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## Sustainable Synthesis of Indole-Based Heterocycles as Anticancer Agents via Green Nanocatalysis

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### ABSTRACT

Indole is an extremely privileged N-heterocycle which is the structural framework of many clinically active anticancer drugs. Alternate methods for the construction of indole-based heterocycles, on the other hand, are heavily dependent on toxic solvents, stoichiometric reagents, and energy-intensive reaction conditions, which are not desirable according to sustainable chemistry principles. The application of biosynthesized or engineered nanocatalytic materials obtained from renewable and environmentally friendly precursors (green nanocatalysis) is a promising approach to achieve a balance between synthetic efficiency and environmental friendliness. A recent literature survey (2023-2026) of the design, characterization and catalytic applications of various types of metal, metal-oxide and magnetically recoverable nanocatalysts for the synthesis of indole-containing heterocyclic scaffolds has been undertaken, along with a study of the anticancer activity of the resulting compounds on representative cell lines (MCF-7, HeLa, A549, MDA-MB-231 and others). Special focus is given to green chemistry indicators (atom economy, E-factor, recyclability of the catalysts), nanocatalyzed multicomponent reactions for indole derivatives, and the main molecular mechanisms (tubulin destabilization, inhibition of kinases and topoisomerases, interaction with DNA/HDAC, mitochondrial apoptosis) contributing to the cytotoxic effect of these molecules. The representative synthetic protocols of the ZnO, CuO, Fe<sub>3</sub>O<sub>4</sub>, Ag and Au nanocatalysts are compared in terms of yield, reaction time and reusability, while recent in vitro and in silico anticancer data are tabulated and

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graphically summarized. The review shows that, to date, green nanocatalysis provides a platform that is scaled-up and low-waste for anticancer drug discovery, and that standardization, toxicological profiling and scale-up to the clinic are the major challenges that are yet to be overcome..

**Keywords**— indole, green chemistry, nanocatalysis, anticancer agents, sustainable synthesis, heterocycles, biosynthesized nanoparticles

## 1. Introduction

Cancer is still one of the top causes of death in the world and the discovery of new scaffolds with greater selectivity and minimized systemic toxicity is continuing to inspire synthetic organic and medicinal chemistry research. Indole is a key structural motif in a wide range of natural products derived from the amino acid tryptophan, various neurotransmitters, and a host of United States Food and Drug Administration (FDA)-approved drugs, including several anti-cancer agents such as sunitinib, osimertinib, panobinostat, and alectinib (Rana et al., 2024). The indole nucleus is highly amenable to extensive substitution in several positions, providing medicinal chemists with an opportunity to optimize electronic, steric, and pharmacokinetic properties, while maintaining the scaffold that is well recognized by several biological targets (Almalki & Baryan, 2024).

While at the same time, the traditional methods of heterocyclic synthesis have become more and more difficult to justify environmentally. The current main routes for indole derivatives include Fischer indolization, Friedel–Crafts reaction alkylation, and others, all of which involve strong Brønsted or Lewis acids, halogenated or aprotic dipolar solvents, high temperatures, and long reaction times, leading to high amounts of chemical waste per mole of product (Kaur et al., 2023). The pharmaceutical industry in particular has been one of the least atom efficient industries of the chemical industry, with E-factors (kg waste/kg product) often ranging between 25–100, whereas in bulk chemical production, E-factors are in the single digits (Nuthi et al., 2023). To address these numbers, a comprehensive effort has been ongoing since Anastas and Warner published their 12 Principles of Green Chemistry to redesign synthetic routes so that waste is prevented from occurring in the first place, atom economy is incorporated from the beginning, safer solvents are used, and catalysis is utilized (Cravotto, 2025; Güres et al., 2023).

One of the most fruitful collaborations between green chemistry and heterocyclic chemistry is nanocatalysis. In addition to being magnetic or easily recoverable by centrifugal, nanoscale catalysts (usually 1–100 nm metal, metal-oxide, or magnetic nanoparticles) have a dramatically increased surface-area-to-volume ratio compared to bulk catalysts, resulting in faster catalytic turnover, less harsh reaction conditions, and most crucially, easy magnetic or centrifugal separation and reuse for multiple cycles (Vaishali et al., 2025). The “green nanocatalysts” that are synthesized using plant extracts, microbial biomass, or agricultural by-products (as reducing and capping agents) instead of using chemical reductants like sodium borohydride or hydrazine, close the sustainability loop at the catalyst preparation and catalyst application stages (Rocha et al., 2024; Saini et al., 2024).

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The merging of nanotechnology and heterocyclic medicinal chemistry is not due to convenience alone. Many of the modern anticancer leads in the indole series are structurally complex hybrids with two and more fused or linked pharmacophores and their synthesis is often fraught with sequential steps which add to the overall solvent load, energy requirement and purification cost of the synthesis. The benefits of such a catalytic system are far beyond environmental accounting, however: not only will the products be cheaper to move from the lab to use in field studies, but fewer purification steps mean fewer chances for epimerization, decomposition, or formation of side products; thereby achieving greater purity and reliability of the biological data ultimately gathered for a candidate compound. This interplay between environmental and pharmaceutical-development incentives has led to one of the most rapidly evolving subfields in the intersection between synthetic and medicinal chemistry in the last three years—green nanocatalysis.

In this review, the convergence of these two research streams – the synthesis of indole-based heterocycles through green, nanocatalyzed approaches, and anticancer assessment of compound libraries – are discussed. The review does not report novel experimental outcomes, but rather aims to (i) list the most important classes of nanocatalysts used for indole chemistry, (ii) compare their green chemistry properties to conventional approaches, (iii) summarize the anticancer activity and proposed mechanisms of representative indole-nanocatalyst derived hybrids, and (iv) highlight the translational gaps that remain to be bridged in the clinical development of the indole class of nanocatalysts. A review of the structural and pharmacological significance of the indole scaffold is provided in Section 2, green nanocatalysis principles and biosynthetic approaches to the preparation of nanocatalysts follows in Section 3, nanocatalyzed synthetic strategies specific to indole heterocycles are discussed in Section 4, and comparison of green chemistry performance metrics is presented in Section 5. Anticancer activity and mechanisms are covered in Section 6, recent advances covered in Section 7, challenges and future directions in Section 8, and practical recommendations in Section 9 before the paper concludes in Section 10.

## 2. Review Methodology

This review is written in a narrative-synthetic format, as is typical of a rapidly evolving interdisciplinary field consisting of synthetic organic chemistry, materials chemistry and pharmacology. The search was conducted on combinations of the keywords "indole," "green synthesis," "nanocatalyst," "nanoparticle," "anticancer" and "cytotoxicity" within a limited time frame, wherever possible, the last three years preceding the preparation of the manuscript (2023–2026), to ensure the review reflects the state of the art. The sources were selected according to their direct relevance to one or more of the three main themes of the review: (i) synthesis or characterization of nanocatalysts, (ii) synthesis of indole or indole-related nitrogen-containing heterocycles using nanocatalysts, and (iii) anticancer evaluation, either in terms of in vitro cytotoxicity or molecular docking or mechanistic study, of indole-based compounds. A few other foundational green chemistry references were also included, such as descriptions of the 12 principles of green chemistry, and quantitative green chemistry metrics, even if these examples did not pertain to indole chemistry, but rather

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synthesis of pharmaceuticals as a whole.

As with a narrative review, no formal systematic-review protocol was used (e.g. PRISMA), and the results are presented thematically, with individual source studies discussed, and specific numerical data (e.g. reported IC<sub>50</sub> values or E-factor ranges) presented descriptively. When reported concentration data were reported in different units (molar or mass concentration) they have been reproduced as published, and this limitation has been explicitly stated in the relevant table. This review provides no new experimental synthesis, characterization or biological data: all synthetic procedures, catalytic performance data and cytotoxicity data referred to herein are taken from and attributed to the primary literature cited.

### 3. Indole: Structural and Pharmacological Significance

The indole ring system is a combination of a benzene ring attached to a pyrrole ring, providing three major points of chemical diversification: the nitrogen (N1), the most nucleophilic carbon of the ring (C3), which is the orthogonally more nucleophilic and therefore the site of the more electrophilic attack, and the benzenoid ring, which is more easily susceptible to the attachment of halogen, alkoxy, and other substituents (Almalki & Baryyan, 2024). It is this aromatic stability and multi-site reactivity that makes indole an extremely versatile scaffold for drug discovery.

The chemical exploits of the scaffold commenced only after it was firmly confirmed by natural indole alkaloids such as serotonin, melatonin, and the vinca alkaloids vincristine and vinblastine, which had already proved to be pharmacologically significant. The indole nucleus is involved in the design of a number of clinically available drugs that interact with the tumor: multi-kinase inhibitors such as sunitinib and nintedanib, anaplastic lymphoma kinase inhibitors like alectinib, epidermal growth factor receptor inhibitors (EGFR) such as osimertinib, and histone deacetylase inhibitors (HDAC) as panobinostat (Rana et al., 2024). In addition to the above mentioned compounds, the medicinal chemistry literature of the last three years includes a large number of indole–pyrazole, indole–quinazoline, indole–pyrimidine, indole–oxindole, and peptide–indole conjugates, which have been tested for their cytotoxicity activity against various solid–tumour and hematological cancer cell lines (Kumar et al., 2025; Toolabi et al., 2025; Küçükbay et al., 2024).

The highlighted applications of the indole scaffold in anticancer research have inspired the development of more eco-friendly synthetic access to substituted indoles, particularly due to the structural complexity of the desired products (often multipharmacophoric hybrids containing two or more pharmacophores) and the strict requirement for pharmaceutical-grade purity and reproducibility in catalytic processes.

#### 3.1 Classical Synthetic Routes and Their Limitations

The very few name reactions known for accessing the indole nucleus and its derivatives have well-established environmental issues. The most commonly taught approach is the Fischer indole synthesis, which involves reaction of an arylhydrazine with a ketone or aldehyde in strongly acidic conditions under high temperature, and produces stoichiometric amount of acidic waste (Kaur et al., 2023) (corrosive mineral acid or Lewis acid catalysts such as concentrated sulphuric acid, zinc chloride or poly phosphoric acid). While the Bischler indole synthesis and the Larock heteroannulation,

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which reacts an ortho-iodoaniline with an internal alkyne under palladium catalysis, expand the range of accessible structures, they also raise their own sustainability problems: particularly, the Larock reaction requires precious-metal palladium catalysts which are expensive, hard to recover from the solution phase reactions, and likely to leach into pharmaceuticals for which there are regulations that limit the amount of palladium that can remain in the active ingredient. Acylation and alkylation of the indole C3 position, however, usually require stoichiometric amount of moisture-sensitive, corrosive, and produce significant aqueous aluminum waste during the work-up process of Friedel–Crafts reaction using aluminum chloride (Almalki & Baryyan, 2024). These limitations have rendered indole a very instructive test bed for the development of greener methodologies: the indole scaffold is so significant in pharmaceutical research, and when it is synthesized in a more environmentally friendly way, the downstream benefit is significantly greater than for less exploited heterocycles.

### 3.2 Diversity of Indole-Based Pharmacophoric Hybrids

Another common feature in the recently published literature concerning anticancer agents is the fusion or linkage of the indole nucleus to a second heterocyclic pharmacophore which is designed to provide dual targeting of different biological targets or a more favorable physicochemical profile of the parent structure. The structures of indole–pyrazole, indole–pyrimidine, indole–quinazoline, indole–oxindole (isatin-derived), indole–thiazole, and indole–chromenone hybrids are common across the literature reviewed and each have their own specific preferences and potencies (Rana et al., 2024; Patil et al., 2026). In particular, isatin (1H-indole-2,3-dione) is a privileged sub-structure in indole Medicinal Chemistry as a naturally occurring oxidized indole with an electrophilic C3 carbonyl that is a useful synthetic handle for Knoevenagel condensation, spirocyclization and Schiff base formation, and prominently featured in nanocatalyzed chalcone and spirooxindole syntheses which have been evaluated for anticancer activity (Cahyana et al., 2023). This structural versatility is one of the major motivations behind the ongoing interest in indole based hybrid design as one of the most prolific approaches in modern-day anticancer medicinal chemistry.

## 4. Green Nanocatalysis: Principles and Rationale

### 4.1 The Twelve Principles of Green Chemistry in Synthetic Practice

According to Anastas and Warner, there are 12 guiding principles in green chemistry: prevention of waste; atom economy; the use of safer solvents and auxiliaries; energy efficiency; design of degradable products; use of catalytic rather than stoichiometric reagents (Gürses et al., 2023). The aspects of heterocyclic synthesis that are particularly relevant are: Atom economy, the use of non-hazardous solvents (water or solvent free) and the use of catalytic and recoverable metal reagents (Ahmad et al., 2024). Recently, a semi-quantitative “green chemistry principle score” has been proposed as a quantitative metric for comparing drug-synthesis routes to these principles, with alternative synthetic pathways being compared on a common score (Nuthi et al., 2023).

### 4.2 Why Nanocatalysts

The two major drawbacks of conventional homogeneous catalysts, such as Brønsted

acids, Lewis acids, transition-metal salts and organocatalysts, are that they are often hard to remove from the reaction mixture and they cannot always be recovered and recycled with significant loss of activity. Both limitations are overcome by heterogeneous nanocatalysts. The high surface-area-to-volume ratio results in high turnover number at the catalytic sites that are concentrated at the surfaces of particles, and for a few cases as few as 1–10 mol% or a few weight percent of catalyst loading, the turnover is comparable to, or greater than, that of bulk or homogeneous analogues (Tang et al., 2024). Magnetic nanocatalysts are usually composed of  $\text{Fe}_3\text{O}_4$  cores coated with catalytically active shells, can be separated easily using an external magnet instead of filtration or extraction, and also reduce the amount of solvents required in the workup (Maleki et al., 2024).

### 4.3 Biosynthesis of Nanocatalysts: Closing the Sustainability Loop

The use of nanocatalysts with toxic reducing agents ( $\text{NaBH}_4$ ,  $\text{N}_2\text{H}_4$ ) or energy demanding physical processes (laser ablation, high-temperature calcination) results in a shift of the environmental impact from the catalyzed reaction to the preparation of the nanocatalyst in the catalyst preparation part. This is where biosynthetic (or “green synthesis”) routes come in. They employ plant extracts, agricultural by-products or microbe cultures as both reducing and capping agents. This route is shown schematically in Fig.2. Phytochemicals like flavonoids, polyphenols, terpenoids and ascorbic acid not only reduce metal ions ( $\text{Ag}^+$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Cu}^{2+}$  and  $\text{Au}^{3+}$ ) to their zero-valence or oxide nanoparticle forms at ambient or mild aqueous conditions, but also adsorb on the surface of the nanoparticles to prevent uncontrolled aggregation (Rocha et al., 2024; Saini et al., 2024). This method was applied to various plant residues such as eucalyptus, pine, citrus, cedar and green-tea residues to generate catalytically and biologically active silver nanoparticles without the use of hazardous chemicals (Rocha et al., 2024). Similar protocols have been reported for zinc oxide, copper oxide, iron oxide, and gold nanoparticles, where the selection of a biological source material will determine the particle size, morphology and catalytic/biomedical activity of the particles produced (Aigbe & Osibote, 2024; Krishna et al., 2024; Dheyab et al., 2024).

Figure 2. Plant/microbe-mediated green biosynthesis route for metal and metal-oxide nanocatalysts used in indole heterocycle synthesis

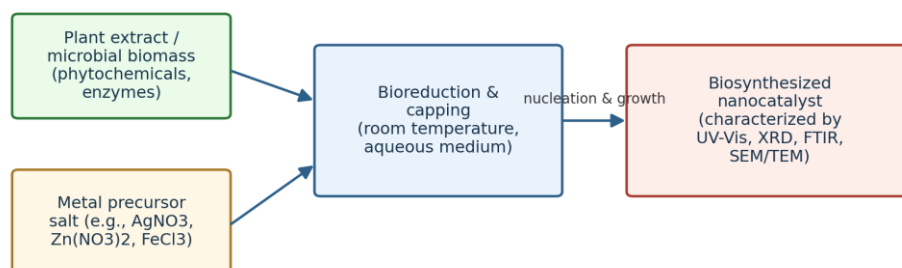


Figure 2. Plant- or microbe-mediated green biosynthesis route for metal and metal-oxide nanocatalysts subsequently applied to indole heterocycle synthesis, showing bioreduction, capping, and characterization stages.

Characterization of biosynthesized nanocatalysts typically combines ultraviolet-visible (UV-Vis) spectroscopy (surface plasmon resonance, particularly diagnostic for Ag and Au nanoparticles), X-ray diffraction (XRD, crystallite size and phase identification), Fourier-transform infrared spectroscopy (FTIR, identification of capping biomolecules), and electron microscopy (SEM/TEM, particle morphology and size distribution) (Saini et al., 2024; Nyabadza et al., 2023).

#### 4.4 Noble Metal and Bimetallic Nanocatalysts

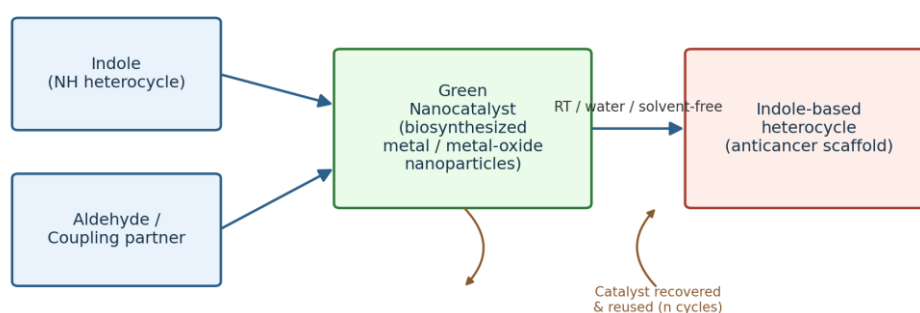
For this reason, silver nanoparticles and gold nanoparticles are in a special niche in the field of green nanocatalysis, as they can be used in both catalytic applications and antimicrobial applications and directly in anticancer applications. Biosynthesized silver nanoparticles (AgNPs) obtained from widely available culinary and medicinal plants as well as plant processing by-products have also been reported to exhibit catalytic activity toward model reduction and condensation reactions, in addition to their intrinsic antimicrobial and cytotoxic properties, thus making them suitable for their application as reaction catalysts as well as co-therapeutic agents (Rocha et al., 2024; Saini et al., 2024). These nanoparticles have been extensively studied for their therapeutic potential in cancer treatment due to their inherent properties, including low intrinsic toxicity, surface-functionalizability, and high optical absorption properties, which are both potentially useful as catalytic supports and as imaging and drug delivery systems (Dheyab et al., 2024; Nisha et al., 2024). More recently, bimetallic nanoparticles (for instance, Au-Ag, Fe-Ni) have been investigated for sensing, catalysis and biomedical applications; and it has been frequently reported that the catalytic activity of the bimetallic analogue is enhanced beyond that of either of the monometallic analogues (Nyabadza et al., 2023). While direct use of bimetallic nanocatalysts in indole heterocycle synthesis is not as well developed as the systems of ZnO/CuO and Fe<sub>3</sub>O<sub>4</sub>, the rapid expansion in the literature dealing with bimetallic nanocatalysis in general indicates that this is a promising future path for methodological expansion in the near-term.

#### 4.5 Copper- and Titanium-Based Green Nanocatalysts

Copper-based nanocatalysts, including CuO, Cu/NiO, and copper-functionalized magnetic supports, have emerged as a particularly cost-effective alternative to precious-metal catalysts for heterocyclic synthesis, combining low raw-material cost with catalytic versatility across Knoevenagel, multicomponent, and coupling reactions relevant to indole chemistry (Mishra et al., 2024; Krishna et al., 2024). Green-synthesized copper nanoparticles have additionally been highlighted as a potential strategy for addressing multidrug resistance in cancer therapy, an application distinct from, but complementary to, their role as synthetic catalysts (Krishna et al., 2024). Titanium dioxide and related metal-oxide nanostructures, while less prominent than ZnO or CuO in the indole-specific literature reviewed here, have been applied under microwave-assisted conditions to related nitrogen-heterocycle syntheses and remain a candidate platform for future extension to indole chemistry given their well-established photocatalytic and Lewis-acidic surface properties.

## 5. Nanocatalyzed Synthetic Strategies for Indole-Based Heterocycles

Figure 1. Generalized scheme for green-nanocatalyzed synthesis of indole-based heterocycles with catalyst recovery/reuse



*Figure 1.* Generalized scheme for green-nanocatalyzed synthesis of indole-based heterocycles, showing convergent addition of indole and a coupling partner in the presence of a recoverable green nanocatalyst, with catalyst recovery and reuse indicated.

The general logic underlying nanocatalyzed indole heterocycle synthesis is summarized schematically in Figure 1: an indole nucleophile and a second coupling partner (an aldehyde, alkyne, or related electrophile) are brought together in the presence of a nanocatalyst that activates one or both reaction partners, typically under ambient temperature, aqueous, or solvent-free conditions; the nanocatalyst is then recovered — by simple filtration, centrifugation, or, in the case of magnetic systems, application of an external magnet — and reused across subsequent reaction cycles. The specific nanocatalyst classes that have been applied to realize this general scheme are surveyed below.

### 5.1 Metal-Oxide Nanocatalysts

The nanoparticles of ZnO have been used extensively in Knoevenagel–Michael cascades and related multicomponent reactions, used to attach indole units to the electrophilic partners, chromenone, dimedone and others. In addition, ZnO nanorods have been employed in the reaction of isatoic anhydride with alkyl bromides in the absence of a solvent, and the catalyst was found to be highly efficient and also reusable without significant decline in activity in subsequent runs (Almalki & Baryyan, 2024). Copper oxide (CuO) nanoparticles have been used as recyclable catalysts in the Knoevenagel condensation reaction of indole with aromatic aldehyde and ethyl cyanoacetate to yield cyanoacrylate indole hybrids that have been assessed for their drug-likeness by an *in silico* absorption, distribution, metabolism, excretion, and toxicity (ADMET) study (Mishra et al., 2024). The related nanocatalyst Cu/NiO, also synthesized by a sol–gel process with the aid of the *Annona muricata* leaf extract, was employed for the synthesis of isatin based chalcones which were later tested for

cytotoxicity against MCF-7 breast cancer cells (Cahyana et al., 2023). From a mechanistic point of view, metal oxide nanocatalysts like ZnO and CuO are considered to mainly provide activation of the carbonyl group of the coupling partner by polarizing it through coordinatively unsaturated metal centers on the surface of the nanocatalyst, and to also provide activation of certain proton transfer steps by surface hydroxyl or oxide centers, which would otherwise require a separate acid or base. This bifunctional surface reactivity, along with the extremely high surface-area-to-volume ratio of nanoscale particles, is generally attributed as the reason for the reported rate accelerations for these systems as compared to metal-oxide bulk catalysts with similar chemical composition (Mishra et al., 2024).

## 5.2 Magnetically Recoverable Nanocatalysts

The Fe<sub>3</sub>O<sub>4</sub> nanoparticles are one of the most extensively studied nanocatalyst classes for indole chemistry, thanks to their easy magnetic recovery, both in their core and functionalized with a second catalytic shell. Zare & Moradi (2023) reported N-doped silica nanospheres functionalized with CuO nanoparticles as highly efficient and magnetically separable catalyst for the multicomponent synthesis of propellane indeno-indole derivatives. Silica coated magnetic nanocatalysts functionalized with o-phenylenediamine have also been used for synthesis of indenoquinoline type of heterocycles under ultrasonic and solvent free conditions with the catalyst being recycled successfully for at least 8 reaction cycles without evident loss of activity (Maleki et al., 2024). At a broader level, magnetic nanoparticle-catalyzed procedures have been reviewed as a green and sustainable approach with particular reference to the synthesis of indole derivatives, with the collection of reaction conditions, catalytic loadings, and green-chemistry metrics reported over the last years in the literature (Vaishali et al., 2025). The practical benefit of magnetic recovery can't be overstated: With a typical heterogeneous-catalyst work-up, the catalyst is removed from the reaction phase by filtration or centrifugation, steps that can be time-consuming, inefficient and lossy, especially for very fine nanoparticulate materials that can go through conventional filter media. On the other hand, magnetic separation requires only seconds using an inexpensive external permanent magnet or electromagnet, and the recyclability of magnetic nanocatalysts is often reported to be > 95%, and this is a key factor for the multi-cycle recyclability numbers reported in Table 1; this feature is a primary reason why magnetic nanocatalysts have been the most extensively studied class of nanocatalysts in the recent literature for indole heterocycle synthesis.

## 5.3 Biosynthesized Metal Nanoparticle Catalysts

In addition to this application in nanomedicine, biosynthesized silver, gold and iron-oxide nanoparticles have been directly used as catalysts in indole forming and other heterocyclization reactions. In addition to seed-priming bioactivity, the general catalytic activity of the silver nanoparticles synthesized from the extracts of neem, mint, tulsi and Bermuda grass has been investigated, highlighting the dual catalytic/biological activity present in many of these reports (Saini et al., 2024). A bioglycerol derived carbon sulfonic acid catalyst, which is also derived from a renewable feedstock, has been employed for the rapid, solvent-less, room temperature synthesis of indolemethane derivatives screened for anticancer activity and evaluated by molecular docking, which represents a fully green synthesis to bioevaluation pipeline (Gogula et

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al., 2023). The glycerol used to make the sulfonated carbon solid acid is a byproduct of biodiesel production, and the raw materials for the entire nanocatalytic process itself are all renewable and inexpensive. This example illustrates that the “green” aspect of a nanocatalytic process is not limited to the biosynthetic origin of the catalyst and its recyclability, but also the biosynthetic origin of the nanocatalyst's support—glycerol, which is a byproduct of biodiesel production, is converted into a sulfonated carbon solid acid that can replace the catalytic function of conventional mineral acids, thus closing the “green” loop at another point in the overall synthetic value chain.

#### 5.4 Multicomponent and Energy-Assisted Protocols

In addition, reaction times and energy input can be further reduced by using other types of activation such as ultrasound, microwave heating or solvent-free grinding in combination with nanocatalysis. This convergent green-methodology approach involves the nanocatalyst reducing the activation barrier for the reactions and the alternative energy source increasing mass and heat transfer rates, as shown in the synthesis of bis(indolyl)methanes by nanosilica catalysis using ultrasonic irradiation and by the combination of nanosilica-catalyzed synthesis and ultrasound in the synthesis of spirooxindole (Almalki & Baryyan, 2024). Multicomponent reactions (MCRs) are reactions that combine three or more reactants into a single heterocyclic product in a single pot, which are especially suitable for nanocatalytic activation due to high atom economy and low intermediate isolation and purification steps (Ahmad et al., 2024).

Representative classes of nanocatalysts, their reported reaction conditions and the green-chemistry performance indicators reported in the literature are summarized in Table 1.

**Table 1** Representative Nanocatalysts Reported for Green Synthesis of Indole-Based Heterocycles

| Nanocatalyst                       | Indole-Based Product Class                               | Typical Conditions                | Reported Recyclability            | Source                   |
|------------------------------------|----------------------------------------------------------|-----------------------------------|-----------------------------------|--------------------------|
| ZnO nanorods / nanoparticles       | Chromenone- and isatoic-anhydride-derived indole hybrids | Solvent-free, RT–80 °C            | Reused with minimal activity loss | Almalki & Baryyan (2024) |
| CuO nanoparticles                  | Cyanoacrylate–indole (Knoevenagel) adducts               | Aqueous/solvent-free, RT          | Recycled across multiple runs     | Mishra et al. (2024)     |
| Cu/NiO nanoparticles (bio-derived) | Isatin-based chalcones                                   | Sol–gel synthesis; mild heating   | Not fully reported                | Cahyana et al. (2023)    |
| CuO-functionalized magnetic N-     | Propellane indeno-indoles                                | Multicomponent, magnetic recovery | High efficiency over              | Zare & Moradi (2023)     |

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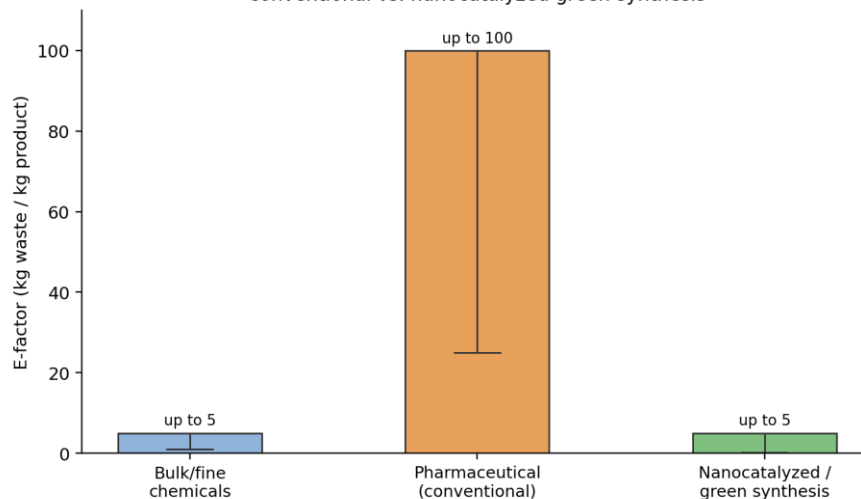
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| Nanocatalyst                                              | Indole-Based Product Class                          | Typical Conditions           | Reported Recyclability            | Source               |
|-----------------------------------------------------------|-----------------------------------------------------|------------------------------|-----------------------------------|----------------------|
| doped silica                                              |                                                     |                              | successive cycles                 |                      |
| Fe <sub>3</sub> O <sub>4</sub> @silica-o-phenylenediamine | Indenoquinoline-fused heterocycles                  | Ultrasonic, solvent-free, RT | ≥ 8 cycles, minimal loss          | Maleki et al. (2024) |
| Bioglycerol-derived carbon sulfonic acid                  | Indolemethanes                                      | Solvent-free, RT, ~5 min     | Recyclable, biodegradable support | Gogula et al. (2023) |
| Biosynthesized Ag nanoparticles                           | General heterocyclization / bioactive intermediates | Aqueous, ambient temperature | Reusable; plant-extract capped    | Saini et al. (2024)  |

## 6. Green Chemistry Performance: Comparative Metrics

One of the main reasons for using nanocatalytic methods is that they can be proven to be better than traditional synthesis in terms of green chemistry metrics. The atom economy, calculated as the ratio of the molecular weight of the desired product to that of all reactants (Braun-Fenders, 2009), and E-factor, which is the ratio of the mass of waste to the mass of product (Nuthi et al., 2023), are the two metrics that dominate the literature. The E-factors for conventional pharmaceutical synthesis range between 25 and above 100, indicate the use of stoichiometric reagents and purification by multi-step methods, while the E-factors of nanocatalyzed, solvent-free or aqueous-phase protocols reported for indole heterocycles are typically well below five and near-quantitative atom economies are achieved in multi-component reactions (Nuthi et al., 2023; Cravotto, 2025). The literature examined for this paper indicates that the general ranges listed in the following table (Graph 1) should be used.

Graph 1. Reported E-factor ranges across sectors, conventional vs. nanocatalyzed green synthesis



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*Graph 1.* Reported E-factor ranges across bulk/fine chemical manufacturing, conventional pharmaceutical synthesis, and nanocatalyzed green synthesis, illustrating the substantially reduced waste intensity associated with nanocatalytic routes (ranges compiled from Nuthi et al., 2023, and Cravotto, 2025).

Atom economy provides a complementary lens on the same underlying phenomenon. Because nanocatalyzed multicomponent reactions typically combine indole, an aldehyde, and a third reactive partner into a single product without the loss of small-molecule by-products beyond water, reported atom economies for these transformations frequently exceed 85–90%, compared with the substantially lower atom economies characteristic of multi-step protecting-group-dependent routes to structurally equivalent hybrids (Ahmad et al., 2024). The combination of high atom economy, low E-factor, and multi-cycle catalyst recyclability constitutes the quantitative basis for describing nanocatalyzed indole synthesis as “green” in a sense that goes beyond qualitative description, and increasingly allows direct, metric-based comparison between competing synthetic routes to the same target molecule (Nuthi et al., 2023).

Recyclability is the second major axis of comparison. Across the nanocatalysts summarized in Table 1, reported reuse spans five to eight or more catalytic cycles with minimal (typically < 10%) loss of yield, a performance level unattainable with homogeneous acid or base catalysts, which are generally consumed or degraded after a single use (Maleki et al., 2024; Zare & Moradi, 2023). Reaction times for nanocatalyzed indole syntheses are also consistently shorter than their conventional counterparts — frequently minutes rather than hours — reflecting both the high surface reactivity of the nanocatalyst and the frequent use of complementary activation methods such as ultrasound (Gogula et al., 2023).

Table 2 consolidates illustrative green-chemistry metric comparisons drawn from the reviewed literature.

**Table 2** *Illustrative Comparison of Green Chemistry Metrics: Conventional versus Nanocatalyzed Indole Synthesis*

| Metric               | Conventional Synthesis                   | Nanocatalyzed Green Synthesis                | Representative Source(s) |
|----------------------|------------------------------------------|----------------------------------------------|--------------------------|
| Typical solvent      | Halogenated or aprotic dipolar solvents  | Water, solvent-free, or bio-derived solvents | Kaur et al. (2023)       |
| Typical E-factor     | 25–100 (pharmaceutical sector)           | < 5 (reported nanocatalyzed routes)          | Nuthi et al. (2023)      |
| Catalyst recovery    | Rarely recoverable; often stoichiometric | Magnetic or centrifugal recovery; reusable   | Maleki et al. (2024)     |
| Reaction time        | Hours                                    | Minutes to a few hours                       | Gogula et al. (2023)     |
| Reaction temperature | Often reflux                             | Ambient to mild heating                      | Zare & Moradi (2023)     |
| Reported             | Not applicable                           | 5–8+ cycles,                                 | Maleki et al. (2024);    |

|               |              |                       |                         |
|---------------|--------------|-----------------------|-------------------------|
| Metric        | Conventional | Nanocatalyzed         | Representative          |
| recyclability | Synthesis    | Green Synthesis       | Source(s)               |
|               |              | minimal activity loss | Zare & Moradi<br>(2023) |

## 7. Anticancer Activity of Indole-Based Heterocycles

### 7.1 Structural Classes and Cell Line Evaluation

The compounds accessed through the nanocatalyzed routes summarized above, together with structurally related indole hybrids reported in the broader medicinal chemistry literature, have been screened predominantly against a recurring panel of human cancer cell lines: MCF-7 and MDA-MB-231 (breast carcinoma), HeLa (cervical carcinoma), A549 (lung carcinoma), HepG2 (hepatocellular carcinoma), and 4T1 (murine breast carcinoma), typically using MTT or sulforhodamine B (SRB) cytotoxicity assays (Patil et al., 2026; Toolabi et al., 2025; Kumar et al., 2025). Ru(II)-catalyzed annulation of indole-2-carboxamides has furnished pyrido-indole-one hybrids exhibiting sub-micromolar cytotoxicity against MDA-MB-231 cells alongside a favorable selectivity index relative to normal HEK-293 and BEAS-2B cells, with the lead compound also shown to disrupt three-dimensional tumor spheroid formation (Kumar et al., 2025). Indole-pyrazole hybrids designed as cyclin-dependent kinase 2 (CDK2) inhibitors have likewise demonstrated potency against MCF-7 cells exceeding that of the reference inhibitor roscovitine, with improved selectivity for cancerous over normal MCF-10A cells (Rana et al., 2024). Passerini multicomponent chemistry has been used to access indole-acetate hybrids with low-micromolar activity against HeLa and MCF-7 cells (Toolabi et al., 2025), while peptide-indole conjugates have been reported to combine antioxidant and cytotoxic activity against MCF-7 and A549 cell lines, supported by density functional theory (DFT) and docking analysis (Küçükbay et al., 2024). Beyond the indole scaffold itself, closely related indoline (2,3-dihydroindole) derivatives have been reported to exhibit complementary bioactivities, including ferroptosis-preventing antioxidant effects and  $\alpha$ -amylase inhibitory activity, illustrating that the reduced, non-aromatic pyrrolidine ring of indoline confers a distinct pharmacological profile relative to the fully aromatic indole nucleus while remaining accessible via structurally related nanocatalyzed synthetic routes (Li et al., 2024; Rehman et al., 2023). This breadth of accessible bioactivity from a single core scaffold — spanning direct cytotoxicity, antioxidant modulation, and enzyme inhibition — further underscores why the indole and indoline nuclei continue to attract disproportionate synthetic-methodology attention relative to many other heterocyclic families.

### 7.2 Molecular Docking and Structure-Activity Relationships

In silico molecular docking has become a near-universal companion to in vitro screening in this literature, providing mechanistic rationalization for observed structure-activity trends. Indole-linked hybrids evaluated against epidermal growth factor receptor (EGFR) wild-type and clinically relevant resistance mutants (T790M, T790M/C797S) have shown docking poses consistent with hydrogen bonding and  $\pi$ - $\pi$  stacking interactions at the ATP-binding pocket, correlating with the observed antiproliferative rank order across the compound series (Patil et al., 2026). Similarly, indole-aminoquinazoline hybrids have been docked against EGFR tyrosine kinase, with

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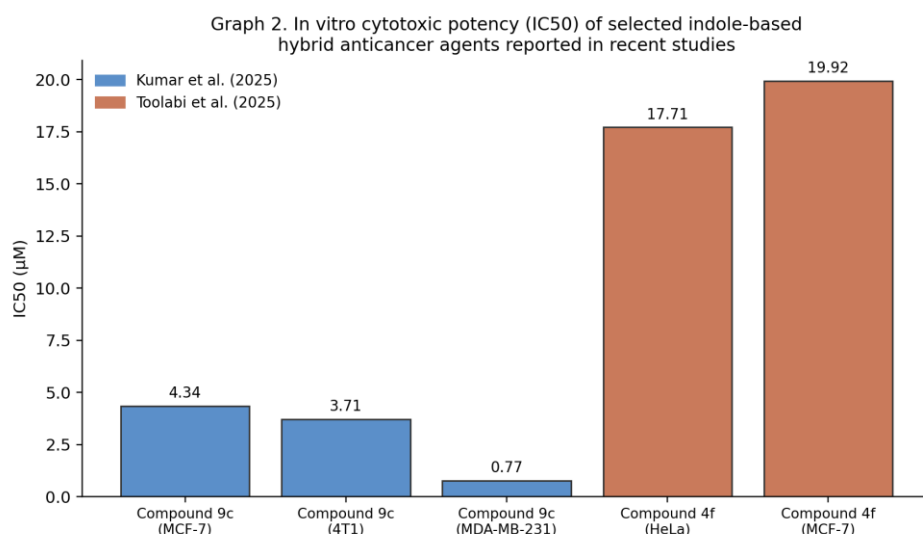
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binding affinities that track closely with measured enzyme inhibition and cellular cytotoxicity (Rana et al., 2024). These combined experimental-computational workflows allow researchers to prioritize synthetic targets before committing to full biological evaluation, further improving the overall efficiency — and by extension the “greenness” — of the drug-discovery pipeline (Toolabi et al., 2025).

### 7.3 Comparative Potency Data

Table 3 collects representative half-maximal inhibitory concentration ( $IC_{50}$ ) values reported for indole-based hybrids across the cell lines discussed above, and Graph 2 presents a subset of these values graphically for direct visual comparison.



*Graph 2.* In vitro cytotoxic potency ( $IC_{50}$ ,  $\mu$ M) of selected indole-based hybrid anticancer agents against representative cancer cell lines, as reported by Kumar et al. (2025) and Toolabi et al. (2025). Lower values indicate greater potency; note the markedly higher potency of compound 9c against the triple-negative MDA-MB-231 line relative to MCF-7 and 4T1.

**Table 3** Representative *In Vitro* Cytotoxicity ( $IC_{50}$ ) Data for Selected Indole-Based Anticancer Hybrids

| Compound / Series             | Cell Line(s) | $IC_{50}$                   | Reference             |
|-------------------------------|--------------|-----------------------------|-----------------------|
| Pyrido-indole-one (9c) hybrid | MCF-7        | $4.34 \pm 0.31 \mu\text{M}$ | Kumar et al. (2025)   |
| Pyrido-indole-one (9c) hybrid | 4T1          | $3.71 \pm 0.39 \mu\text{M}$ | Kumar et al. (2025)   |
| Pyrido-indole-one (9c) hybrid | MDA-MB-231   | $0.77 \pm 0.03 \mu\text{M}$ | Kumar et al. (2025)   |
| Indole-acetate hybrid (4f)    | HeLa         | $17.71 \mu\text{M}$         | Toolabi et al. (2025) |
| Indole-acetate hybrid (4f)    | MCF-7        | $19.92 \mu\text{M}$         | Toolabi et al. (2025) |
| Indole-linked hybrid (MP2-5)  | MCF-7        | $102.28 \mu\text{g/mL}$     | Patil et al. (2026)   |

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| Compound / Series            | Cell Line(s) | IC <sub>50</sub> | Reference           |
|------------------------------|--------------|------------------|---------------------|
| Indole-linked hybrid (MP2-2) | HepG2        | 91.37 µg/mL      | Patil et al. (2026) |

*Note.* Values are reproduced as reported in the cited primary studies; units (molar versus mass concentration) are retained as published and are not directly interconvertible without compound molecular weights.

#### 7.4 Mechanisms of Anticancer Action

Four recurring themes of mechanism appeared in the literature examined. First, tubulin-binding indole derivatives alter the dynamics of microtubules, causing cancer cells to stop at the G2/M phase of the cell cycle and eventually leading to apoptosis (Rana et al., 2024). Second, the kinase directed indole hybrids, most notably EGFR and CDK2 inhibitors, inhibit abnormal, hyperactive and/or dysregulated pro-proliferative signaling characteristically observed in tumor cells (Patil et al., 2026; Rana et al., 2024). Third, HDAC and topoisomerase inhibitors, both of which are derivatives of indole, have cytotoxic effects by interfering with chromatin remodeling and DNA replication, respectively (Rana et al., 2024). Fourth, and convergently, many indole hybrids eventually activate the intrinsic (mitochondrial) apoptotic pathway including depolarization of mitochondrial membranes, release of cytochrome c and a resulting activation of the caspase-3 pathway (Kumar et al., 2025). These convergent mechanistic approaches are shown in a schematic way in figure 3. It is noteworthy that some of the anticancer platforms that use nanoparticles as synthetic catalysts, apart from the catalytic activity itself, also make use of ROS generation as a direct cytotoxicity mechanism, which is linked to the redox activity of the surface of metal oxide nanoparticles (Khafaga et al., 2025; Krishna et al., 2024).

Figure 3. Representative mechanistic pathways by which indole-based heterocycles exert anticancer activity in tumor cells

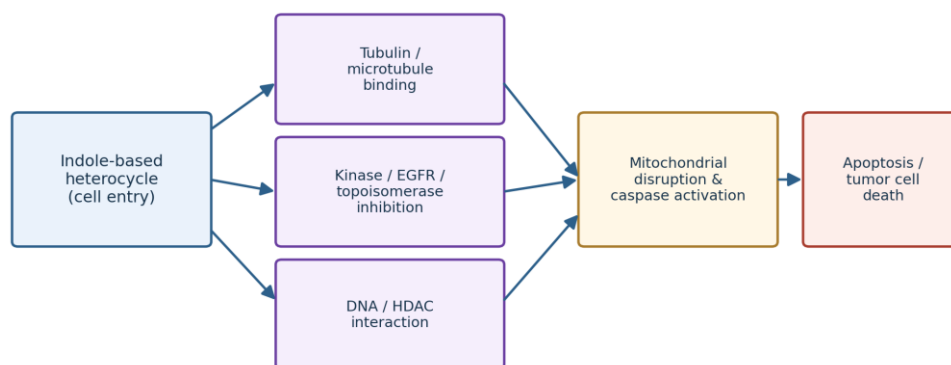


Figure 3. Representative convergent mechanistic pathways by which indole-based heterocycles exert anticancer activity, culminating in mitochondrial apoptosis.

It is worth emphasizing that these mechanistic categories are not mutually exclusive, and a growing body of evidence suggests that the most potent indole-based anticancer hybrids frequently engage more than one target simultaneously — a property sometimes described as polypharmacology. Multi-kinase inhibitors such as sunitinib, for instance, achieve clinical efficacy precisely because they inhibit several structurally

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related receptor tyrosine kinases rather than a single isolated target, reducing the likelihood that a tumor can escape treatment through a single resistance-conferring mutation (Rana et al., 2024). Nanocatalyzed multicomponent synthesis is particularly well suited to generating the structurally hybrid molecules capable of this polypharmacological engagement, since a single one-pot reaction can append two or more distinct pharmacophoric fragments onto the indole core in a single synthetic operation, in contrast to the longer, more resource-intensive sequential routes that would otherwise be required to access equivalent hybrid architectures.

Table 4 summarizes the principal molecular targets and downstream cellular consequences associated with indole-based anticancer agents in the reviewed literature.

**Table 4** *Principal Molecular Targets and Mechanistic Outcomes of Indole-Based Anticancer Agents*

| Mechanistic Target                     | Representative Consequence                | Molecular | Illustrative Reference |
|----------------------------------------|-------------------------------------------|-----------|------------------------|
| Tubulin / microtubule assembly         | G2/M cell cycle arrest                    |           | Rana et al. (2024)     |
| EGFR (wild-type and resistant mutants) | Inhibition of proliferative signaling     |           | Patil et al. (2026)    |
| Cyclin-dependent kinase 2 (CDK2)       | Cell cycle arrest, selective cytotoxicity |           | Rana et al. (2024)     |
| DNA topoisomerase                      | Impaired DNA replication                  |           | Rana et al. (2024)     |
| Histone deacetylase (HDAC)             | Altered chromatin remodeling              |           | Rana et al. (2024)     |
| Mitochondrial membrane / caspase-3     | Intrinsic apoptosis                       |           | Kumar et al. (2025)    |
| Nanoparticle surface redox activity    | Reactive oxygen species (ROS) generation  |           | Khafaga et al. (2025)  |

### 7.5 Selectivity and Therapeutic Index Considerations

Potency against a cancer cell line is a necessary but insufficient criterion for anticancer drug candidacy; selectivity relative to non-malignant cells is equally critical to the clinical relevance of a compound series. Several of the studies reviewed here explicitly incorporate normal-cell counter-screens into their evaluation protocols: pyrido-indole-one hybrid 9c, for example, was reported to retain roughly ten-fold selectivity for the aggressive MDA-MB-231 triple-negative breast cancer line relative to normal HEK-293 kidney and BEAS-2B lung epithelial cells (Kumar et al., 2025), while indole-pyrazole CDK2 inhibitors were evaluated against normal MCF-10A breast epithelial cells alongside MCF-7 tumor cells to establish a selectivity index exceeding that of the reference compound roscovitine (Rana et al., 2024). Such counter-screening is essential because many cytotoxic mechanisms — tubulin disruption and DNA intercalation in particular — are not intrinsically tumor-selective, and a compound's clinical value depends on a therapeutic window sufficiently wide to permit dosing that damages malignant tissue while sparing healthy tissue. The consistent inclusion of selectivity data in the most recent (2024–2026) indole hybrid literature reflects an encouraging

maturation of experimental design standards within this research area, moving beyond simple potency ranking toward pharmacologically meaningful characterization.

## 8. Recent Advances and Emerging Directions (2023–2026)

The latest (2024–2026) literature deviates in several ways from previous literature in this area. The first is a transition from "green-to-bioactive" pipelines, in which the same research groups present the biosynthesis of a catalyst, its synthesis of indole heterocycle, and biological studies of its anticancer properties in a single study, which they previously were presenting as discrete research programs (Gogula et al., 2023; Cahyana et al., 2023). Second, there has been growing interest in the use of nanoparticles not just as catalysts but as therapeutic or drug delivery agents: nanoparticles synthesized using green methods with metal oxides are now being developed to be direct therapeutic agents, taking advantage of their own intrinsic ROS generation activity (Khafaga et al., 2025); and gold nanoparticles produced using plants are reviewed for their use in both cancer therapy and targeted drug delivery (Nisha et al., 2024). Third, computational and cheminformatic tools, such as molecular docking, ADMET prediction, and density functional theory, are now routinely included in the green-synthesis reports, not limited to dedicated medicinal chemistry publications, as part of the multidisciplinary, efficiency-oriented drug discovery (Mishra et al., 2024; Küçükbay et al., 2024). Fourth, the magnetic and mesoporous nanocatalyst architectures are still being optimised for multiple recyclability, and recently, nanotubes with 8 or more catalytic cycles were reported (Maleki et al., 2024).

Another new trend is the integration of nanocatalysis with other non-thermal activation techniques. In particular, the use of nanocatalysts, such as nanosilica, yolk-shell magnetic architectures, and various systems based on ZnO, has been repeatedly combined with ultrasonic irradiation to facilitate indole heterocyclization by acoustic cavitation, which allows the generation of transient, very high-energy micro-environments that enable reagent mixing and mass transfer without the need to heat the bulk of the reaction medium, as is applied in conventional reflux (Almalki & Baryyan, 2024). This combination is especially ideal for achieving one of the goals of green chemistry: the use of lower levels of energy than are typically required for long reflux times, and often eliminating the need for solvents completely. A parallel and, in some ways, complementary approach is microwave-assisted nanocatalysis: microwave irradiation produces efficient and uniform heating, that can decrease the reaction time from hours to minutes and increase the yield and purity of products (Almalki & Baryyan, 2024). The development and merging of these energy-assisted, nanocatalyzed techniques will probably be a useful pathway to indole heterocycle synthesis in the years to follow.

## 9. Challenges and Future Perspectives

Despite this progress, several challenges continue to constrain the translation of green-nanocatalyzed indole chemistry into clinically viable anticancer therapeutics. Batch-to-batch variability in biosynthesized nanoparticles — arising from natural variation in plant extract composition, seasonal harvesting differences, and inconsistent extraction protocols — complicates the standardization that pharmaceutical manufacturing

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requires (Rocha et al., 2024). Comprehensive toxicological and biocompatibility profiling of nanocatalyst residues that may persist in final products remains comparatively underdeveloped relative to the synthetic and in vitro anticancer literature, and represents a critical gap before any nanocatalyzed indole-based candidate could progress toward preclinical development (Krishna et al., 2024). Scale-up from laboratory (milligram-to-gram) to pilot or industrial scale introduces additional engineering challenges — heat and mass transfer, nanoparticle aggregation, and consistent catalyst recovery — that are rarely addressed in the primarily academic literature reviewed here (Cravotto, 2025). Finally, while in vitro cytotoxicity and molecular docking data are abundant, in vivo efficacy, pharmacokinetic, and selectivity data for indole-nanocatalyst-derived compounds remain comparatively scarce, underscoring the continued gap between promising bench-scale chemistry and validated therapeutic candidates (Kumar et al., 2025).

Future research directions that emerge from this synthesis include the development of standardized biosynthesis protocols with defined phytochemical inputs, systematic head-to-head comparison of nanocatalyst classes using common green-chemistry metrics, expanded in vivo validation of lead indole hybrids, and continued integration of machine-learning-assisted docking and ADMET prediction to prioritize synthetic targets before committing laboratory resources (Nuthi et al., 2023; Patil et al., 2026).

There is another complication, however, that is little discussed in the primary synthetic literature, but which will ultimately decide whether or not green-nanocatalyzed indole chemistry will yield approved therapeutics: regulatory and intellectual property issues. The regulatory requirements for the amount of metal residue in active pharmaceutical ingredients (APIs) tend to be more stringent for a new compound developed using a nanocatalyst, which typically requires extensive analytical data, such as by inductively coupled plasma mass spectrometry (ICP-MS), to show that the catalyst-derived metal residue is below acceptable limits, compared to magnetically recoverable catalysts, for which this is often easier to achieve. Accessibility and benefit-sharing to biosynthetic methods are also underdeveloped, as the chemistry shifts from proof-of-concept in academia to commercialization, especially when relying on source organisms from regions with high levels of biodiversity, such as the Nagoya Protocol.

## 10. Practical Recommendations for Researchers and Reviewers

Based on these patterns found in the literature from 2023-2026 surveyed in this paper, a few practical suggestions can be made for those who are designing new studies in this field, and for reviewers and readers of those studies. First, metrics of Green Chemistry, namely, E-factor, atom economy, catalyst turnover number, and number of recycle cycles should be explicitly and consistently reported, not just qualitatively with words like “eco friendly” or “green” without quantitative substantiation; one possible framework for this is the cumulative Green Chemistry approach (Nuthi et al., 2023). Second, a normal-cell counter-screen should be routinely obtained in addition to testing of cancer cell lines, allowing calculation of a selectivity index (not just potency data). Third, residual amounts of nanocatalyst metals in isolated products should be determined and reported, both for eventual regulatory submission and to ensure that the cytotoxicity observed is not due to trace amounts of the nanocatalyst metal in the

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product, rather than the desired organic product. Fourth, when biosynthesis processes are used, the source material, defined as the plant species, plant part, geographic origin and extraction procedure, should be completely described to ensure the reproducibility of the nanoparticles, since the size and morphology of the nanoparticles are well known to depend on these variables. Lastly, authors should consider uploading or referencing raw spectroscopic and biological data and where possible, use an integrated evaluation of in vitro and in silico (docking, ADMET) studies as these integrated studies have been provided the most convincing mechanistic supports in the literature.

## 11. Conclusion

Green nanocatalysis is a scientifically sound and increasingly documented approach to indole containing heterocycles, which balances synthetic efficiency with also being environmentally friendly. In all the reviewed literature, ZnO, CuO-based and Fe<sub>3</sub>O<sub>4</sub>-based metal nanoparticle catalysts demonstrate shorter reaction times, high atom economy, significantly lower E-factors and multi-cycle recyclability in comparison to conventional methods of acid or base catalysis, in addition to being easy to prepare structurally diverse indole hybrids with proven in vitro anticancer activity against breast, cervical, lung and hepatic cancer cell lines. Mechanistic investigations converge to tubulin, kinase, topoisomerase, HDAC and mitochondrial apoptotic pathways as major pathways that mediate these compounds cytotoxicity with the help of molecular docking, which is gaining increasing importance for rationalizing and predicting structure-activity relationships. While all of this still needs to be done, the synthetic and pharmacological work outlined in this review suggests green nanocatalysis is a viable, sustainable platform for future anticancer drug discovery.

The reviewed literature here allows three main conclusions to be drawn. Green nanocatalysis is not a methodological curiosity anymore and has emerged as a well established, actively being pursued approach to preparing heterocycles — a growing family of nanocatalyst classes (metal-oxide, magnetic, noble-metal and bimetallic) with specific benefits in terms of cost, reusability and functional-group tolerance. Second, the anticancer evaluation of indole-based hybrids accessed through these routes has matured methodologically, increasingly incorporating selectivity counter-screens, molecular docking, and mechanistic assays alongside simple potency measurement, generating a more pharmacologically credible evidence base than potency data alone could provide. Third, and most importantly for the field's future trajectory, the environmental and pharmaceutical-development case for green nanocatalysis are mutually reinforcing rather than competing objectives: routes that minimize waste and energy consumption also tend to be shorter, more reproducible, and more amenable to the quality-control standards that eventual clinical development would demand. This alignment of incentives suggests that continued investment in green-nanocatalyzed indole chemistry is likely to yield returns not only in environmental terms but in the practical efficiency of the anticancer drug-discovery pipeline itself.

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