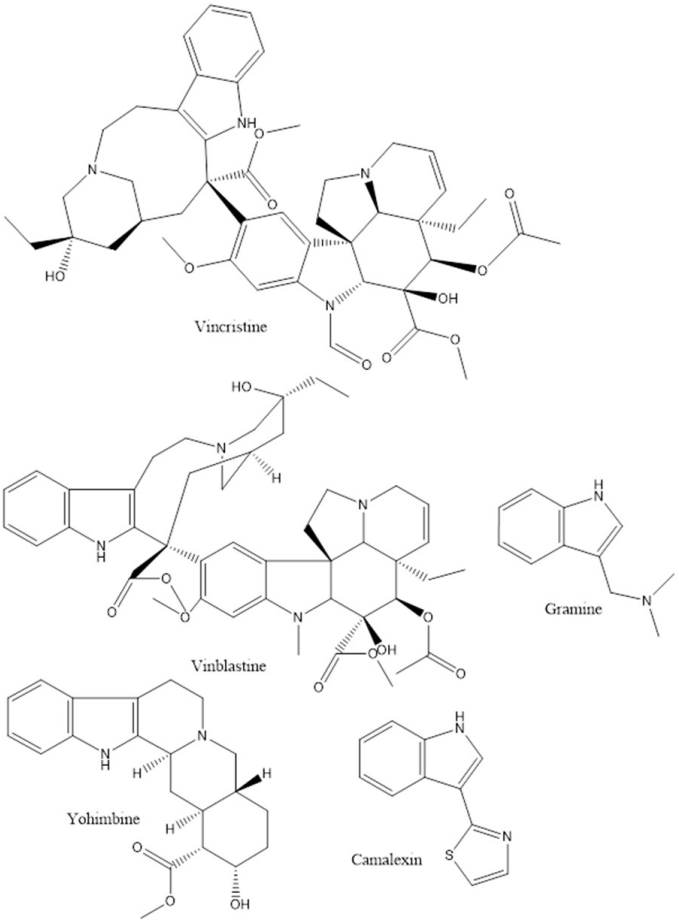

Figure 1. Some of the naturally occurring indole phytochemicals exhibits anti-cancer and anti-inflammatory activity.

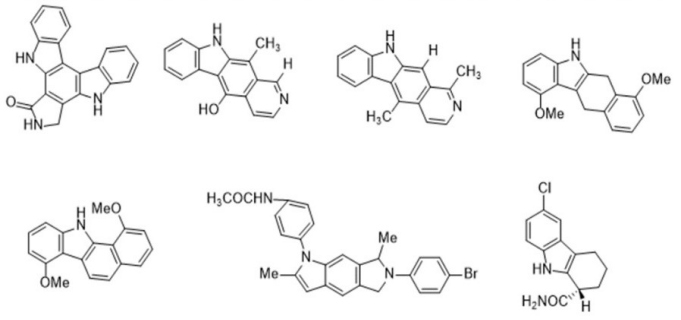

Figure 2. Biologically active fused indole.

types (Huo et al., 2022). Sirtuin inhibition promotes the reexpression of tumour suppressor genes that have been silenced, which inhibits the development of cancer cells. However, only a small number of small molecules Sir2 inhibitors have been discovered thus far. Therefore, more inhibitors are required to better understand SIRT2's biological function and investigate its potential therapeutic applications. We created our target molecule (containing indolo[2,3-b]indoles) (Figure 3) from a known inhibitor EX-527 due to our long-term interest in the development of novel sirtuin inhibitors and the significance of indoles as favoured structural motifs in medicinal chemistry.

The designing was based on simulations of the *in-silico* binding of a representative chemical, 2A, in the yeast Sir2 catalytic pocket. The analysis revealed that 2A bound deeply within the active site (docking score -5.8) and that sulfonyl oxygen interacted with the side chain amino group of ASN 35 via an H-bond (Zhang et al., 2015).

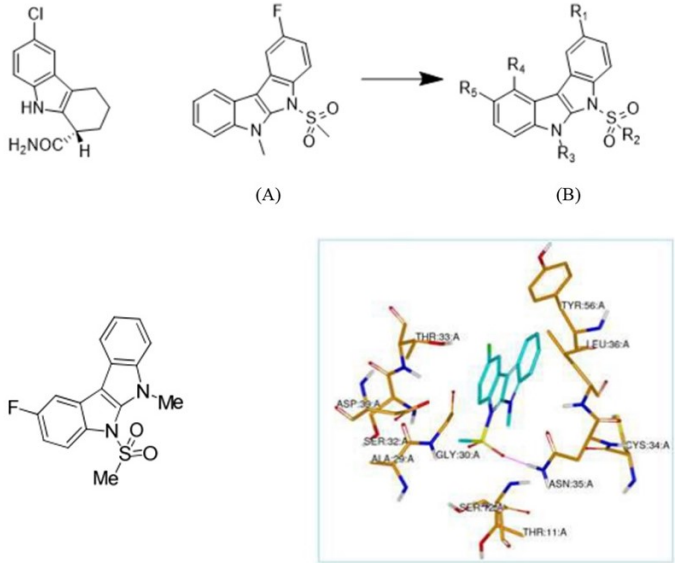

Figure 3. A/B created as new sirtuin inhibitors while figure A showed yeast Sir2 binding mode (PDB ID: 1Q1A)

2.3. Arylation Reaction

Recent years have seen a lot of interest in the intramolecular direct arylation that produces fused heteroaromatics via a radical route or transition metal-catalyzed single or double C-H bond activation16. Through C-C bond formation processes, these techniques provide rapid access to a wide range of complicated chemical structures (Islam et al., 2018). Particularly, the functionalization of hydrocarbons by transition metal catalysts has become a flexible method for forming C-C bonds on arene motifs. Among them, the intramolecular direct C-3 arylation of hetero aromatic compounds with aryl halides by C-H bond activation, catalysed by palladium, has grown in popularity as a technique for producing C-C bonds that lead to intricate polycyclic ring structures (T.P. Singh & Singh, 2017). Ma and Kozikowski stated the intramolecular cyclization/arylation of an indole switched by 2-bromo benzoyl at C-2 in 1991. This reaction took place in the occurrence of [Pd(PPh3)4] as a catalyst and KOAc as a base, and the result was a tetracyclic product in 95% of the time (Figure 4) (T.P. Singh & Singh, 2017).

Similar intramolecular cyclization of an indole substituted by 2-iodobenzylcarbamate at C-2 using 5 mol% Pd(OAc)2 and 10 mol% PPh3 with Ag2CO3 as a base was reported by Joseph and coworkers in 2007 and resulted in the production of a seven membered ring in 90–96% yield (Figure 5) (Dhiman et al., 2022).

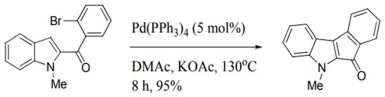

Figure 4. Synthesis of 5-methylindeno [2,1-b]indol-6(5H)-one.

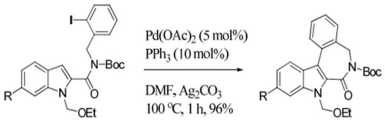

Figure 5. Synthesis of azapine-1-carboxylate

An indole with a (2-bromobenzyl)-butylamine derivative as a 2-substituent yielded the dihydrobenzoazepine fused indole in a high yield in study by Fujii in 2007 and colleagues using a similar catalyst and CsOAc as base (Figure 6) (Dhiman et al., 2022).

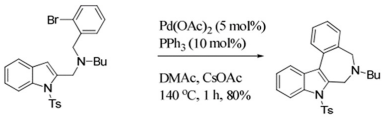

Figure 6. Synthesis ofdihydrobenzoazepine

An intramolecular cyclization of an indolizine with a 2-bromobenzoyl group substituted at C-2 to produce a tetracyclic molecule in 43% yield was reported by Matsuda and coworkers in 2003 in the presence of a base of Ag2CO3 and a catalyst of Pd(OAc)2/PPh3 (Figure 7) (Kumari & Singh, 2019).

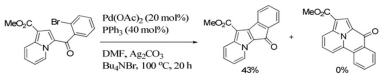

Figure 7. Synthesis ofindeno[1,2-b]indolizine

Smet and colleagues reported in 1999 that the synthesis of modified rubicenes was made possible by intramolecular cyclization of 1,5-dichloroanthracene that had two 1-methylpyrrol-2-yl substituents at positions C-9 and C-10 (Figure 8) (Kumari & Singh, 2019).

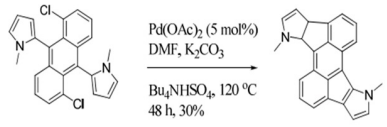

Figure 8. Synthesis of rubicenes

3. BIOLOGICAL ACTIVITY

3.1. Antimicrobial activity

Indole derivatives can possess antimicrobial properties, helping herbal plants resist bacterial, fungal, and other microbial infections. These compounds act as natural defense mechanisms, protecting the plant from pathogens antimicrobial activity, and this property has been extensively studied in various contexts. Indole itself, as well as its derivatives, has demonstrated antimicrobial effects against bacteria, fungi, and other microorganisms (Kaur et al., 2018).

Daly et al. (2011) developed a new method involving the reaction between indole and aryldiazonium salts, resulting in the synthesis of 2-aryl-3-(arylazo)indoles. These compounds exhibited significant anti-MRSA and anti-LLVRE properties. Structure-activity relationship (SAR) investigations revealed that substituting the metabolically unstable azo group with ether oxygen or thioether sulfur atoms did not diminish their activity Top of Form (Daly et al., 2011).

3.2. Antioxidant activity

Indole derivatives function as antioxidants, scavenging free radicals and reducing oxidative stress in herbal plants. This activity helps maintain the plant's cellular integrity and protects it from damage caused by environmental stressors. Antioxidants are compounds that help neutralize reactive oxygen species (ROS) and free radicals in the body, thereby protecting cells from oxidative stress and damage. Indole derivatives found in various natural sources, including herbal plants, have demonstrated antioxidant activity through different mechanisms

Furthermore, in the study conducted by Estevão et al. (2010) develop new antioxidant candidates utilizing the indole scaffold. Various derivatives of tryptophan and tryptamine, particularly prenylated indole compounds, were synthesized, and their ability to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) was investigated. The substitution pattern in the compound library included alkyl chains at positions N-1 and C-2 of the indole nucleus, such as prenyl and isopentyl chains, along with different groups at the side chain (C-3) to explore potential radical stabilization effects. The findings revealed that tryptophan, tryptamine, N-phthaloyl tryptamine, and N-prenyl tryptophan exhibited the highest activity against peroxyl radicals (ROO●), surpassing that of Trolox, the control. The scavenging activity against hypochlorous acid (HOCl) was also assessed, with tryptophan and tryptamine displaying IC_{50} values of 3.50 ± 0.4 and 6.00 ± 0.60 μM, respectively. Notably, significant activity was observed for N-prenyl tryptophan with an IC_{50} of 4.13 ± 0.17 μM and the C-2 prenylated derivative with 4.56 ± 0.48 μM. The investigation was extended to RNS, with the most promising results obtained against peroxynitrite anion (ONOO-) in the presence of $NaHCO_3$. N-alkylated tryptophan exhibited high activity with an IC_{50} of 14.0 ± 6.8 μM. These findings suggest that the tested compounds effectively scavenge both ROS and RNS, and the extent of radical stabilization depends strongly on the type and position of substituents on the indolic moiety. Additionally, the dissipation of radicals within the indolic system appears crucial for the observed antioxidant activity (Estevão et al., 2010).

3.3. Neuroprotective activity

Indole derivatives may have neuroprotective effects, potentially contributing to the plant's ability to withstand environmental stress and protect its cellular components, including nerve cells. Neuroprotection refers to the ability of certain compounds to preserve the structure and function of neurons, protecting them from damage and degeneration. While the research in this area is ongoing, some indole derivatives have shown promise in exhibiting neuroprotective effects.

In this study, the author synthesised new functionalized indole derivatives with structures supporting neuroprotective activity, utilizing L-tryptophan (TRP) as the starting material. The potential neuroprotective effects of these newly synthesized agents against acrylamide (ACR)-induced neurotoxicity were investigated in adult female rats. Several novel indole derivatives were synthesized, including indolylmethyl pyridine derivatives 9a,b, pyrimidinylindolyl propanone derivatives 12a-c, pyrazolylindolyl propanone derivatives 14a,b, and indolyl tetrazolopropanoic acid derivative 17, with their chemical structures confirmed through analytical and spectral analysis. Administration of ACR (intraperitoneal, 50 mg/kg body weight) alone led to a significant increase in brain malondialdehyde (MDA) levels and lactate dehydrogenase (LDH) activity, along with a notable decrease in brain monoamine levels and antioxidant enzyme activity. Treatment with indole derivatives 9b, 12c, 14a, and 17 (intraperitoneal, 50 mg/kg body weight) prior to ACR exposure demonstrated neuroprotective activity, with varying intensities depending on the structure of each compound. Compound 17, featuring a tetrazole ring attached to the TRP moiety, exhibited the strongest neuroprotective effect. Additionally, all tested compounds exhibited antioxidant properties, showing promising efficacy against oxidative stress induced by ACR administration (Mohareb et al., 2011).

3.4. Anticancer activity

Indole derivatives, particularly those found in plants like *Catharanthus roseus* (Madagascar periwinkle), exhibit anticancer activities. Vinca alkaloids, derived from *C. roseus*, are used

in cancer chemotherapy due to their ability to inhibit cell division. Anticancer properties, and some of these compounds are being investigated for their potential use in cancer treatment. Several indole-containing compounds derived from plants or synthesized in the laboratory have shown promising anti-cancer activities (Sachdeva et al., 2020).

Sachdeva et al. (2020) reported a research conducted by Andreani et al. (1998), on 3-indolylmethylene-2-indolinone derivatives to assess their potential as antitumor agents. These compounds, resembling 3-(2-chloro-3-indolylmethylene)-1,3-dihydroindol-2-ones, featured two indole systems separated by a heterocycle (either pyridine or piperazine) instead of a methine bridge. The antitumor activity of the synthesized compounds was evaluated using a human cell line screen. Interestingly, the pyridine derivatives (designated as compound 1) exhibited significantly higher activity compared to the piperazine derivatives (designated as compounds 2, 3, and 4). Notably, the presence of halogens, methoxy, and dimethylamino groups yielded interesting results. Compound 1, with a chlorine substituent at the 4 position of the indole (R1=Cl), demonstrated exceptional activity. However, the activity decreased when the halogen was positioned at the 5 (R2=Cl) and 6 positions (R3=Cl) of compound 1. Additionally, the compound containing the 5-methoxy-2-indolinone moiety underwent the first *in vivo* experiment using the hollow fiber assay, where it exhibited significant activity (Figure 9) (Sachdeva et al., 2020).

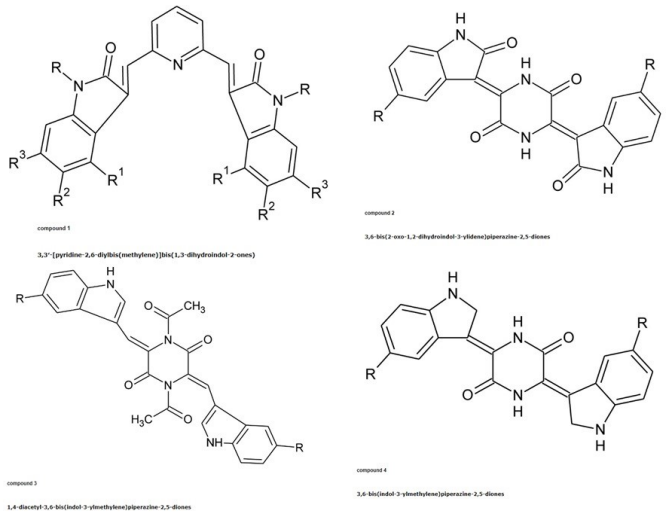

Figure 9. Reported most prominent anti-cancer agent.

3.5. Anti-inflammatory activity

The convoluted natural response of vascular tissue to harming improvements, like microbes, harmed cells, or aggravations, is known as inflammation (Latin, inflammation, to set on fire). It is an attempt by the organism to protect itself by removing the harmful stimuli and starting the tissue's healing process. Infection and inflammation are not the same thing. Even occasionally, an infection will cause inflammation. The following terms should not be used as synonyms: Exogenous pathogens are what cause infection, whereas an organism's response to a pathogen is inflammation. According to one definition, inflammation is the body's response to injury and entails a number of changes to the connective tissue and terminal vascular bed. These changes aim to get rid of the harmful substances and repair the injured tissue. All compound arbiters are known to be created during irritation, which is portrayed by redness, heat expanding, agony, and loss of capability, either directly or indirectly. Acute and chronic inflammation is the two categories for it (Bariwal et al., 2018; Mondal et al., 2020).

3.5.1 *Acute Inflammation*

Acute inflammation is a rapid and short-lived immune response to injury or infection. It involves the release of inflammatory mediators, increased blood flow, and recruitment of immune cells to the affected area. Acute inflammation is a protective mechanism aimed at eliminating pathogens and promoting tissue healing (Palmisano et al., 2010; Zang et al., 2019). The traditional signs of inflammation, such as swelling, redness, pain, and heat, as well as a temporary loss of function brought on by the influx of plasma and leukocytes into the tissue, characterise acute inflammation, a short-term process. As long as there are harmful stimuli present, it continues, and it stops when the stimuli are eliminated and broken down or blocked off by scarring (Devi et al., 2021).

Devi et al. (2021) conducted a comprehensive review on the recent advancements and mechanisms of action of indole derivatives as potential anti-cancer agents. The review elucidates multiple mechanisms through which indole derivatives exhibit promising anti-cancer properties, including cell cycle arrest, aromatase inhibition, estrogen receptor regulation, tubulin inhibition, tyrosine kinase inhibition, topoisomerase inhibition, and NFkB/PI3/Akt/mTOR pathway modulation. Their findings underscored the diverse pharmacological actions of indole derivatives, which encompass apoptosis induction, aromatase inhibition, estrogen receptor regulation, tyrosine kinase inhibition, tubulin assembly disruption, NFkB/PI3/Akt/mTOR pathway modulation, and HDAC inhibition. These derivatives demonstrated significant activity against various cancer cell lines.The study concludes that indole derivatives hold significant potential in cancer therapy due to their multifaceted mechanisms of action. Further exploration of indole derivatives could lead to advancements in cancer treatment and unveil their hidden therapeutic potential (Devi et al., 2021).

3.5.2 *Chronic inflammation*

Chronic inflammation is a prolonged immune response that persists over time, often leading to tissue damage and disease progression. It is characterized by increased levels of inflammatory markers and immune cell infiltration, contributing to various chronic conditions such as arthritis, cardiovascular diseases, and autoimmune disorders. Mononuclear immune cells (monocytes, plasma cells, lymphocytes, and macrophages)

infiltrate chronically inflamed tissue, which leads to tissue death and attempts at repair such as angiogenesis and fibrosis. Exogenous pathogens are diverse and include bacterial infection, mainly caused by Mycobacterium tuberculosis, whereas endogenous pathogens induce chronic acute inflammation (G.S. Singh & Mmatli, 2011). Although several cytokines with pro-inflammatory properties have been identified so far, only the two most significant cytokines are discussed in detail.

A polypeptide hormone known as tumour necrosis factor-a (TNF-a), TNF-a is newly synthesised by many cell types in response to activation by endotoxins, inflammatory mediators, or cytokines. Tightly controlled transcriptional and post transcriptional mechanisms control the production of TNF-a. The relative concentration, duration of cell exposure, and availability of additional mediators that can work in concert with this cytokine can all affect the overall biological action of TNF-a. A range of metabolic pathways, including the transduction of a signal at least partially regulated by guanine-nucleotide binding governing protein, are activated by the formation of the TNF-a receptor complex. Through the production of the second messenger pathway and the stimulation of adenyl cyclase phospholipases and protein kinases, it is amplified (Yu et al., 2020).

A multipurpose cytokine that influences different cell types is interleukin. Proinflammatory cytokines comprising tumour necrosis factor (TNF) and IL-lb cause a variety of target cells to produce IL-6. According to reports, the pathogenesis of myocardial damage in myocarditis and ischemic heart disease is reportedly aided by EL-6 and other pro-inflammatory cytokines (Yu et al., 2020). Recent research has focused on new aspects of BL-6 activity in myocardial damage, such as its function as an anti-inflammatory. When mice were stimulated with lipopolysaccharide, BL-6 reduced the production of EL-1 and TNF and had positive effects on mouse viral myocarditis (Suleman et al., 2021).

The cornerstones of every arthritis treatment plan include rest, physical activity, a healthy diet, and education about how to utilise your joints properly. Surgery is the only available treatment for both acute and chronic pain. However, reducing weight and improving joint use can help manage pain. COX-2 inhibitors and NSAIDs like ibuprofen and naproxen are two medications that are currently on the market that help to relieve pain. These medications minimise oedema without the need for more potent medications like cortisone and other steroids. The more recent COX-2 inhibitors are NSAID-like in their mode of action (Suleman et al., 2021).

Selective COX-2 inhibitors significantly increased the effectiveness of treatment; nevertheless, not all patients responded to it, and these medications also have a number of side effects, including gastrointestinal bleeding, myocardial infarction, and strokes. Inhibiting TNF-a has so provided RA patients with a promising new treatment option to address the issue of inflammation. Anti-TNF-a medications including adalimumab, etanercept, and infliximab have been demonstrated to not only lessen illness signs and indications but also to stop joint destruction. TNF-a inhibitors, however, have not yet demonstrated any additional beneficial benefits on heart failure in cardiac studies. Therefore, it is imperative to create TNF-a synthesis inhibitors that are either more effective or have fewer side effects than current medications (Suleman et al., 2021). Moreover, the biological activities have been systematically represented in the Figure 10.

4. FUTURE PERSPECTIVES

Indole derivatives have garnered considerable attention in the field of phytochemical and pharmacological research due to their diverse biological activities and potential therapeutic applications. A comprehensive review titled "Phytochemical and Pharmacological Intervention of Indole and their Derivatives" provides valuable insights into the current state of research and future perspectives in this area. This review encompasses various aspects, including the synthesis of indole derivatives, their bioactivities, and their potential therapeutic applications. One of the key future perspectives highlighted in this review is the exploration of novel synthetic strategies for the preparation of indole derivatives. Traditional synthetic methods have been extensively studied, but there is a growing need for the development of more efficient and environmentally friendly synthetic routes. Green chemistry principles, such as microwave-assisted synthesis, catalytic reactions, and solvent-free conditions, hold promise for the rapid and sustainable synthesis of diverse indole derivatives. Future research efforts may focus on optimizing these synthetic methodologies to streamline the production of indole-based compounds with enhanced pharmacological properties.

In addition to synthesis, the review emphasizes the importance of elucidating the structure-activity relationships (SAR) of indole derivatives. Understanding how structural modifications impact the biological activities of indole compounds is crucial for the rational design of potent therapeutics. Advanced computational techniques, such as molecular docking and quantitative structure-activity relationship (QSAR) modeling, can provide valuable insights into the SAR of indole derivatives. Integrating computational methods with experimental studies can accelerate the discovery of novel indole-based drugs with improved efficacy and selectivity.Top of Form

Although, several studies have been published on indole base components synthesis and their pharmacology, still urgency of microbiological research and the development of new, powerful antimicrobial drugs have increased due to the growing clinical significance of drug-resistant bacterial infections. Numerous studies demonstrate how overusing and misusing antibiotics causes bacteria to develop antibiotic resistance. There is a persistent need for antimicrobial drugs that can combat pathogenic microorganisms that are resistant to the existing form of treatment. Furthermore, immunocompromised people with infectious diseases, such as those with HIV infection, have a harder time treating them. Recent research demonstrates that using a suitable dosing regimen with prominently effective antimicrobial medicines not only completely exterminates

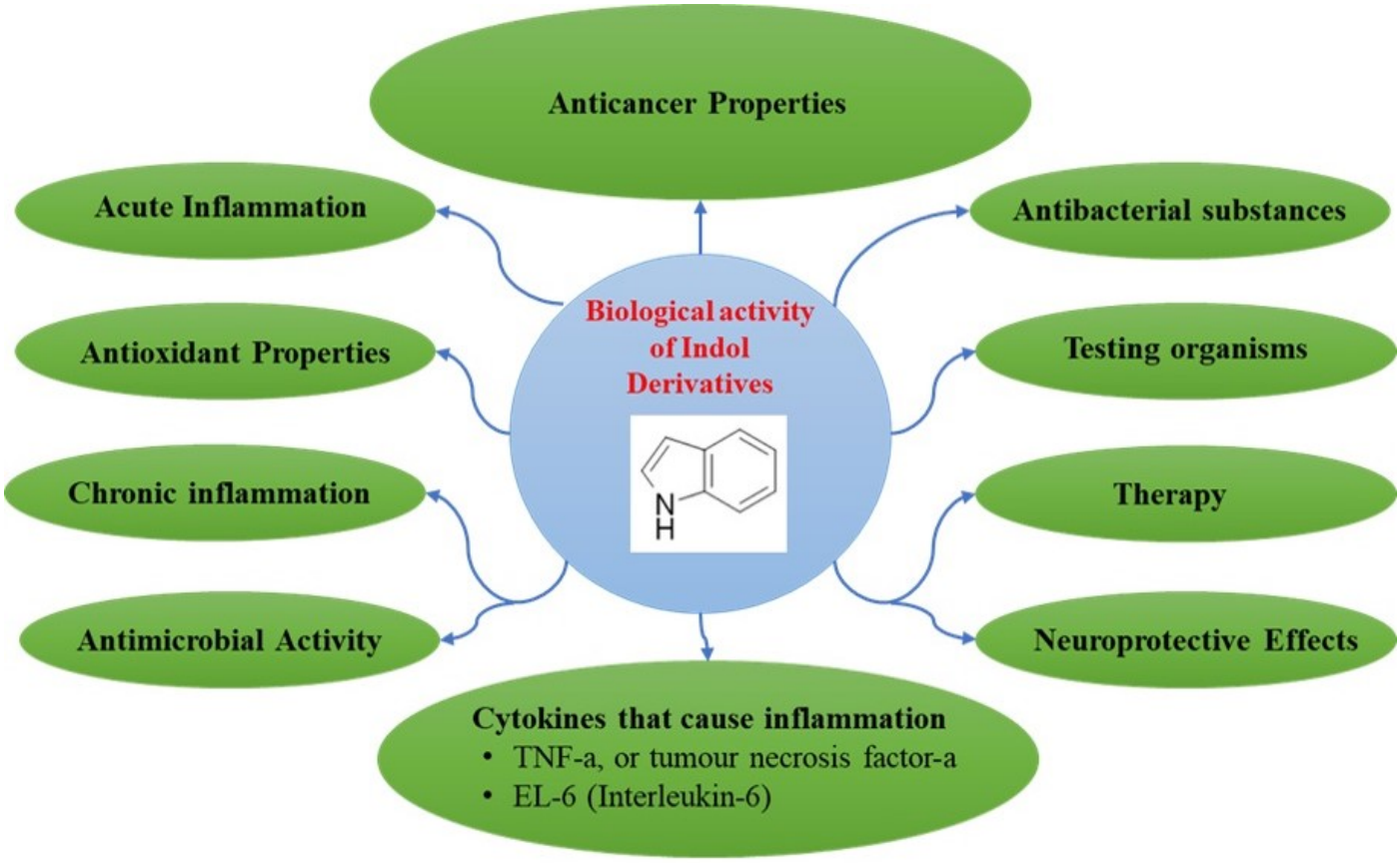

Figure 10. Biological Activity of indole Derivatives

bacterial growth but also reduces the likelihood of resistance forming. Since rational approaches to counteract the resistance can now be developed, the basis of both intrinsic and acquired resistance has made a significant contribution to the design of new entities. One of the best prospective treatments for numerous infectious diseases will be the creation of novel potential medications with a lower side effect profile than currently available drugs (Sarkar et al., 2013; Suleman et al., 2021; Yen et al., 2019).

Furthermore, the study underscores the therapeutic potential of indole derivatives in various disease conditions. Indole compounds have exhibited promising pharmacological activities, including anti-cancer, anti-inflammatory, antimicrobial, antioxidant, and neuroprotective effects. Future research directions may involve investigating the mechanisms of action underlying these bioactivities and exploring their clinical applications. Preclinical and clinical studies are essential for validating the efficacy and safety of indole-based therapeutics, ultimately paving the way for their translation into clinical practice.

Moreover, the review highlights the importance of exploring natural sources for the discovery of bioactive indole derivatives. Natural products, such as plants, marine organisms, and microorganisms, represent a rich source of structurally diverse indole compounds with potential medicinal properties. Bioassay-guided isolation and characterization of indole derivatives from natural sources can lead to the identification of novel drug leads and scaffolds for further development. Additionally, the review emphasizes the significance of phytochemical profiling and metabolomic studies in uncovering the chemical diversity of indole-containing natural products.

Another future direction identified in the review is the exploration of innovative drug delivery systems for indole derivatives. Nanotechnology-based approaches, such as nanoparticles, liposomes, and micelles, offer opportunities for targeted drug delivery, improved bioavailability, and reduced systemic toxicity of indole-based therapeutics. Incorporating indole derivatives into nanocarrier systems can enhance their pharmacokinetic profiles and therapeutic outcomes, thereby advancing their clinical utility. The review on "Phytochemical and Pharmacological Intervention of Indole and their Derivatives" provides a comprehensive overview of the current research landscape and future perspectives in this field. Continued exploration of synthetic methodologies, SAR studies, therapeutic applications, natural sources, and drug delivery systems will undoubtedly drive further advancements in indole-based drug discovery and development, ultimately benefiting patients worldwide.

5. CONCLUSION

In conclusion, the phytochemical and pharmacological interventions involving indole and its derivatives represent a vast and promising area of research with diverse applications. Indole derivatives are found abundantly in various medicinal plants, offering a wide array of bioactive compounds with significant pharmacological potential. Through comprehensive studies, researchers have elucidated the diverse pharmacological activities of indole derivatives, including anti-inflammatory, antimicrobial, anticancer, antidiabetic, and neuroprotective properties, among others. These compounds interact with various molecular targets within the body, modulating physiological pathways to exert their therapeutic effects. Additionally, indole derivatives have shown promise in drug discovery and development, serving as lead compounds for the synthesis of novel pharmaceutical agents with improved efficacy and safety profiles. Moreover, the synergy between phytochemicals present in medicinal plants containing indole derivatives further enhances their therapeutic potential through complementary or synergistic effects. The pharmacological interventions of indole and its derivatives hold immense significance in the treatment and management of various diseases, offering alternative or adjunctive therapeutic options. Furthermore, the exploration of structure-activity relationships and pharmacokinetic profiles of indole derivatives continues to drive advancements in drug design and optimization, paving the way for the development of more potent and selective therapeutic agents. However, challenges such as bioavailability, toxicity, and pharmacokinetic vaSalvatoreriability remain pertinent in harnessing the full therapeutic potential of indole derivatives. Future research efforts should focus on addressing these challenges through innovative formulation strategies, pharmacokinetic optimization, and targeted delivery systems to enhance the clinical translation of indole-based therapies. Overall, the comprehensive review underscores the importance of indole derivatives in modern pharmacotherapy and highlights the ongoing efforts to harness their full therapeutic potential for the benefit of human health.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors thanks Sunder Deep Pharmacy College, Dasna, Ghaziabad, Uttar Pradesh, 201009 for providing the facilities to conduct the studies smoothly.

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Divya Singh—Research concept and design; Rajeev Kharb—Data analysis and interpretation; Vijay Kumar—Writing the article; Satish Sharma-Critical revision. All authors read and approved the final version of the article.

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