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REVIEW ARTICLE

Coumarin derivatives in pharmaceutical and biomedical engineering: Advances in design, synthesis, and therapeutic applications

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ABSTRACT

Background: Coumarin derivatives have emerged as pivotal compounds in pharmaceutical and biomedical research due to their multifaceted therapeutic potential. Naturally occurring in a wide range of plants, coumarins exhibit diverse biological activities including antimicrobial, anticancer, antioxidant, anti-inflammatory, and anticoagulant effects. Their structural versatility, comprising fused benzene and α-pyrone rings, offers a valuable scaffold for the design of novel pharmacophores targeting complex diseases such as cancer, neurodegenerative disorders, and infectious diseases. **Methods:** This review synthesizes recent advancements in the design, synthesis, and therapeutic applications of coumarin derivatives. It explores traditional synthetic routes such as the Pechmann and Perkin condensations alongside modern environmentally friendly techniques including microwave-assisted synthesis and solvent-free reactions. Furthermore, the article examines mechanistic insights into coumarins' bioactivity, involving pathways like apoptosis induction, oxidative stress modulation, and inhibition of molecular targets including carbonic anhydrases, kinases, and efflux pumps. **Results:** Numerous coumarin derivatives have demonstrated significant *in vitro* and *in vivo* bioactivity. Antimicrobial derivatives showed broad-spectrum efficacy, including multidrug-resistant pathogens. Anticancer coumarins exhibited cytotoxicity in several human cancer cell lines, with some outperforming standard chemotherapeutics. Derivatives also showed potent antioxidant effects, primarily through radical scavenging and modulation of redox signaling pathways. On the other hand, the synthesis of hybrid coumarin molecules further enhanced biological efficacy and solubility, addressing key pharmacokinetic challenges. **Conclusion:** Coumarins represent a versatile and promising class of compounds for future drug development. Ongoing innovation in green chemistry and molecular design is essential to overcome existing limitations such as low aqueous solubility and regulatory restrictions. This review reinforces coumarins' potential as lead structures in pharmaceutical engineering, advocating for continued exploration of their applications across therapeutic domains.

Keywords: Coumarin derivatives; green synthesis; pharmaceutical applications; anticancer activity; antioxidant properties; biomedical

1. Introduction

Coumarin derivatives have garnered significant attention in both pharmaceutical sciences and biomedical engineering due to their remarkable structural and biological diversity[1]. These naturally occurring compounds, abundantly found in plant species, as illustrated in **Figure 1**, such as tonka bean (*Dipteryx odorata*), sweet clover (*Melilotus* spp.), woodruff (*Galium odoratum*), sweet grass (*Hierochloë odorata*), and hop (*Humulus lupulus*), possess a broad spectrum of pharmacological activities[2]. Notably, coumarins and their derivatives have demonstrated potent antimicrobial[3], antiviral[4], anti-inflammatory[5], anticoagulant[6], anticancer[7], antioxidant[8], anti-HIV[9], and neuroprotective (anti-Alzheimer) effects[10], among others. Their wide-ranging therapeutic potential has prompted sustained interest in their development as lead structures in drug discovery, fueling efforts toward their synthesis via both traditional and environmentally friendly (green chemistry) methods.

Figure 1. Examples of coumarin-containing plants.

The scientific interest in coumarins dates to the early 19th century, when aromatic oils extracted from natural sources such as tonka bean and vanilla grass were first characterized. Through refinement and purification, dihydrocoumarin emerged as the earliest identified derivative. Structurally, coumarins are defined by the fusion of a benzene ring with an α-pyrone moiety, a scaffold that underpins many biologically active plant secondary metabolites[11]. Over time, significant advances have been made in optimizing their synthesis and tailoring their structures to enhance pharmacological efficacy[12]. This progress is reflected in the evolving strategies for their design and application, as illustrated throughout the present work.

2. Historical background

Coumarins, first isolated from plant sources in the early 1820s, began attracting scientific attention in 1868 when Wright and Pfordtisol successfully isolated furanocoumarins from the *Ammi* genus. However, it was not until 1939 that coumarins gained substantial pharmacological interest, following Marrian's discovery of their anticoagulant properties. This breakthrough marked the beginning of coumarin-based therapies, which are now employed in the prevention and treatment of conditions such as venous thrombosis, cerebral infarction, and angina pectoris[13]. The structural versatility of the coumarin scaffold has allowed for

the development of numerous natural and synthetic derivatives with a wide spectrum of pharmacological activities. These compounds have demonstrated potential across various therapeutic domains, including anti-inflammatory, antiviral, antimicrobial, and anticancer applications[14]. Moreover, the integration of the coumarin nucleus with other heterocyclic systems—such as steroids, 1,2,4-triazoles, 1,2,3-triazoles, dipyrano[3,2-*c*]chromenes, and pyrazoles—has yielded many bioactive molecules with enhanced efficacy and therapeutic value[15].

Driven by these promising properties, significant efforts have been dedicated to synthesizing novel coumarin derivatives and evaluating their biological activity. Notably, coumarins were initially employed in the treatment of lymphedema in the 1930s, and their therapeutic applications have since expanded to include various forms of cancer[16]. Recent advances have also focused on developing coumarin analogs incorporating N-fused pyrrole rings, alongside investigations into their photophysical characteristics[17]. Although naturally occurring in substances such as tonka beans, cassia, and certain rodenticides, coumarins continue to captivate researchers. Their unique chemical framework, combined with a broad pharmacological profile, has secured their place as a focal point in medicinal chemistry and drug discovery[18].

3. Synthesis of coumarin derivatives

The structural diversity of coumarins can be achieved through various synthetic strategies and rational molecular design. Traditionally, the construction of the coumarin core has relied on classical organic reactions, including the Perkin, Pechmann, Knoevenagel, and Wittig condensations. Among these, the Pechmann reaction and its modified versions remain the most widely utilized due to their efficiency and simplicity[19]. In recent years, there has been a significant shift toward greener and more sustainable synthetic practices. Contemporary methods now incorporate techniques such as microwave-assisted synthesis, solvent-free protocols, solid-supported reactions, and other environmentally benign approaches[20]. These innovations aim to reduce reaction times, enhance yields, lower environmental impact, and streamline purification steps. The continued evolution of coumarin synthesis not only aligns with principles of green chemistry but also supports the development of novel bioactive agents[21]. Coumarin-based scaffolds have shown promising pharmacological activities, including antimicrobial[22], anticancer[23], antiviral[24], antioxidant[25], anti-inflammatory[26], anticoagulant[27], and antidiabetic[28] effects. Consequently, the synthesis of coumarin derivatives remains a vibrant and essential area of interest in medicinal and pharmaceutical chemistry.

Traditional synthesis methods

Apart from their natural occurrence, coumarins can be efficiently synthesized through well-established chemical routes using cost-effective starting materials. One of the earliest and most traditional methods is the Perkin reaction, which typically involves the condensation of salicylaldehyde with acetic anhydride. For example, researchers employed a Perkin-type approach to synthesize a series of 7-substituted-4-methylcoumarins during their investigation of the anticancer potential of these derivatives[29]. In addition to the Perkin reaction, other widely used methods for the synthesis of substituted coumarins include the Claisen condensation and the Pechmann reaction. However, these conventional procedures often necessitate harsh conditions—such as high temperatures, strong bases, or dehydrating agents—which pose environmental and safety concerns[30].

To address these limitations, more sustainable alternatives have recently been explored. Notably, the use of ionic liquids as green, task-specific solvents has gained attention for enabling coumarin synthesis under milder conditions[31]. For instance, 1-butyl-3-methylimidazolium hexafluorophosphate functionalized with sulfuric acid has demonstrated excellent catalytic efficiency in the Pechmann condensation, facilitating high-yield reactions without the need for additional solvents[32]. Remarkably, this ionic liquid can be reused at

least six times without a significant decrease in activity, highlighting its potential for greener synthetic applications. Furthermore, the method has shown broad substrate compatibility, accommodating a range of salicylaldehydes, aromatic aldehydes, and active methylene compounds[33].

Modern synthetic techniques

Designing novel scalemic coumarin derivatives using conventional synthetic approaches remains a significant challenge for synthetic chemists. Over time, various studies have highlighted the unique biological and phytochemical characteristics of coumarin-based compounds, prompting ongoing efforts to develop more efficient and sustainable synthesis routes. In response to increasing environmental concerns, green chemistry has emerged as a vital field of research, gaining considerable attention for its potential to facilitate the in situ generation of coumarin derivatives with reduced ecological impact[34].

Among the modern tools employed in this context, microwave-assisted synthesis has proven to be a powerful technique for producing pharmacologically and biologically active molecules. Microwave irradiation enables chemical transformations to proceed rapidly—often within seconds or minutes—while enhancing reaction efficiency, product yield, and selectivity. As a result, a variety of synthetic strategies utilizing microwave technology for coumarin construction have been established[35]. Additionally, ion exchange resins have attracted interest as catalysts in organic synthesis due to their high catalytic efficiency, environmental friendliness, economic feasibility, ease of handling, and reusability[36]. Despite the remarkable biological potential and structural diversity of coumarin scaffolds, the application of ion exchange resins in their synthesis remains relatively underexplored in the scientific literature, highlighting a promising avenue for future research[37].

Green chemistry approaches

Due to the pivotal structural features of the coumarin scaffold, extensive research has been dedicated to optimizing its synthesis through more sustainable and efficient approaches, as recorded in **Table 1**. Among these, microwave-assisted synthesis has emerged as a promising strategy, offering both economic advantages and improved environmental compatibility. In parallel, the increasing interest in solid-supported reactions has led to the development of acid- and base-catalyzed coumarin syntheses on inorganic solid media—methods that minimize the reliance on hazardous organic solvents and align well with the principles of green chemistry[38]. Environmental sustainability has become a key driver in the design of new synthetic routes for coumarin analogues. As a result, solvent-free techniques and the use of eco-friendly reagents or green solvents have gained prominence in recent studies[39]. Traditional methods such as the Pechmann and Knoevenagel condensations, recognized for their simplicity, low cost, and high chemoselectivity, have been revisited and refined under milder, greener conditions to meet modern synthetic demands[40].

Table 1. Green chemistry strategies in the design and synthesis of some coumarin derivatives.

Coumarin derivative	Green chemistry approach employed in its synthesis	Acquired advantage(s)	Ref.
7-Hydroxy-4-methylcoumarin	Microwave-assisted Pechmann condensation (solvent-free, solid acid catalyst)	Rapid reaction, high yield, reduced energy consumption, and elimination of harmful solvents	[41]
3-Acetylcoumarin	Solvent-free Knoevenagel condensation using L-proline as a biodegradable catalyst	Environmentally friendly, reusable catalyst, and high atom economy	[42]
4-Substituted coumarins	Ultrasound-assisted synthesis using ionic liquids	Mild conditions, improved selectivity, and recyclable reaction medium	[43]
7-Amino-4-methylcoumarin	Aqueous medium using bio-based catalyst (citric acid)	Nontoxic catalyst, water as solvent, and high yield	[44]
Pyrazolylcoumarin	Solvent-free multicomponent reaction using solid-supported acid catalyst	Atom economy, waste minimization, and shorter reaction times	[45]

Coumarin derivative	Green chemistry approach employed in its synthesis	Acquired advantage(s)	Ref.
3-Carboxycoumarin	One-pot synthesis in ethanol using silica-supported Lewis acid catalyst	Low toxicity solvent, high product purity, and energy efficiency	[46,47]
7-Ethyl-4-hydroxycoumarin	Mechanochemical grinding (solvent-free, no heating)	Zero solvent waste, energy saving, and simplified work-up	[48]
Coumarin-thiazole hybrid	PEG-400 as green solvent with mild heating	Biodegradable solvent, improved solubility, and enhanced reaction rate	[49]
4-(Chloromethyl)coumarin	Pechmann reaction catalyzed by natural clay under solvent-free conditions	Inexpensive catalyst, reusable, and reduced environmental footprint	[50,51]
3-Arylcoumarins	Water-based synthesis using nanocatalyst derived from plant extract	Renewable catalyst source, eco-friendly process, and enhanced biocompatibility	[52]

Table 1. (*Continued*)

4. Biological activities of coumarin derivatives

Coumarin derivatives continue to attract significant interest due to their broad spectrum of biological activities, which support their potential use in therapeutic development. Both naturally occurring and semisynthetic coumarins have been extensively investigated for their antimicrobial[53,54], anticancer[55,56], antioxidant[57,58], antiviral[59,60], and antidiabetic[61,62] properties. These compounds are increasingly recognized for their valuable contributions to pharmaceutical chemistry and drug discovery. However, challenges such as limited solubility and chemical stability have hindered their clinical and industrial applications. As a result, the use of coumarins in food, cosmetics, and pharmaceutical formulations is restricted in several countries to prevent adverse effects associated with overexposure[63].

Efforts are ongoing to discover and develop new coumarin derivatives with enhanced pharmacological profiles, particularly those that demonstrate potent antibacterial effects with minimal toxicity. Additionally, derivatives such as 4-hydroxycoumarins have shown promising antioxidant and anti-inflammatory potential, which has prompted further exploration of their therapeutic relevance[64]. Studies have confirmed that coumarin derivatives exhibit antioxidant activity in both *in vitro* and *in vivo* models. Their antioxidant effects are primarily attributed to the inhibition of pro-inflammatory enzymes like cyclooxygenase and lipoxygenase, thereby reducing the production of their respective metabolites[65]. These protective effects stem from the compounds' ability to neutralize reactive oxygen species (ROS) through mechanisms such as hydrogen atom transfer and electron donation, highlighting their role as effective free radical scavengers[66].

Antimicrobial properties

Owing to their structural diversity and distinctive mechanisms of action, natural products remain invaluable sources of bioactive molecules with therapeutic relevance, particularly in the context of antimicrobial drug discovery. Several coumarins—such as antennarin, alloimperatorin, and isoimperatorin isolated from *Cnidium dziwnowiense*, as well as prantschimgin from *Peucedanum luxurians*—have demonstrated notable antimicrobial effects[67]. While higher plants are the predominant source of coumarins, various bacterial and fungal species also contribute to the natural diversity of these secondary metabolites[68]. Importantly, the pharmacological profiles of both natural and synthetic coumarins can be significantly influenced by strategic modifications on the coumarin core. Structural alterations, particularly through functional group substitution at specific positions, have been shown to enhance biological activity[69].

In this context, several derivatives of 7-hydroxycoumarin were synthesized to improve the antimicrobial efficacy of the parent compound. These novel derivatives were screened *in vitro* for antibacterial activity against a range of Gram-positive and Gram-negative bacterial strains, as well as for antifungal activity against six fungal species, employing the filter paper disc diffusion method. The results revealed that all

synthesized compounds exhibited considerable antimicrobial activity[70]. Furthermore, selected potent derivatives were subjected to *in vivo* evaluation using the agar well diffusion method against four fungal species, confirming their enhanced growth-inhibitory potential. These findings suggest that such structural modifications of the coumarin framework could pave the way for the development of new, effective antimicrobial agents[71].

Anticancer activity

Cancer remains one of the leading global health challenges, marked by uncontrolled cellular proliferation and the potential for metastasis. Although current treatment modalities—such as surgery, chemotherapy, radiotherapy, and hormone therapy—have significantly improved patient outcomes, the demand for more effective and less toxic anticancer agents continues to drive drug discovery efforts[72]. In this context, natural products and their synthetic analogs have maintained a central role in anticancer drug development. Among the most impactful chemotherapeutic agents is cisplatin, which has inspired the synthesis and screening of a wide array of structurally related compounds[73]. Of particular interest are α- and β-unsaturated ketones like chalcones, known for their versatile biological activities. These enone motifs have been strategically integrated into scaffolds such as quinolines, xanthones, flavones, and flavonoids to explore their anticancer potential[74].

Recent studies have shifted attention toward coumarin-based compounds and their metal complexes for anticancer applications. A notable example includes the synthesis of metal complexes incorporating thiocyanate, carbonyl, and bipyridine ligands, which have been structurally characterized and evaluated for cytotoxicity using MTT assays on Caco-2 cells[75]. Moreover, coumarin derivatives containing sulfur and nitrogen atoms have emerged as potent inhibitors of Scavenger Receptor Class B Type I, demonstrating promising antitumor activity. Innovative structures, such as octahydropyrrolo[1,2-*a*]pyrazine-coumarin hybrids, have shown notable cytotoxicity across a spectrum of human cancer cell lines, including MCF-7, HeLa, A549, BGC-823, HT-29, A2780, and HCT116[76]. Additionally, both natural and synthetically modified coumarins have displayed significant antiproliferative properties, with certain fluorinated analogues surpassing the performance of established chemotherapeutic agents like etoposide[77].

Antioxidant effects

Coumarin and its derivatives are well-recognized for their diverse biological activities, particularly their antioxidant, anticancer, anti-inflammatory, antiallergic, and relatively low-toxicity properties. These features play a critical role in combating oxidative stress, making coumarins attractive candidates for applications in both medical and pharmaceutical fields[78]. Their antioxidant potential is largely attributed to the presence of conjugated double bonds within their chemical structure, which allows them to donate electrons or hydrogen atoms. This ability facilitates the neutralization of free radicals, thereby protecting cells from oxidative damage[79].

Experimental studies, particularly those utilizing the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay, have demonstrated that coumarin derivatives effectively donate hydrogen atoms to stabilize free radicals. This activity prevents cellular injury by converting reactive species into more stable, non-toxic molecules[80]. The mechanism underlying this effect often involves hydrogen atom transfer from hydroxyl groups present on the coumarin ring, resulting in a stabilized molecular structure. Furthermore, structure–activity relationship analyses have been extensively employed to investigate how specific structural modifications influence antioxidant efficacy[81]. These studies have confirmed that certain substitution patterns on the coumarin scaffold can significantly enhance radical scavenging capacity, providing valuable insights for the design of more potent antioxidant agents[82].

5. Therapeutic applications

Coumarins have demonstrated broad therapeutic relevance, as illustrated in **Figure 2**, functioning as antimicrobial, anticancer, antiviral, antioxidant, and anticoagulant agents[83]. Moreover, their photophysical properties have enabled applications in the design of fluorescent probes and photoactive molecules, further highlighting their utility in biomedical engineering and diagnostic platforms[84]. Recent advancements in coumarin-based medicinal chemistry have emphasized rational drug design and innovative synthetic approaches, particularly in the fields of antimicrobial and anticancer drug discovery[85]. These efforts have uncovered the ability of coumarin derivatives to interfere with a range of cellular processes and metabolic pathways, including those involved in cell proliferation, oxidative stress, and microbial resistance mechanisms[86].

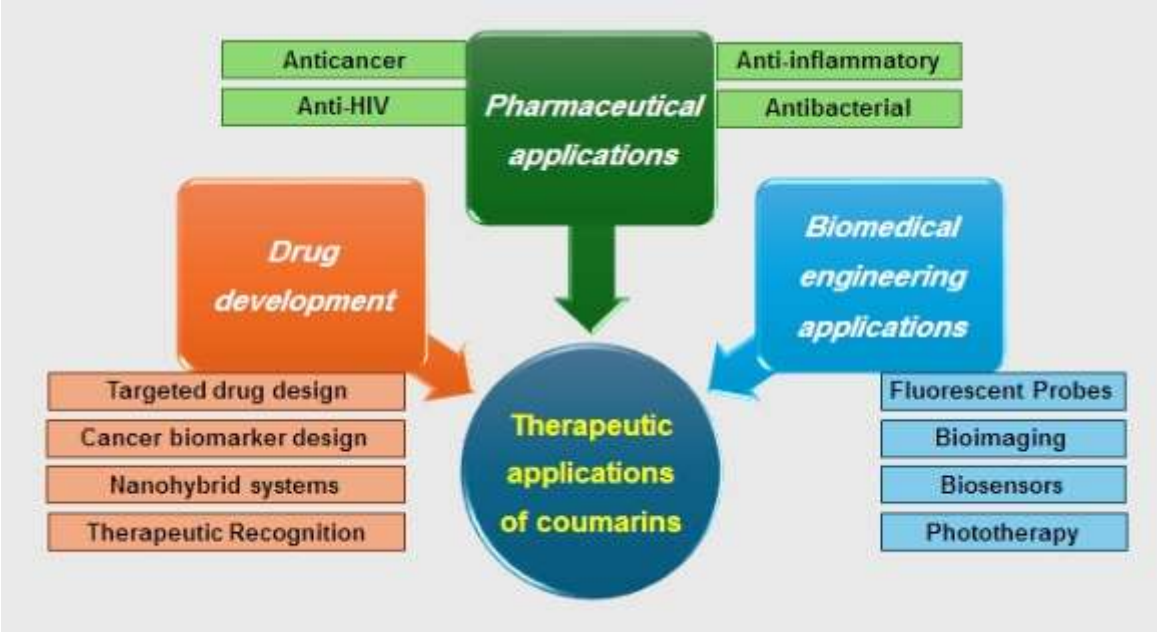

Figure 2. Illustration representing the most important therapeutic applications of coumarin derivatives.

Naturally occurring coumarins are predominantly derived from the secondary metabolism of higher plants, especially from woody tissues of genera such as *Cassia*, *Sophora*, and *Gorgon Padilla*. Experimental studies have shown that these molecules exhibit promising biological effects, including antimicrobial, antifungal, antiviral, antitubercular, antioxidant, and anticancer properties, primarily through modulation of molecular targets and genetic pathways involved in disease progression[87]. In the pursuit of enhanced bioactivity, the synthesis of hybrid molecules combining coumarin with other pharmacophores—such as flavonoids—has garnered significant attention. These hybrid scaffolds offer synergistic therapeutic benefits, paving the way for the development of novel drug candidates with improved efficacy against infectious diseases and cancer[88–90].

Pharmaceutical applications

Coumarin derivatives constitute a prominent class of phenolic compounds recognized for their broad-spectrum therapeutic potential in both pharmaceutical and biomedical applications[91]. These bioactive molecules exhibit a wide array of pharmacological activities, including anticancer[92], anti-inflammatory[93], anti-Parkinson's disease[94], anti-Alzheimer's disease[95], antibacterial[96], and antioxidant[97] effects. Such versatility has made them attractive scaffolds in drug discovery and development, where both natural and synthetic analogs are actively investigated for enhanced efficacy and market viability. Particularly in the field of oncology, ring-substituted coumarin derivatives have garnered significant interest due to their promising cytotoxic and antioxidant profiles[98]. Contemporary synthetic strategies, including

environmentally friendly chemistry approaches, have enabled the development of structurally diverse coumarin frameworks such as simple, fused, and biscoumarins, many of which have shown notable bioactivity[99]. Beyond anticancer properties, certain coumarin-based compounds have been successfully integrated into commercial formulations for cosmetic and anti-HIV purposes[100].

Furthermore, the coumarin nucleus has been associated with a multitude of additional therapeutic effects, including anticoagulant, antifungal, antidepressant, antihyperglycemic, antiallergic, and anti-inflammatory activities. This wide-ranging bioactivity is attributed to the chemical flexibility of the coumarin scaffold, which allows for extensive structural modification and optimization[101]. Extensive literature supports the continued exploration of coumarins as multifunctional agents[102], particularly emphasizing their antioxidant[103], cytotoxic[104], antipsychotic[105,106], and antimicrobial[107] properties in the development of novel therapeutic agents.

Biomedical engineering applications

The fused benzopyranone structure inherent to coumarins serves as an effective fluorophore, enabling their extensive application as donor or acceptor units in two-photon absorption systems[108]. Two-photon fluorescence microscopy has emerged as a powerful tool in biological imaging, offering several advantages over conventional fluorescence techniques, such as enhanced tissue penetration, reduced phototoxicity, and minimal background fluorescence. This modality has been successfully applied to visualize intracellular components such as mitochondria, lysosomes, and nuclei. However, its use in imaging lipid droplets (LDs) remains relatively limited[109]. These particles are dynamic and omnipresent cellular organelles involved in critical functions including lipid storage, lipogenesis, lipolysis, and protein sequestration. They play essential roles in maintaining cellular energy balance and metabolic regulation; however, dysregulation of LDs is implicated in various pathological conditions, such as obesity, atherosclerosis, and neurodegenerative diseases like Parkinson's disease[110]. Therefore, the development of fluorescent probes that enable accurate imaging of LDs under both physiological and pathological states is of paramount importance for advancing biomedical research and clinical diagnostics[111].

Drug development

Coumarins have emerged as valuable scaffolds in rational drug design due to their ability to engage in topology-guided binding with specific biological targets. This targeted approach allows for the precise modulation of key cellular pathways, laying the foundation for strategic synthetic modifications to enhance therapeutic efficacy[112]. Their structural adaptability facilitates strong interactions with cancer-associated biomarkers, reducing tumor cell resistance and offering a versatile framework for the development of novel pharmacologically active compounds[113].

Recent advances include the development of multifunctional nanohybrid systems combining coumarins with hyaluronic acid. These hybrid systems have shown the capacity to bypass conventional lysosomal thiol metabolic routes by inducing microtubule depolymerization, thereby opening new directions for anticancer drug delivery[114]. In particular, coumarin-based agents that disrupt mitosis exhibit pronounced anticancer effects, as the mitotic phase represents a vulnerable window during which cancer cells are highly susceptible to therapeutic damage and apoptosis. Such mechanisms are critical for next-generation anticancer therapies[115].

In the realm of infectious diseases, the growing threat of multidrug-resistant bacteria has undermined the efficacy of conventional antibiotics. One of the major mechanisms of multidrug-resistance involves bacterial efflux pumps, which actively expel therapeutic agents. Coumarins show promise in inhibiting these pumps and restoring drug sensitivity[116]. Furthermore, several important molecular targets in medicinal chemistry—including mammalian topoisomerase II, glycogen synthase kinase 3β, human chorionic

gonadotrophin, heat shock protein 90, and HIV-1 integrase—are being explored in the context of coumarin-based inhibition[117].

The integration of green chemistry principles into the synthesis of coumarin derivatives has gained momentum, reflecting an increased commitment to environmentally sustainable drug development. Owing to their structural diversity and broad spectrum of bioactivities, many coumarin derivatives have already received Food and Drug Administration (FDA) approval or are recognized as naturally occurring compounds with potent biological effects[118]. These agents play significant roles in modulating pathways vital for the survival of pathogens and malignant cells, underscoring their importance in antibacterial, antifungal, antiviral, and anticancer therapeutics[119].

6. Mechanisms of action

Coumarins exhibit a broad spectrum of biological activities through diverse cellular and molecular pathways. Their anticancer potential, as shown in **Figure 3**, is mediated by several cellular mechanisms, including the induction of apoptosis, disruption of mitochondrial membrane potential, suppression of DNA synthesis, and arrest of the cell cycle[120]. These effects are regulated by the modulation of key molecular targets such as p-glycoprotein, tumor suppressor proteins (p53 and p21), caspases, cyclin-dependent kinases, matrix metalloproteinases, extracellular signal-regulated kinases, nuclear factor kappa B, B-cell lymphoma-2, and intracellular ROS[121]. Coumarins also demonstrate antioxidant properties, notably through ROS scavenging and the activation of the Nrf2 pathway, which governs the expression of cellular antioxidant defenses. Furthermore, their ability to inhibit carbonic anhydrase IX—an enzyme frequently upregulated in hypoxic tumor microenvironments—adds to their anticancer repertoire[122].

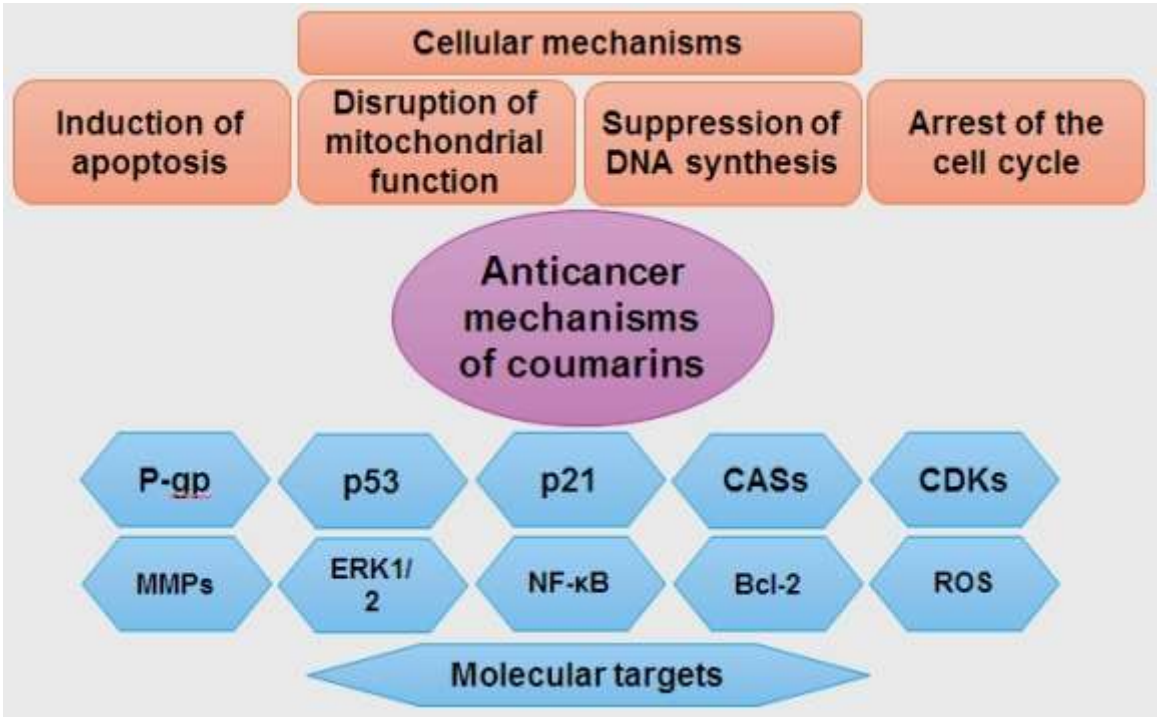

Figure 3. The cellular mechanisms and molecular targets of coumarins' anticancer potential.

p-glycoprotein (P-gp), tumor suppressor proteins (p53 and p21), caspases (CASs), cyclin-dependent kinases (CDKs), matrix metalloproteinases (MMPs), extracellular signal-regulated kinases (ERK1/2), nuclear factor kappa B (NF-κB), B-cell lymphoma-2 (Bcl-2), and intracellular reactive oxygen species (ROS).

Globally, chronic and life-threatening diseases such as cancer, AIDS, and Alzheimer's disease remain significant public health challenges. In response, researchers are actively exploring innovative molecular frameworks using both national and international structural databases. This strategy—often described as the search for a "universal parent structure"—has recently led to the development of hybridized coumarin derivatives with enhanced pharmacological profiles[123]. These multifunctional compounds have shown promising antimicrobial, anticancer, and neuroprotective (anti-Alzheimer) properties, positioning them as valuable candidates for further drug development and clinical exploration[124].

7. Challenges in coumarin research

Research on coumarins continues to face several limitations, primarily due to their inherent chemical instability, high activation energy barriers during synthesis, and poor aqueous solubility[125]. Numerous studies have highlighted the photoinstability of coumarin derivatives, particularly their tendency to undergo photo-induced cyclization and dimerization reactions. These stability issues can compromise their performance in both research and therapeutic applications[126]. Synthetic challenges also persist, especially in coupling reactions, where significant catalytic barriers often hinder the efficient modification of the coumarin core. Such synthetic constraints limit the structural diversification needed to fully explore their pharmacological potential[127]. Additionally, like many natural products, coumarins often suffer from low water solubility, which negatively impacts their physicochemical profiles and pharmacokinetic behavior—key considerations in the development of viable drug candidates[128].

From a regulatory standpoint, safety concerns have prompted strict oversight. In the United States, the FDA monitors the inclusion of coumarin in natural remedies due to potential toxicity. Similarly, the European Council Directive restricts its concentration in cosmetic formulations to a maximum of 0.2% in Eau de Toilette and 0.4% in Eau de Parfum[129]. Despite these challenges, coumarin derivatives have shown considerable promise in pharmacology, with several compounds demonstrating potent antimicrobial, anticancer, and antioxidant activities. These findings reinforce the value of the coumarin scaffold as a versatile and promising template in modern drug discovery and development[130].

Stability and solubility issues

Owing to their favorable safety and tolerability profiles, coumarins and their derivatives are frequently incorporated into alcohol-free formulations of cosmetics and household products[131]. The increasing emphasis on sustainable practices in chemical synthesis has also contributed to a renewed interest in coumarins. Advances in green chemistry have enabled the environmentally friendly synthesis of these compounds, promoting their broader adoption in various industries[132].

In the realm of therapeutic applications, several coumarin derivatives are known to modulate key biological processes such as platelet aggregation, and they also exhibit notable anticoagulant and antimicrobial effects. However, their clinical use is not without limitations[133]. Many coumarin-based compounds require prolonged treatment durations—typically ranging from three to six months—and often suffer from poor aqueous solubility[134]. Additionally, their stability can be compromised by factors such as light exposure, chemical degradation, and metabolic transformations, which can restrict their effectiveness and applicability[135].

Regulatory challenges

Despite their diverse potential, the widespread commercial application of natural coumarins remains constrained by several limitations. These include their low natural yield, labor-intensive extraction and purification processes, susceptibility to hydrolysis in alkaline environments, poor water solubility, high photosensitivity, and the lack of standardized international regulatory frameworks. Collectively, these

challenges hinder the broader adoption of coumarins as active pharmaceutical ingredients in both clinical and industrial settings[136–138].

8. Future directions in coumarin research

Ongoing advances in synthetic chemistry have led to the development of more efficient, selective, and practical methodologies for the preparation of coumarins derivatives. The success of these synthetic strategies often depends on the type of catalyst used, which directly influences both the reaction pathway and product yield. In recent years, growing attention has been directed toward adopting green chemistry approaches, aiming to minimize environmental impact while maintaining synthetic efficiency[139].

Historically, groundbreaking contributions in this field have emerged from global researchers. Notably, transformative methods introduced by South Korean and Chinese scientists have significantly advanced genetic engineering and drug delivery applications, particularly in the areas of transformation and transfection technologies[140]. Coumarins remain among the most prominent examples of plant-derived natural products used as starting materials in modern drug discovery. Their structural framework has been pivotal in the synthesis of pharmacologically active agents, especially those used in the management of neurodegenerative disorders such as Alzheimer's disease and epilepsy[141]. Moreover, structural modifications of natural coumarins have led to the discovery of novel compounds with potent biological activities, supporting their potential as lead candidates in the treatment of cancer, HIV/AIDS, hepatitis, and other serious diseases[142].

Innovative synthesis methods

In recent years, innovative synthetic approaches to coumarins have significantly advanced, driven by the growing demand for sustainable, efficient, and selective methods that align with both pharmaceutical and environmental goals. Traditional methods, such as the Pechmann, Knoevenagel, and Perkin condensations, although foundational, often suffer from limitations like harsh reaction conditions, low atom economy, and poor substrate tolerance. Consequently, researchers have turned their focus to modern synthetic strategies that improve yield, selectivity, and functional group compatibility while reducing environmental impact[143]. One notable innovation is the application of microwave-assisted synthesis, which offers a rapid and energy-efficient alternative to conventional heating. This technique significantly shortens reaction times and enhances yields by promoting uniform heating and accelerating molecular interactions. In parallel, ultrasound-assisted synthesis has gained traction, particularly in facilitating the Knoevenagel condensation under milder conditions. These energy-enhanced methods reduce solvent consumption and contribute to the principles of green chemistry[144].

Another breakthrough lies in the development of catalyst-free and solvent-free protocols, which minimize toxic waste and lower operational costs. For instance, solvent-free Pechmann reactions conducted under thermal or mechanochemical conditions have demonstrated remarkable efficiency and eco-friendliness[145]. Additionally, biocatalytic approaches utilizing enzymes such as lipases and peroxidases offer regioselective coumarin synthesis under mild and aqueous conditions, aligning with nature-inspired synthetic principles[146]. Multicomponent reactions have also emerged as powerful tools in coumarin chemistry. These one-pot reactions allow the construction of structurally diverse coumarin derivatives with high atom economy, making them ideal for library generation in drug discovery[147]. Furthermore, the use of transition-metal catalysis, including palladium-, copper-, and iron-mediated couplings, has expanded the scope of coumarin functionalization, enabling the incorporation of pharmacologically relevant moieties at specific positions on the coumarin core[148].

More recently, photocatalysis and electrochemical synthesis have shown promise in constructing coumarin derivatives with minimal environmental burden. These methods harness light or electrical energy

to drive reactions, often eliminating the need for chemical oxidants or reducing agents[149]. The integration of flow chemistry and automation further enhances scalability and reproducibility, positioning coumarin synthesis at the forefront of modern organic synthesis[150]. Altogether, these innovative strategies, as shown in **Figure 4**, reflect a paradigm shift in coumarin chemistry—one that prioritizes sustainability, precision, and adaptability to meet the complex demands of medicinal and materials science.

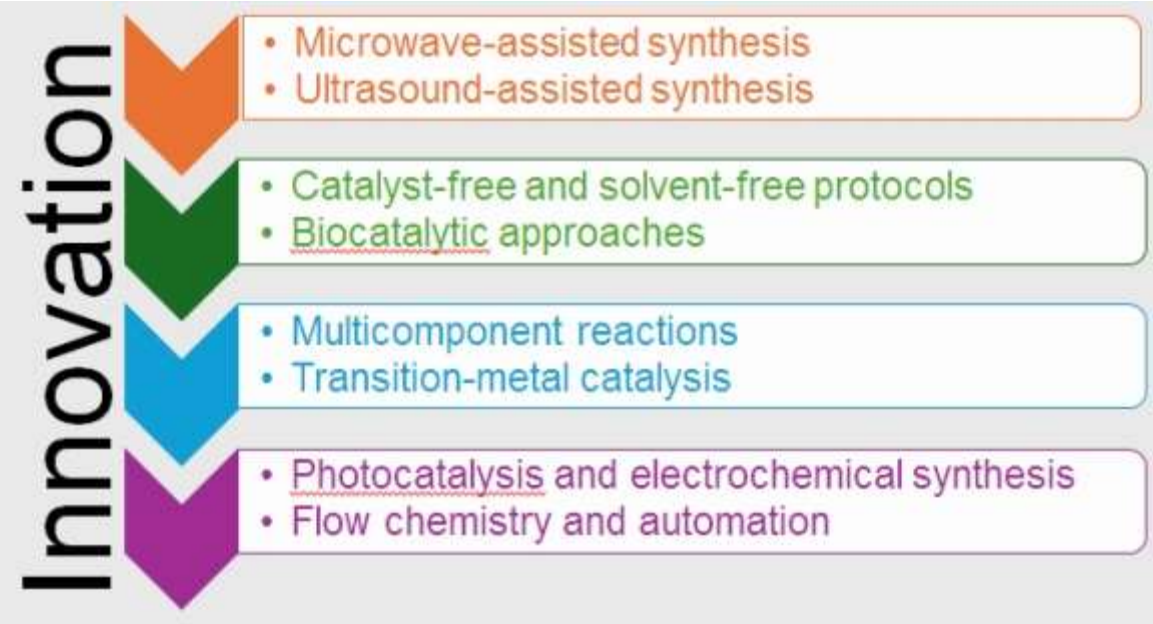

Figure 4. The innovation in the synthesis of coumarin derivatives.

New therapeutic targets

Recent years have witnessed a surge in research dedicated to identifying novel therapeutic targets, with a particular focus on designing molecules capable of selective interaction with critical biological systems[151]. Among these, coumarin derivatives have emerged as promising candidates, especially in the context of targeting DNA topoisomerases. These enzymes play a pivotal role in DNA replication and transcription, making them attractive targets for drug development[152]. The strategic modification of coumarin scaffolds to interact with these enzymes offers a compelling approach for anticancer therapy[153].

One emerging avenue involves the polyamine metabolic pathway, which has garnered interest due to its dual role in normal cellular processes and cancer progression. Polyamines are integral to cell proliferation and differentiation, but their dysregulation is often associated with aggressive, metastatic forms of breast cancer[154]. In this regard, amino alcohol derivatives based on coumarin[155] and benzimidazole[156] structures have shown the ability to inhibit this pathway. Notably, several of these derivatives have demonstrated significant anticancer activity in preclinical models of breast cancer, highlighting their potential as therapeutic agents[157].

Additionally, coumarins have been identified as a novel class of selective inhibitors of human mitochondrial carbonic anhydrases (hCAs), particularly the VA and VB isoforms. These mitochondrial enzymes are implicated in key metabolic pathways, including gluconeogenesis and lipogenesis. Their inhibition may contribute to modulating energy metabolism and body fat storage, offering a potential strategy for anti-obesity interventions[158]. Coumarin[159] and 2-thioxocoumarin[160] analogues have therefore been explored as structural templates for the development of selective mitochondrial hCA inhibitors. Their unique binding characteristics open new possibilities for designing agents that could impact metabolic disorders through targeted enzyme modulation.

9. Case studies of coumarin derivatives

One promising application lies in the ability of coumarins to serve as antibiotic-enhancing agents, particularly in overcoming microbial resistance. A key strategy to combat resistance involves protecting antibiotics from enzymatic degradation by resistant bacteria and reactivating antibiotics that have become ineffective[161]. Notably, the reversible inhibition of β-lactamase enzymes—responsible for deactivating β-lactam antibiotics—has emerged as a valuable approach[162]. In this context, the coumarin derivatives psoralen and bergapten (**Figure 5**) have been evaluated for their ability to reversibly inhibit TEM-1 class A β-lactamase, thereby restoring the efficacy of the β-lactam antibiotic ampicillin[163].

In addition to their antimicrobial role, coumarins have demonstrated potent anticancer properties. For instance, 4-methyl-7-substituted coumarin derivatives have been shown to inhibit aromatic amino acid decarboxylase, an enzyme implicated in the progression of vascular endothelial adenocarcinoma[164]. Another bioactive coumarin, 4-hydroxy-3,7-dimethyl-2*H*-chromen-2-one—known as antengolin (**Figure 5**)—extracted from the anteng horned melon (*Cucumis metuliferus*), exhibits notable antihistaminic activity and has served as a lead structure for designing new H1 receptor antagonists[165]. Moreover, coumarins derived from *Micromelum falcatum*—micromelin and micromelinol (**Figure 5**)—have been reported to reverse multidrug resistance in the P388 mouse leukemia cell line at concentrations as low as 3.4 μM, highlighting their potential in cancer therapeutics[166]. Another mechanism through which coumarins exert anticancer effects is via inhibition of aromatase, the enzyme responsible for converting androgens into estrogens[167].

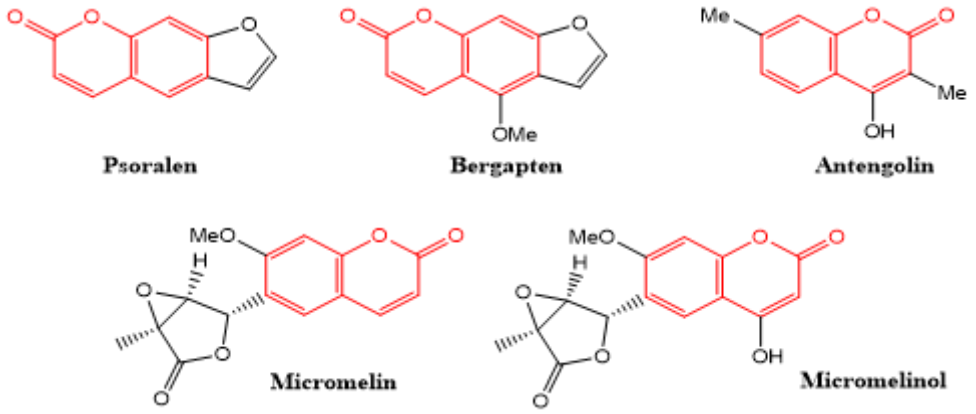

Figure 5. Chemical structures of some bioactive coumarin derivatives, in which the coumarin core is highlighted in red.

9.1. Market trends and commercial applications

Coumarins have gained increasing commercial relevance due to their wide-ranging biological activities and diverse industrial applications. Originally recognized for their natural fragrance and presence in many plants, coumarins have since emerged as valuable scaffolds in pharmaceutical, cosmetic, food, and agrochemical industries. The global market for coumarin derivatives is steadily growing, driven by rising demand for safer therapeutics, natural flavoring agents, and eco-friendly agrochemicals[168]. With their ability to serve as core structures in drug development—particularly for anticoagulants[169], anticancer agents[170], and antimicrobials[171]—coumarins continue to attract attention from pharmaceutical companies and research institutions alike.

In the pharmaceutical sector, coumarin-based drugs such as warfarin, acenocoumarol, and phenprocoumon are well-established anticoagulants used for preventing thrombosis and embolism. Additionally, novel synthetic derivatives are under development for applications in cancer therapy, neurodegenerative disorders, and infectious diseases[172]. The appeal of coumarins in drug discovery stems from their structural versatility, favorable pharmacokinetics, and ability to modulate key biological targets such as kinases, topoisomerases, and cytochrome P450 enzymes[173].

Beyond pharmaceuticals, coumarins are widely employed in the fragrance and cosmetic industries due to their pleasant scent and fixative properties. They are common ingredients in perfumes, body lotions, and soaps[174]. In the food industry, naturally occurring coumarins are used as flavoring agents, especially in vanilla and cinnamon substitutes, although their use is regulated due to potential hepatotoxicity at high doses[175]. Furthermore, coumarins have been utilized in optical brighteners, laser dyes, and fluorescent probes in the chemical and biochemical industries, reflecting their importance in material sciences[176].

In agriculture, coumarin derivatives are being explored as eco-friendly pesticides, herbicides, and antifungal agents. Their ability to inhibit plant-pathogenic fungi and pests, combined with their biodegradability, makes them promising candidates for sustainable crop protection strategies. The integration of coumarins into green chemistry frameworks aligns with the global push toward environmentally conscious solutions[177]. Overall, the market trends for coumarins reflect a dynamic shift from traditional natural uses to high-value commercial applications across health, beauty, and technology sectors. With ongoing advancements in synthetic methods and molecular design, coumarins are poised to become even more prominent in the global bioeconomy.

9.2. Ethical considerations in coumarin-related research

The exploration of coumarins for pharmaceutical, biomedical, and industrial applications necessitates a robust ethical framework to guide responsible research and development. Coumarins, whether derived from natural sources or synthesized in the laboratory, must be evaluated for safety, efficacy, and environmental impact before advancing to clinical or commercial use[178]. Ethical research begins with a commitment to transparency and scientific integrity, ensuring that data related to pharmacological effects, toxicology, and synthesis methods are reported accurately and reproducibly. Misrepresentation of results, data manipulation, or selective reporting not only undermines scientific credibility but also poses risks to public health when such compounds are considered for therapeutic use[179].

One of the central ethical considerations in coumarin research involves safety assessment and human health. Certain natural and synthetic coumarins have shown hepatotoxicity or phototoxicity at high doses, prompting regulatory restrictions on their use in foods and cosmetics in some countries. Therefore, thorough preclinical testing—including acute and chronic toxicity studies, mutagenicity assays, and pharmacokinetic profiling—is essential[180]. Researchers must prioritize minimizing harm to both human participants and laboratory animals. Ethical use of animals in research demands adherence to the principles of the 3Rs—*Replacement*, *Reduction*, and *Refinement*—to ensure human treatment and scientifically justified experimental design[181].

Moreover, the sourcing of coumarins from plants and marine organisms raises additional ethical issues related to biodiversity conservation and sustainable use of natural resources. Many coumarin-rich species are endemic or slow-growing, making overharvesting a threat to ecological balance[182]. Researchers have an ethical obligation to obtain raw materials legally and responsibly, ideally in collaboration with local communities and in compliance with international agreements such as the Nagoya Protocol on Access and Benefit-Sharing [Link]. Benefit-sharing arrangements, particularly with indigenous groups whose traditional knowledge may inform the use of certain coumarin-producing plants, are vital to ensure equitable outcomes and respect for cultural heritage[183].

Finally, as coumarins continue to be explored for anticancer, antimicrobial, and neuroprotective properties, ethical considerations in clinical translation become critical. Clinical trials involving coumarin-based drugs must uphold informed consent, patient safety, and independent oversight through institutional review boards or ethics committees[184]. Participants must be fully informed about potential risks and benefits, and vulnerable populations should be protected from exploitation. Overall, ethical research in the field of

coumarins not only safeguards individuals and ecosystems but also strengthens the credibility and societal trust in scientific innovation[185].

10. Conclusion

From ancient botanical remedies to modern therapeutic breakthroughs, coumarins have traversed a remarkable scientific journey. As highlighted throughout this review, these versatile benzopyrone derivatives continue to inspire researchers with their diverse pharmacological properties, synthetic adaptability, and therapeutic promise. Their ability to function as antimicrobial, anticancer, antioxidant, anti-inflammatory, and anticoagulant agents underscores their relevance in addressing some of today's most pressing health challenges. Whether acting as enzyme inhibitors, efflux pump modulators, or fluorescence-based diagnostic tools, coumarins have firmly established themselves at the intersection of pharmaceutical innovation and biomedical engineering. Despite the strides made in synthetic methodologies and molecular design—especially under the green chemistry paradigm—challenges such as poor aqueous solubility, photoinstability, and regulatory constraints still limit their broader application. However, these barriers are not insurmountable. Advances in nanotechnology, hybrid drug systems, and targeted delivery mechanisms offer promising solutions that can unlock the full clinical potential of coumarin-based compounds.

Looking ahead, the future of coumarin research lies in interdisciplinary collaboration and ethically grounded innovation. By integrating medicinal chemistry, pharmacology, materials science, and environmental sustainability, the next generation of coumarin derivatives could yield highly specific, low-toxicity therapeutics tailored to complex diseases such as cancer, Alzheimer's, and multidrug-resistant infections. Moreover, ethical sourcing, benefit-sharing, and inclusive clinical practices must remain central to the research agenda to ensure responsible scientific progress. In conclusion, coumarins are not just chemical curiosities of the past; they are vital components of the therapeutic future. Withc continued exploration and thoughtful innovation, these nature-derived compounds may well lead the next wave of safe, effective, and sustainable biomedical interventions.

Conflict of interest

The authors declare no conflict of interest.

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