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REVIEW ARTICLE

# Coumarins from nature to nurture: A sustainable resource for drug discovery and beyond

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## ABSTRACT

Coumarins, a class of benzopyrone derivatives predominantly found in plants, have garnered extensive scientific interest for their broad-spectrum biological activities and promising applications across pharmaceutical, agricultural, and cosmetic sectors. Their historical use in traditional medicine, combined with modern evidence supporting their therapeutic potential, positions coumarins as valuable natural scaffolds for drug development and sustainability-driven innovation. This review explores the natural diversity, biosynthesis, biological activities, and sustainable development strategies associated with coumarins. Emphasis is placed on their role in modern pharmacology, the advances in synthetic biology, and their applications within the context of environmental conservation and green chemistry. A comprehensive analysis was conducted using peer-reviewed literature obtained from major databases including PubMed, Scopus, and Web of Science. Key topics include coumarin biosynthesis, plant and microbial sources, traditional and modern applications, and sustainability practices related to their extraction and commercialization. Coumarins demonstrate potent antimicrobial, antioxidant, anti-inflammatory, and anticancer properties, many of which are linked to structural variations in their core scaffold. Advances in metabolic engineering and synthetic biology have enabled scalable production and derivatization. Coumarin-based compounds are increasingly being applied in skincare formulations, eco-friendly agrochemicals, and as templates in drug discovery. Ethical sourcing, conservation strategies, and regulatory frameworks play critical roles in ensuring sustainable utilization. Coumarins exemplify the convergence of natural product chemistry and sustainable innovation. Their structural diversity, bioactivity, and multifaceted applications underscore their importance in both traditional and modern contexts. Future research should focus on biosynthetic optimization, novel therapeutic targeting, and integration into circular bioeconomy frameworks to maximize their scientific and societal impact.

***Keywords:*** coumarins; natural products; sustainable chemistry; biosynthesis; drug discovery; synthetic biology

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## 1. Introduction

Coumarins are naturally occurring compounds characterized by a bicyclic structure derived from ortho-hydroxycinnamic acid. In plants, they are commonly synthesized from phenolic precursors and serve as part of the organism's defense system against microbial pathogens and herbivores[1]. Their widespread distribution across the plant kingdom, along with their remarkable structural diversity, has made coumarins a focal point in natural product research. This core scaffold has inspired the development of a wide array of functional derivatives, many of which exhibit significant therapeutic potential[2]. Dietary and naturally occurring coumarins have been associated with diverse biological effects, including antioxidant[3], antimicrobial[4], anti-inflammatory[5], anticoagulant[6], and anticancer[7] activities. The modification of their chemical framework has yielded new analogs with enhanced

bioactivity, and several of these compounds are currently advancing through various stages of preclinical and clinical development for diseases such as cancer, diabetes, cardiovascular disorders, and neurodegenerative conditions[8].

In recent years, sustainable approaches to the extraction and synthesis of coumarins have gained momentum. Technological advances in extraction methods, coupled with improved tools for chemical characterization, have facilitated the recovery and production of marine and terrestrial coumarin derivatives[9]. Despite their therapeutic promise, natural coumarins have historically been underexplored in comparison to other natural products. However, current research trends are revitalizing interest in this class of compounds. This review highlights key developments in the biological evaluation of coumarins, including recent discoveries and pharmacological applications. It also discusses modern strategies for the eco-friendly production of these compounds and explores chemical modifications aimed at improving their pharmacodynamic and pharmacokinetic properties.

## 2. Historical background of coumarins

The initial identification of the compound now known as coumarin is credited to Vogel, who in 1820 isolated it from the tonka bean (*Dipteryx odorata*, **Figure 2a**) and named it after its characteristic sweet, vanilla-like aroma[10]. Later, in 1868, A. Reissert achieved the first synthetic preparation of coumarin using salicylic acid and acetic anhydride, marking a significant milestone in organic synthesis[11]. Although tonka bean remained the primary source of coumarin, its occurrence in various other botanical species was soon recognized. This included the roots of *Angelica archangelica* (**Figure 2b**), the leaves of *Melilotus alba* (**Figure 2c**), and the flowers of *Aristolochia clematitis* (**Figure 2d**)[12]. Coumarin's pleasant fragrance and its ability to release aroma at very low concentrations made it a popular additive in the flavor and fragrance industries, particularly as a food flavor enhancer and perfume ingredient. Often, it is combined with other aromatic compounds to produce complex scent profiles[13].

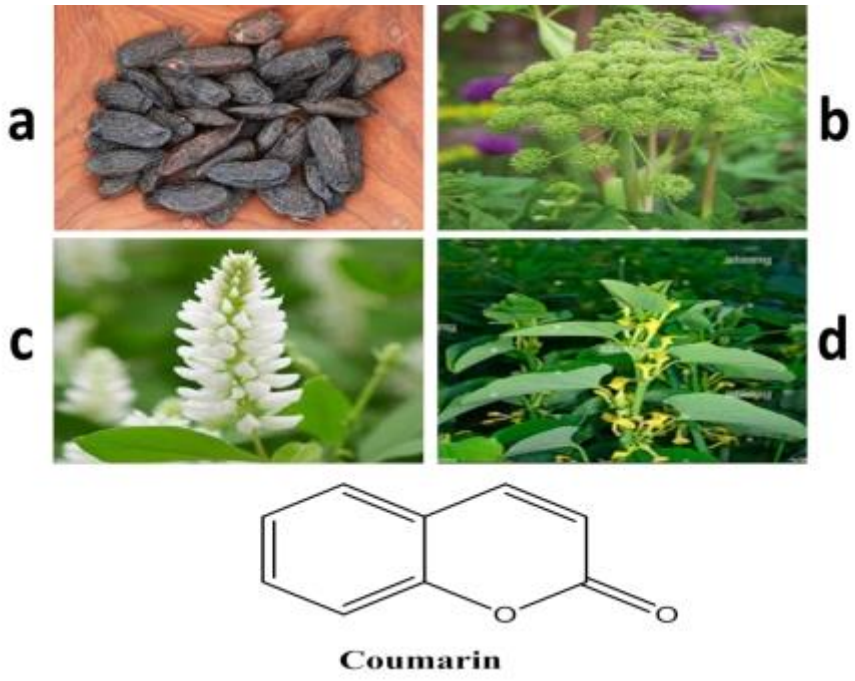


**Figure 1.** The chemical structure of coumarin and some of its plant sources.

The therapeutic promise of coumarins gained prominence following the discovery of their diverse biological activities, which ignited considerable interest in synthesizing and exploring their pharmacological derivatives[14]. A pivotal milestone in this field was the development of warfarin, a coumarin-based anticoagulant, which catalyzed extensive research into related compounds. This led to the synthesis and

pharmacological assessment of more than 3000 analogues. Notably, the 4-hydroxy-3-aryl-1*H*-coumarin-2-one derivatives demonstrated remarkable anticoagulant potency, exhibiting efficacy at low doses and a significantly prolonged half-life in both preclinical and clinical evaluations, outperforming warfarin in these respects[15]. These advances highlighted the critical role of the aryl substitution at the C6 position in enhancing biological activity, a structural feature that continues to guide the rational design of new coumarin-derived therapeutic agents[16].

## 3. Natural sources of coumarins

Coumarins are naturally occurring secondary metabolites produced by many plants as part of their defense strategies against pathogenic microorganisms and herbivorous predators. Beyond the plant kingdom, these compounds are also biosynthesized by certain fungi and bacteria, with some microbial species capable of yielding them in appreciable quantities[17]. Over the past few decades, a growing body of scientific literature has aimed to map the distribution of coumarins across the plant kingdom. These efforts have contributed to identifying specific families, genera, and species characterized by high coumarin content or, conversely, by their absence[18].

Among all biological sources, as illustrated in **Figure 2**, plants remain the predominant producers of coumarins, as they synthesize a broad range of these compounds through well-regulated biosynthetic pathways. Notable coumarin derivatives, such as umbelliferone, esculetin, esculin, and aesculetin, are often found in high concentrations in the aerial parts of certain *Bussowia* species, which belong to the Rubiaceae family, endemic to Hawaii[19]. These compounds are of significant interest due to their potent antioxidant and anticancer properties. Other major coumarin-rich plant families include Rutaceae, Moraceae, and Apiaceae. Among them, the Apiaceae family is especially known for its high coumarin content, with several of its members serving as valuable sources for use in traditional medicine, food preservation, and the cosmetic industry. However, despite their importance, the biosynthetic pathways responsible for coumarin production in Rutaceae remain largely unexplored[20].

Coumarins and their derivatives have also gained attention for their potential use as environmentally sustainable bio-pesticides, insect repellents, and herbicides. This has spurred increased research interest in alternative sources, such as microorganisms. Some fungal genera—namely *Penicillium*, *Aspergillus*, and *Chrysosporium*—have been studied as microbial producers of coumarins, although only select species within these genera have demonstrated significant production capacity[21]. Additionally, fungi such as *Tritirachium*, *Calcarisporiella*, and *Monodictys* have been proposed as promising sources. A noteworthy finding also revealed that a pathogenic bacterium could biosynthesize 7-methoxycoumarin, further expanding the microbial landscape of coumarin producers. Other genera, including *Trichoderma*, *Bacillus*, and *Burkholderia*, have also been reported to produce coumarins in measurable quantities[22]. Despite these discoveries, one of the main limitations in utilizing plants and microbes for coumarin production remains the typically low yield obtained through extraction processes. This challenge continues to motivate the search for enhanced biosynthetic strategies and scalable biotechnological approaches for coumarin production[23].

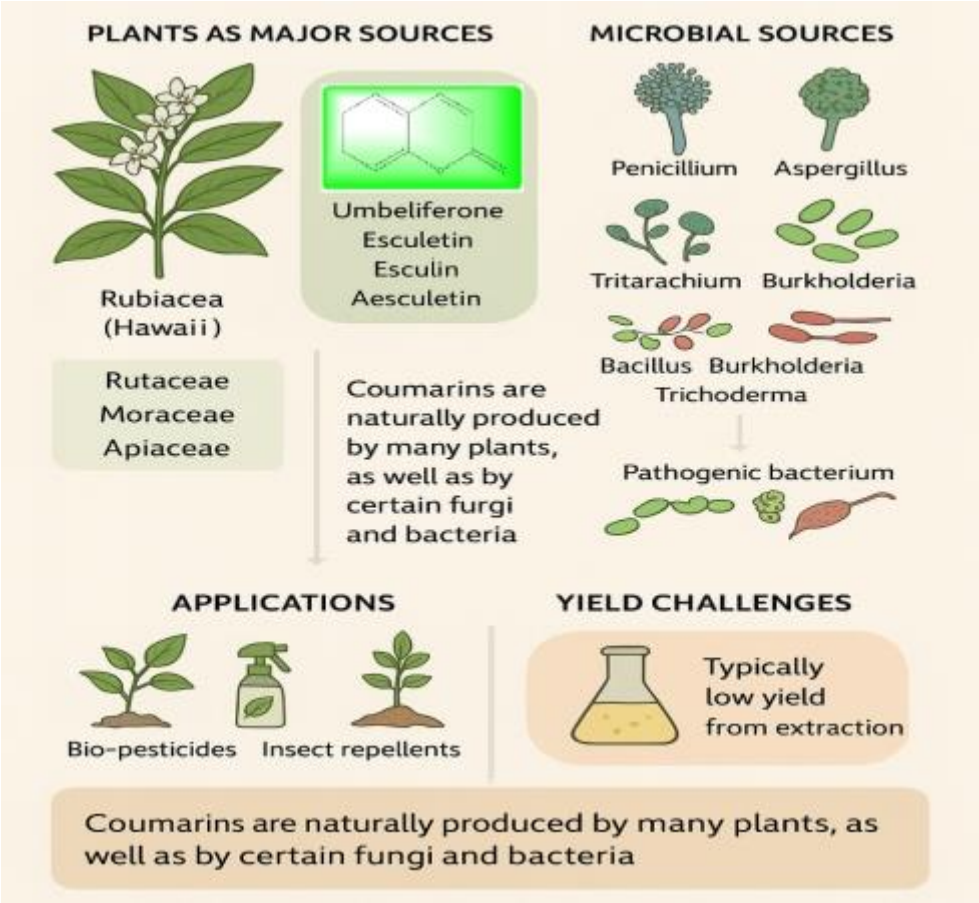


**Figure 2**. Coumarin producers in nature.

### 3.1. Plants as primary sources

There has been a sustained and growing scientific interest in plant-derived natural products, particularly those obtained from medicinal and aromatic plants, due to their potential benefits for human health[24]. These plants produce a wide array of secondary metabolites, which are often responsible for their therapeutic and biological effects. Among these, coumarins—classified chemically as 2*H*-1-benzopyran-2-ones—stand out as a significant group of bioactive compounds naturally occurring in many plant species[25], as reported in **Table 1**. Historically, coumarin-containing plants such as *Melilotus*, *Angelica*, and *Cinnamomum* have been used in traditional medicine, valued for their therapeutic efficacy long before their chemical constituents were formally identified[26]. Advances in analytical technologies, especially chromatographic and spectroscopic techniques, have greatly facilitated the isolation and structural characterization of coumarins. These methods have revealed the wide-ranging biological activities of coumarins, which include antioxidant, anticancer, anticoagulant, antimicrobial, and photoprotective effects[27].

From a pharmaceutical perspective, coumarins are now recognized as a promising chemotype in drug discovery and development. They are being explored not only as phytomedicines and nutraceuticals but also as lead compounds for new drug formulations[28]. However, the production of pharmacologically active coumarins is still largely dependent on plant extraction and purification. This reliance presents several challenges, including limited biomass availability, seasonal variation in compound yield, and high costs associated with cultivation, extraction, and purification processes[29]. To overcome these obstacles, innovative strategies such as synthetic biology and metabolic engineering are being explored[30]. These approaches aim to reconstitute plant biosynthetic pathways within microbial hosts, allowing for scalable, sustainable, and

controlled production of specific coumarins. Such biotechnological advances hold promises for optimizing yield and expanding the structural diversity of coumarins available for pharmaceutical applications[31].

Coumarins are distributed across a wide range of plant families. The Apiaceae, Fabaceae, and Rutaceae families alone account for most known coumarin-producing species. Additional coumarins have been identified in plants belonging to the Asteraceae, Brassicaceae, Moraceae, Boraginaceae, Cistaceae, and Lamiaceae families. Moreover, regional biodiversity hotspots, such as French Guiana and China, have yielded endemic species producing structurally unique coumarins[32]. Notably, the genus *Agarista* (Ericaceae) has recently been identified as a new source of coumarins, while members of the Erythropalaceae family have emerged as producers of 2*H*-chromenes. The continuing refinement of isolation and characterization techniques is enabling the discovery of novel coumarins from a broader range of plant species[33]. Furthermore, elucidating new biosynthetic pathways and expanding libraries of chemically diverse coumarins may enhance their utility in pharmaceutical research, offering new avenues for therapeutic innovation[34].

**Table 1**. Natural plant-derived coumarins with their origins and biological activities.

| Natural coumarin | Scientific name of sourced plant | Plant family | Biological activity | Ref. |
|---|---|---|---|---|
| Scopoletin | *Scopolia japonica* | Solanaceae | Anti-inflammatory and antioxidant | [35] |
| Umbelliferone | *Angelica archangelica* | Apiaceae | Photoprotective and anti-inflammatory | [36] |
| Aesculetin | *Aesculus hippocastanum* | Sapindaceae | Antioxidant and anti-inflammatory | [37] |
| Esculin | *Aesculus hippocastanum* | Sapindaceae | Vasoprotective and anti-edematous | [38] |
| Bergapten | *Citrus bergamia* | Rutaceae | Photosensitizing and anticancer | [39] |
| Xanthotoxin | *Ammi majus* | Apiaceae | Psoralen therapy and anti-psoriatic | [40] |
| Herniarin | *Herniaria glabra* | Caryophyllaceae | Spasmolytic and antimicrobial | [41] |
| Coumarin | *Dipteryx odorata* | Fabaceae | Anticoagulant and antifungal | [42] |
| Daphnetin | *Daphne odora* | Thymelaeaceae | Anti-inflammatory and anticancer | [43] |
| Imperatorin | *Angelica dahurica* | Apiaceae | Anticancer and neuroprotective | [44] |
| Osthole | *Cnidium monnieri* | Apiaceae | Osteogenic and neuroprotective | [45] |
| Isopimpinellin | *Pastinaca sativa* | Apiaceae | Anticancer and antifungal | [46] |
| Psoralen | *Psoralea corylifolia* | Fabaceae | Photosensitizing and antibacterial | [47] |
| Angelicin | *Angelica archangelica* | Apiaceae | Antiviral and anticancer | [48] |
| Marmesin | *Ruta graveolens* | Rutaceae | Antioxidant and anticancer | [49] |
| Methoxsalen | *Ammi majus* | Apiaceae | Psoralen therapy and vitiligo treatment | [50] |
| Sphondin | *Heracleum sphondylium* | Apiaceae | Antifungal and phototoxic | [51] |
| Decursin | *Angelica gigas* | Apiaceae | Antiangiogenic and anticancer | [52] |
| Esculetin | *Cichorium intybus* | Asteraceae | Antioxidant and hepatoprotective | [53] |
| Daphnin | *Daphne mezereum* | Thymelaeaceae | Analgesic and anti-inflammatory | [54] |
| Cnicin | *Cnicus benedictus* | Asteraceae | Antimicrobial, bitter tonic | [55] |
| Visnagin | *Ammi visnaga* | Apiaceae | Antispasmodic, vasodilatory | [56] |
| Isobergapten | *Peucedanum ostruthium* | Apiaceae | Antiviral and antifungal | [57] |
| Fraxidin | *Fraxinus excelsior* | Oleaceae | Antioxidant and anti-inflammatory | [58] |
| Pimpinellin | *Pimpinella anisum* | Apiaceae | Antimicrobial and hepatoprotective | [59] |

## 3.2. Microbial production

Microorganisms have emerged as promising alternative sources for the production of natural products, including coumarin and its derivatives. Several bacterial and fungal species are capable of synthesizing coumarins, as reported in **Table 2**, typically in precursor forms such as aglycones or glycosylated compounds[60]. Compared to traditional plant-based sources, microbial systems offer distinct advantages for drug discovery and biotechnological applications. These include rapid growth rates, flexible metabolic pathways, the ability to thrive in diverse and controlled environments, and the potential to utilize renewable feedstocks[61]. The remarkable structural diversity of coumarins produced by microbes is attributed to their polyketide-based biosynthesis and ecological interactions. Given the generally low yields of coumarin compounds from plant cell cultures, significant efforts have been directed toward identifying and optimizing microbial strains capable of efficient and cost-effective production[62].

Historically, the exploration of microbially derived coumarins has been largely empirical. However, recent advances in recombinant DNA technology and a deeper molecular understanding of biosynthetic pathways have revolutionized the field. These breakthroughs have paved the way for metabolic engineering and synthetic biology approaches that enable industrial-scale microbial synthesis of coumarin scaffolds, extending well beyond the limited range of naturally occurring analogues[63]. For instance, through genetic modification, pathways such as that for walkerol biosynthesis have been successfully introduced and expressed in engineered microbes[64]. In the following section, the natural biosynthetic routes of coumarins are explored, highlighting the genes and enzymatic machinery involved in enabling their heterologous production in microbial systems.

**Table 2**. Natural microbe-derived coumarins with their origins and biological activities

| Natural coumarin | Scientific name of sourced microbes | Microbial type | Biological activity | Ref. |
|---|---|---|---|---|
| Scopoletin | *Escherichia coli* | Gram-negative bacterium | Antibacterial | [65] |
| Umbelliferone | *Staphylococcus aureus* | Gram-positive bacterium | Antibacterial | [66] |
| Esculetin | *Candida albicans* | Fungus | Antifungal | [67] |
| Aesculetin | *Pseudomonas aeruginosa* | Gram-negative bacterium | Antibacterial | [68] |
| Xanthotoxin | *Aspergillus niger* | Fungus | Antifungal | [69] |
| Bergapten | *Bacillus subtilis* | Gram-positive bacterium | Antibacterial | [70] |
| Isopimpinellin | *Klebsiella pneumoniae* | Gram-negative bacterium | Antibacterial | [71] |
| Imperatorin | *Streptococcus pyogenes* | Gram-positive bacterium | Antibacterial | [72] |
| Psoralen | *Saccharomyces cerevisiae* | Fungus | Antifungal | [73] |
| Daphnetin | *Mycobacterium tuberculosis* | Acid-fast bacterium | Antibacterial | [74] |
| Heraclenin | *Salmonella typhi* | Gram-negative bacterium | Antibacterial | [75] |
| Osthole | *Enterococcus faecalis* | Gram-positive bacterium | Antibacterial | [76] |
| Auraptene | *Fusarium solani* | Fungus | Antifungal | [77] |
| Coumarin | *Listeria monocytogenes* | Gram-positive bacterium | Antibacterial | [78] |
| Marmesin | *Cryptococcus neoformans* | Fungus | Antifungal | [79] |
| Suberosin | *Helicobacter pylori* | Gram-negative bacterium | Antibacterial | [80] |
| Oxypeucedanin | *Neisseria gonorrhoeae* | Gram-negative bacterium | Antibacterial | [81] |
| Phellopterin | *Proteus mirabilis* | Gram-negative bacterium | Antibacterial | [82] |
| Columbianadin | *Microsporum gypseum* | Fungus | Antifungal | [83] |
| Decursinol | *Trichophyton rubrum* | Fungus | Antifungal | [84] |

| Natural coumarin | Scientific name of sourced microbes | Microbial type | Biological activity | Ref. |
|---|---|---|---|---|
| Praeruptorin A | *Clostridium difficile* | Gram-positive bacterium | Antibacterial | [85] |
| Rutarin | *Penicillium chrysogenum* | Fungus | Antifungal | [86] |
| Sphondin | *Rhizopus oryzae* | Fungus | Antifungal | [87] |
| Bicoumarin | *Actinomyces israelii* | Gram-positive bacterium | Antibacterial | [88] |
| Methylgalbanate | *Serratia marcescens* | Gram-negative bacterium | Antibacterial | [89] |

**Table 2.** (*Continued*)

# 4. Biosynthesis of coumarins

Coumarins are a class of plant secondary metabolites primarily synthesized through the shikimic acid pathway. This biosynthetic route begins with the deamination of L-phenylalanine, leading to the formation of L-tyrosine, which is then dehydrated to yield *trans*-cinnamic acid. Through enzymatic hydroxylation, *trans*-cinnamic acid is converted to *p*-coumaric acid, which is subsequently activated by conjugation with coenzyme A (CoA) to form *p*-coumaroyl-CoA. At this metabolic junction, *p*-coumaroyl-CoA can follow two divergent pathways[90]. One branch continues into the phenylpropanoid pathway responsible for lignin biosynthesis, while the other enters the coumarin-specific pathway. The latter involves a sequence of enzymatic reactions including ortho-hydroxylation, hydroxylation, and lactonization, largely mediated by cytochrome P450 monooxygenases and 4-coumarate:CoA ligase enzymes[91]. These steps culminate in the formation of coumarins through a final enzymatic cyclization reaction. While this general biosynthetic framework is conserved across many angiosperms, interspecies variations arise due to differences in enzyme availability and pathway-specific regulation[92].

The biosynthesis of coumarins is tightly controlled at both genetic and biochemical levels. Genetically, regulation involves the activity of transcription factors and promoter regions of biosynthetic genes. Several key genes involved in coumarin biosynthesis have been cloned and characterized, revealing that transcription factors from the MYB, bHLH, WD-repeat, and NAC families play pivotal roles in modulating gene expression[93]. In particular, the MYB transcription factors MrMYB1 and MrMYB2 from medicinal plants have been linked to variations in volatile coumarin levels. Environmental stimuli, such as UV-B radiation, can also influence coumarin biosynthesis[94]. For instance, transcription factors FT1 and FT2 are activated under UV-B exposure, thereby inducing the expression of several coumarin pathway genes. Additionally, transient silencing of SlMYB12 or SlMYB1 in tomato leaves via virus-induced gene silencing has been shown to suppress the synthesis of key coumarin precursors, further highlighting the significance of transcriptional regulation in this pathway[95].

## 4.1. Metabolic pathways

The biosynthesis of coumarins in plants initiates with the enzymatic conversion of L-phenylalanine to *trans*-cinnamic acid, a reaction catalyzed by phenylalanine ammonia-lyase (PAL). Various isoforms of PAL have been characterized across numerous plant species and can be broadly grouped into five distinct categories based on their cDNA sequences[96]. Group I consists of PALs identified in both monocotyledonous and some dicotyledonous plants, such as wheat, rice, maize, and potato, and these have been extensively studied. Group II includes sequences archived in gene databases, while Group III encompasses PALs derived from fruits such as sweet and sour cherries and pears—many of which are responsive to reactive oxygen species (ROS) and are classified as ROS-induced AmPALs[97]. Group IV represents PALs from a broader range of flowering plants, and Group V is composed exclusively of monocot PALs, some of which exhibit atypical substrate specificity and do not act on phenylalanine[98].

Phenylalanine serves as a central precursor not only for coumarins but also for a diverse array of secondary metabolites including phenylpropanoids, flavonoids, anthocyanins, stilbenes, and certain phytoalexins[99]. These compounds are widely distributed in various plant tissues such as roots, leaves, stems, and flowers, contributing to plant defense, pigmentation, and overall fitness. Advancements in synthetic biology have opened the door for reconstructing plant metabolic pathways in microbial hosts, thereby offering a sustainable platform for the large-scale biosynthesis of coumarins for pharmaceutical applications[100]. To achieve this, the native coumarin biosynthetic pathway must be systematically optimized. Critical to this process are four key enzymes that regulate the flow and specificity of the pathway: PAL, cinnamate-4-hydroxylase , 4-coumarate-CoA ligase, and hydroxycinnamoyl-CoA shikimate/quinate hydroxycinnamoyl transferase. These enzymes catalyze the initial and rate-limiting steps, guiding the metabolic flux toward coumarin formation[101].

### 4.2. Genetic regulation

Understanding the regulatory networks that control coumarin biosynthesis is crucial for enhancing and manipulating their production. Recent transcriptomic and metabolomic studies have shed light on the gene expression patterns and metabolic fluxes that regulate distinct coumarin biosynthetic branches in plants[102]. These studies underscore the remarkable diversity of coumarins and their derivatives, which play key roles in plant defense mechanisms against herbivores and pathogens. Moreover, plant growth-promoting microorganisms have been shown to enhance coumarin accumulation in angiosperms, suggesting a synergistic interaction that supports plant resilience[103]. While several host plants have been identified as possessing a rich repertoire of coumarin biosynthetic genes, a comprehensive understanding at genomic, transcriptomic, and metabolomic levels remains an ongoing need.

Elucidating the function and regulation of key genes could pave the way for engineering coumarin-rich plant lines or introducing these biosynthetic traits into microbial systems for sustainable production[104]. However, such genetic interventions must be carefully assessed to avoid unintended ecological or physiological consequences. Interestingly, gene expression profiles can be used to cluster related biosynthetic pathways based on shared metabolites[105]. For example, the coordinated expression of genes associated with 5-hydroxyferulic acid and 4-phenyl-3-butenoic acid correlates with the production of coumarins such as osthole[106]. Additionally, other metabolite clusters—such as those yielding columbianetin, umbellacins, scoparone, and scopoletin—highlight the convergence of these biosynthetic networks on compounds with defensive roles[107]. In conclusion, integrating gene expression data with metabolite profiling offers a promising strategy for dissecting the complexity of coumarin biosynthesis and unlocking its potential for agricultural and pharmaceutical applications.

## 5. Chemical properties of coumarins

### 5.1. Structural characteristics

Coumarins are a diverse group of naturally occurring and synthetically accessible compounds defined by their core 2*H*-chromen-2-one structure, which consists of a fused benzene ring and an α-pyrone moiety. The versatility of coumarins arises from the wide range of substitution patterns, particularly at key positions on the ring system. Among these, the C-7 position is the most commonly modified, with substitutions such as hydroxy, methoxy, or methyl groups known to enhance biological activity[108]. Modifications at other positions also contribute to the structural diversity—psoralens and 6-narcotine derivatives represent C-6 substitutions, while Marfey's coumarins exemplify substitution at C-8. On the other hand, coumarins can exist in tautomeric forms, typically displaying a keto form in solid state and an enol form in aqueous environments[109]. Each tautomeric form imparts distinct physicochemical properties to the molecule. The nature of the substituents, along with the size and geometry of fused ring systems and steric or electrostatic effects, plays a crucial role in determining molecular interactions and biological recognition[110].

One notable feature of many coumarins is their fluorescence, which is commonly exploited during natural product isolation. However, the intensity and color of fluorescence can vary significantly among different coumarins and do not consistently correlate with sampling time or specific compound identity[111]. Nuclear magnetic resonance studies support the existence of a dynamic equilibrium between keto and enol tautomers. Complementary quantum chemical calculations suggest that the keto form is typically more stable, especially when bulky groups are present at positions C-7 or C-8[112]. When smaller substituents are introduced at these sites, the equilibrium may shift, potentially resulting in a mixed tautomeric state, particularly when solvent effects are accounted for[113]. Therefore, the techniques used for compound isolation and purification have a significant impact on the measured physical properties of coumarins, such as fluorescence stability, quantum yield, and emission lifetime[114]. Understanding these influences is essential for accurate characterization and application of coumarin-based molecules in both research and pharmaceutical contexts[115].

### 5.2. Reactivity and stability

The coumarin scaffold, the simplest member of the chromone ring family, consists of a fused benzopyran structure that serves as a fundamental chemical framework. Its structural simplicity, lacking bulky or reactive substituents that could hinder reactivity, contributes to its versatility in synthetic chemistry[116]. Despite this apparent simplicity, coumarins exhibit a rich diversity of reactivity patterns that have been harnessed for targeted and efficient chemical transformations. Over the years, both academic and industrial research has continued to advance innovative applications of coumarins, ranging from their use as fluorescent probes to agents in phototherapy and drug formulation technologies[117].

A particularly intriguing property of coumarins lies in their photophysical behavior, their capacity to emit light, often triggered by external stimuli such as temperature, dry conditions, or exposure to solvents and air. These emissions can span from fleeting flashes to prolonged luminescence, yet the underlying mechanisms, such as why only certain coumarins fluoresce, remain incompletely understood[118]. Recent findings suggest that the stabilization of coumarins' excited electronic states via halogen bonding or intermolecular hydrogen bonds enhances singlet fission, enabling precise photonic control over electron relaxation and spontaneous co-crystallization in solid-state systems. This has been observed in dehalogenated coumarin structures and their halogenated intermediates. Moreover, mechanical stimuli have been shown to activate specific halogenated coumarin–benzoic acid co-crystals, releasing high-energy phosphorescent β-enone precursors[119].

In contrast, α,β-unsaturated carbonyl derivatives of coumarins are predicted to effectively neutralize superoxide radicals due to their potential for long-lived singlet excited states, possibly enhanced by the presence of heavy atoms[120]. Furthermore, the solubility and stability of coumarins can be finely tuned through pH modulation and by forming stable associations with co-formers, metal cations, biocompatible polymers, or pH-responsive single-chain amphiphilic liposomes. These formulation strategies have become mainstream, broadening the therapeutic and functional utility of coumarin-based compounds[121].

## 6. Biological activities of coumarins

Coumarins have emerged as a key class of bioactive compounds, attracting extensive scientific interest owing to their wide-ranging pharmacological activities, as recorded in **Table 3**. These naturally occurring molecules exhibit noteworthy antimicrobial, antioxidant, anticoagulant, and anticancer properties, making them valuable candidates in the search for new therapeutic agents. As a result, coumarins have become a central theme in pharmaceutical research, with ongoing studies exploring their full potential in drug development[122]. This section aims to simply highlight the multifaceted therapeutic promise of coumarins, focusing on their diverse biological actions and their evolving significance in contemporary medicine.

**Table 3**. Coumarin derivatives with potent biological activities along with their mechanisms of action.

| Coumarin derivative | Natural or synthetic | Biological activity | Mechanism of action | Ref. |
|---|---|---|---|---|
| Scopoletin | Natural | Anti-inflammatory | Inhibits COX-2 and NF-κB signaling | [123] |
| Umbelliferone | Natural | Antioxidant | Scavenges ROS | [66] |
| Esculetin | Natural | Hepatoprotective | Inhibits lipid peroxidation and enhances antioxidant enzymes | [124] |
| Daphnetin | Natural | Anticancer | Inhibits protein kinase and downregulates VEGF | [125] |
| Warfarin | Synthetic | Anticoagulant | Inhibits vitamin K epoxide reductase | [126] |
| Dicoumarol | Natural | Anticoagulant | Blocks vitamin K cycle enzymes | [127] |
| 7-Hydroxycoumarin | Synthetic | Antimicrobial | Disrupts bacterial cell wall synthesis | [128] |
| 6,7-Dihydroxycoumarin | Synthetic | Antioxidant | Inhibits lipid peroxidation | [129] |
| Coumarin-3-carboxylic acid | Synthetic | Anticancer | Inhibits topoisomerase I | [130] |
| Aesculetin | Natural | Antidiabetic | Enhances insulin sensitivity | [131] |
| Xanthotoxin | Natural | Anti-psoriatic | Intercalates DNA and inhibits cell proliferation | [132] |
| Imperatorin | Natural | Anti-inflammatory | Suppresses MAPK and NF-κB pathways | [133] |
| Isopimpinellin | Natural | Anticancer | Induces apoptosis in cancer cells | [134] |
| Bergapten | Natural | Photosensitizer | Enhances UVA-induced DNA damage | [135] |
| 3-(2-Benzothiazolyl)-7-(diethylamino)-2*H*-1-benzopyran-2-one | Synthetic | Fluorescent marker | Used in lipid trafficking studies | [136] |
| Auraptene | Natural | Chemopreventive | Suppresses tumor growth via apoptosis | [137] |
| Herniarin | Natural | Antimicrobial | Disrupts microbial membrane integrity | [138] |
| 7-Ethoxycoumarin | Synthetic | Probe substrate | Used in cytochrome P450 assays | [139] |
| Coumarin-3-aldehyde | Synthetic | Antibacterial | Inhibits bacterial DNA replication | [140] |
| Ferujol | Natural | Fertility enhancer | Modulates estrogenic activity | [141] |
| Marmesin | Natural | Phototoxic agent | DNA crosslinking under UV exposure | [142] |
| Coumarin-sulfonamide hybrids | Synthetic | Carbonic anhydrase inhibitor | Inhibits CA IX/XII isoenzymes | [143] |
| 4-Hydroxycoumarin | Natural | Anticoagulant precursor | Used to synthesize anticoagulant drugs | [6] |
| Coumestrol | Natural | Phytoestrogenic | Binds estrogen receptors | [144] |
| Hydroxyacetylcoumarin | Synthetic | Anticancer | Induces caspase-mediated apoptosis | [145] |

## 6.1. Antimicrobial properties

Coumarins, whether derived from natural sources or synthesized in the laboratory, can exert both beneficial and potentially harmful effects on human health. Notably, their antimicrobial properties have been widely documented[146]. Natural coumarins isolated from various plants have demonstrated significant activity against a broad spectrum of microorganisms, including bacteria, viruses, and fungi[147]. In parallel, numerous synthetic coumarin derivatives have been developed and evaluated for their selective antibacterial potency, particularly against drug-resistant strains such as *Enterococcus faecalis*, *Staphylococcus aureus*, and *Bacillus anthracis*[148]. In the context of fungal infections, coumarins have shown promising anticandidal activity. Several compounds in this class effectively inhibit the growth of *Candida* species, with a notable impact on *Candida albicans*[149]. Beyond growth inhibition, some coumarins have been reported to downregulate the expression of key virulence factors, thereby reducing the pathogen's ability to colonize and invade host tissues[150]. These findings underscore the potential of coumarins as valuable scaffolds for the development of novel antimicrobial therapies.

### 6.2. Antioxidant activities

Aging is a complex and progressive biological process characterized by the gradual accumulation of cellular and molecular damage over time. This deterioration is driven by a combination of intrinsic factors, such as genetic predisposition, and extrinsic influences, including environmental exposure, dietary habits, and sedentary lifestyles[151]. Among the various contributors to aging, oxidative stress, primarily induced by free radicals, is considered a major underlying mechanism. ROS like hydrogen peroxide, superoxide anions, and hydroxyl radicals can impair cellular structures by interacting with critical biomolecules, including proteins, lipids, and nucleic acids, ultimately compromising cellular function and integrity[152].

Antioxidants play a vital role in defending against oxidative damage. These compounds function either by neutralizing free radicals through electron donation, scavenging reactive species, or chelating metal ions involved in radical formation. Both natural and synthetic antioxidants have shown promise in slowing the progression of age-related disorders, including diabetes, obesity, cancer, and arthritis[153]. Given the pivotal role of oxidative stress in the aging process, there is a growing scientific interest in identifying new antioxidant agents, particularly those derived from natural sources[154]. Traditional medicine and ethnobotanical knowledge have guided the exploration of various plants known for their antioxidant properties. Among these, coumarins have demonstrated notable antioxidant activity and hold potential in mitigating oxidative damage linked to aging and related diseases[155].

### 6.3. Anticancer effects

Coumarins have garnered considerable attention for their multipotent antitumor properties in humans. Numerous studies have documented a wide array of coumarin derivatives with notable anticancer activity[156]. One of the earliest and most significant findings in this area involved umbelliprenin, a natural coumarin derivative isolated from *Ruta graveolens* (commonly known as rue, a member of the Umbelliferae family). This compound was among the first naturally occurring coumarins identified with pronounced anticancer potential. Subsequent investigations confirmed that umbelliprenin exerted cytotoxic effects against various cancer cell lines, particularly human hepatocellular carcinoma cells. As a selinane-type monoterpenoid, umbelliprenin emerged as a promising candidate for therapeutic development against liver cancer[157]. Mechanistic studies revealed that its anticancer activity involves the induction of oxidative stress and the promotion of autophagic cell death. Specifically, in BEL-7402 hepatoma cells, umbelliprenin enhances the phosphorylation of extracellular signal-regulated kinase, leading to cytotoxic autophagy[158].

While much of the research on coumarins has emphasized their direct cytotoxicity against tumor cells, recent findings have expanded our understanding of their role in immunomodulation[159]. For instance, certain coumarins have been shown to influence nitric oxide production in activated macrophages, highlighting their involvement in immune-mediated pathways of apoptosis and autophagic cell death[160]. Over the past decade, interest has grown in the relationship between tumor-associated macrophages and the progression of cancers such as breast and renal carcinomas. Emerging preclinical data from murine models have further suggested that coumarins may modulate the tumor microenvironment by influencing macrophage behavior, potentially opening new avenues for immunotherapeutic strategies, including targeting enzymes relevant to leukemia treatment[161].

## 7. Coumarins in traditional medicine

### 7.1. Historical uses

The historical use of coumarin-containing plants in traditional medicine dates back to ancient civilizations, well before the advent of modern pharmacology. One of the earliest documented sources, the Ebers Papyrus from ancient Egypt, outlines over 700 therapeutic remedies derived from medicinal plants, highlighting their role in maintaining health and treating various ailments[162]. Among these, the lotus flower was notable for its

psychoactive properties, attributed to its alkaloid content. Intriguingly, historical accounts suggest that beeswax, used in mummification processes, may have absorbed bioactive compounds such as coumarins from *Cinnamomum camphora* (camphor tree), thereby contributing to the preservation of bodies[163]. Some modern hypotheses even propose that the synergy between lotus-derived coumarins and wax layers acted as a natural embalming barrier, inhibiting microbial decomposition.

In traditional Chinese medicine, *Angelica sinensis* (commonly known as dong quai) has been used for centuries, particularly in the management of gynecological disorders. This plant is rich in coumarin derivatives, which are believed to underpin many of its therapeutic effects, especially those related to blood circulation and hormonal balance[164]. Beyond Asia and Egypt, coumarin-containing plants have been consumed for health-related purposes across Europe and South America. Herbs such as parsley, carrot, and celery, as well as the Tonka bean, native to South America, have long been part of traditional diets and medicinal regimens. Interestingly, coumarins are also naturally present in some fermented products like liquors, gin, and whiskey, where they contribute not only to the sensory characteristics but also to anecdotal health benefits reported in folk medicine[165]. Historically, such beverages were consumed for various ailments, including respiratory issues, muscle paralysis, and headaches[166].

### 7.2. Cultural significance

The therapeutic relevance of coumarins in traditional medicine is often overshadowed by the emphasis placed on their modern pharmacological applications and commercial value. Nonetheless, the historical roots of plant-based medicine trace back millions of years, far earlier than the advent of written language or formalized science[167]. Early hominin species, dating back over 4 million years, are believed to have instinctively incorporated medicinal plants into their diets to combat illness and promote well-being. Archaeobotanical evidence, including the analysis of ancient dental plaques, supports the use of therapeutic flora by human ancestors at least 1.5 million years ago[168].

As human civilization progressed, this primal knowledge evolved into more structured healing practices. The earliest written medical records, clay tablets from Mesopotamia over 5,000 years old, document the use of plant-derived remedies, including those likely to contain coumarins[169]. Priests and healers of early cultures played a central role in the codification and transmission of this medicinal wisdom. Across continents and generations, from the Far East and the Indian subcontinent to the Arab world, Europe, and the Americas, traditional knowledge continued to flourish, sometimes fading and at other times blossoming anew, ultimately laying the groundwork for contemporary medicine[170]. Plants rich in coumarins have held symbolic and ritualistic value in many cultures. In the Mediterranean, for instance, the Melilotus species—known for their sweet scent and coumarin content—were linked to Demeter, the Greek goddess of harvest and fertility. Likewise, the flowering *Amorpha fruticosa* was associated with Persephone, the deity of the underworld, symbolizing transformation and renewal[171].

Floral extracts like those from *Citrus aurantium* (bitter orange) were historically revered for their aromatic and therapeutic properties, with records of ecclesiastical figures using them in spiritual supplications[172]. *Angelica archangelica*, whose coumarin-rich roots and blossoms exude a distinctive fragrance, was celebrated as a divine gift, believed to protect against disease and misfortune. These botanical elements, appreciated for their aromatic allure and healing potential, frequently adorned sacred ceremonies, marking life's major transitions with both medicinal and symbolic grace[173].

## 8. Modern applications of coumarins

The structurally diverse and chemically versatile core of coumarins has positioned them as highly valuable scaffolds in contemporary drug design and development. Traditionally sourced from medicinal plants, herbals, and ethnobotanical remedies, coumarins continue to gain prominence across modern pharmaceutical

research[174]. Their expanding therapeutic potential reflects a growing convergence of interdisciplinary fields—including nanotechnology, polymer and solid-state chemistry, nanostructured delivery systems, coordination chemistry, and the development of biocompatible drug carriers[175]. These advances have enabled the creation of innovative coumarin-based formulations with enhanced bioavailability and targeted delivery profiles.

Ongoing bioactivity evaluations of coumarins, particularly those isolated from newly documented and pharmacologically relevant plants, have further highlighted their potential in treating infectious diseases[176,177] and various cancers[178,179]. Coumarins are being explored not only as therapeutic agents but also as biological probes, antimetastatic compounds, and adjuvants. The momentum of coumarin research is strongly supported by diverse synthetic methodologies, including combinatorial chemistry, photochemical modifications, asymmetric synthesis, and hybrid biosynthetic routes that integrate natural and chemical transformations[180].

Beyond the pharmaceutical realm, coumarins have also found significant roles in industrial applications. While their use in traditional medicine often garners attention, it is important to recognize that several coumarin derivatives are already in clinical or commercial use, pointing to their established relevance and future potential[181]. The resurgence of interest in natural healthcare systems such as Ayurveda and Traditional Chinese Medicine has further intensified focus on coumarins, emphasizing their inclusion in formulations aimed at holistic wellness[182].

Moreover, there is increasing scientific interest in standardizing coumarin content in traditionally used medicinal herbs, especially in gynecological applications[183]. Advances in understanding plant biosynthetic pathways—such as the regulation of *mbGATT* in response to molecular stress and its role in the biosynthesis of coumarins like esculin and umbelliferone from L-phenylalanine precursors—offer promising strategies to optimize the therapeutic profiles of these plants[184]. These developments suggest that harmonizing traditional plant composition with modern biosynthetic insights could lead to improved outcomes for a variety of health conditions[185].

## 8.1. Pharmaceutical developments

Coumarins represent a structurally diverse and biologically active class of natural products, widely regarded as valuable scaffolds in drug discovery. A notable botanical source of these compounds is *Melilotus officinalis*, commonly known as yellow sweet clover. The seeds and flowers of this plant yield a range of coumarin derivatives, with the essential oil extracted from its blossoms comprising over 30 phytoconstituents. Among these, the major compounds include 3-(1-acetoxyethenyl)-7-methoxy-2*H*-chromen-2-one, pentadecane, hexadecanoic acid, and 7-methoxy-3-(1-methoxyethyl)-2*H*-chromen-2-one[171].

In recent pharmacological investigations, piricet, a compound with neuroprotective properties, has been associated with a delay in Alzheimer's disease progression, albeit with modest symptom improvement. Furthermore, naturally occurring coumarins such as umbelliferone, esculetin, and escin have demonstrated ROS scavenging capacity, thereby attenuating oxidative stress in hyperglycemic cellular environments by reducing mitochondrial ROS production. Another noteworthy coumarin glycoside, umbelliferone-7-O-glucopyranosyl(1→3)-glucopyranoside, was recently isolated from the roots of *Angelica dahurica*. This compound and its analogues exhibited mild antiproliferative effects against HeLa cells[186]. Additionally, certain coumarins, particularly pyranocoumarin derivatives, have been shown to exert anti-inflammatory and anti-angiogenic effects, including the suppression of chemokine-mediated leukocyte transmigration, highlighting their potential in the treatment of inflammatory conditions[187].

Computational approaches have further accelerated the identification of bioactive coumarins. In a recent study, a machine learning-based screening of 65 coumarin derivatives identified several compounds with potent angiotensin-converting enzyme inhibitory activity, and predictive modeling highlighted 15 derivatives with favorable pharmacological profiles. In parallel, digital phytochemical mining revealed at least 180 antifungal coumarin derivatives from plant species endemic to Madagascar[188]. Lastly, research into *Ferula*

*persica* root-derived coumarins has demonstrated their immunomodulatory potential, particularly in allergic airway inflammation. These compounds appear to inhibit dendritic cell activation and suppress the differentiation of naïve T cells into Th2 cells, thereby mitigating the onset of allergic responses[189].

## 8.2. Cosmetic industry

The growing consumer awareness surrounding the potential risks of synthetic ingredients has significantly increased interest in natural compounds as key components of cosmetic formulations[190]. Among these, coumarins are drawing attention not only for their diverse biological activities but also for their symbolic connection to human interaction. Present in various plants and known to induce physiological responses such as blushing or subtle pheromone-like effects, coumarins may play a role in enhancing human connectivity and well-being[191]. This raises intriguing questions: Can incorporating coumarins into cosmetics contribute not only to individual care but also to fostering more authentic and sustainable human relationships? And when we consider sustainability, should we limit our focus only to a product's ingredients?

In the case of coumarins, sustainability extends well beyond composition. These compounds, derived from renewable and biodiverse plant sources, offer potential benefits for the entire product lifecycle. Their natural origin suggests low ecological toxicity and high biodegradability, making them less likely to pose harm when released into soil or water systems during product disposal[192]. As such, the integration of coumarins into eco-conscious cosmetic development aligns with the broader movement towards "green" beauty, creating formulations that support both personal and planetary health[193].

Functionally, coumarins are highly versatile in cosmetic science. They serve as fragrance enhancers, colorants, preservatives, and UV-protective agents. Consequently, they are commonly incorporated into products such as deodorants, sunscreens, shampoos, lotions, and oral hygiene items[194]. One promising area of research involves screening coumarins for their ability to modulate and enhance fragrance profiles in cosmetic formulations. With over 1,700 naturally derived fragrance molecules already meeting certification standards for natural cosmetics, coumarins offer a sustainable alternative to synthetic aroma compounds. Their inclusion may influence not only formulation strategies but also aesthetic and cultural trends in perfumery, resonating with traditions in herbal medicine and fragrance craftsmanship, particularly in historic centers of botanical trade[195]. Ultimately, the incorporation of coumarins into dermo-cosmetics and fine fragrance products reflects a broader paradigm shift, from synthetic convenience to bioinspired, sustainable innovation, redefining beauty as a holistic interplay between nature, health, and human experience.

## 8.3. Agricultural uses

Coumarins exhibit notable antioxidant and antimicrobial activities, which have positioned them as promising candidates for use as natural food preservatives[196]. Beyond the food industry, coumarins have also found valuable applications in agriculture due to their bioactive properties. Within plants, these compounds often function as natural insect deterrents, playing a dual role as both repellents and, in some cases, attractants depending on the insect species and coumarin structure. For instance, aphids have demonstrated varying behavioral responses to coumarins: some are repelled by specific coumarin derivatives, while others are attracted, particularly in scenarios where sweet clover is already infested, releasing volatile signals that draw additional aphids[197]. Other insect groups, such as beetles, ladybird beetles, and leafhoppers, are also influenced by the presence of coumarins, which can disrupt their host-selection processes. Interestingly, the presence of coumarins in certain plant species is often correlated with a reduced occurrence of pest insects, suggesting their role in enhancing plant defense mechanisms[198].

Given these properties, coumarins are being explored for their integration into integrated pest management strategies. Furthermore, their allelopathic potential—whereby they affect the growth of neighboring plants or microorganisms—has shown promise in controlling crop-invading fungal pathogens,

including those responsible for common diseases in wheat and rice[199]. Notably, some plant species naturally secrete higher levels of coumarins, while genetic modifications, such as gene knockouts, have led to increased coumarin exudation compared to wild-type counterparts. This opens new avenues for leveraging coumarin biosynthesis in sustainable agricultural practices[200].

## 9. Sustainable harvesting practices

Over the past few decades, the development of effective therapeutic agents has increasingly relied on a combination of semisynthesis and total synthesis, which often build upon natural product frameworks. Nature-inspired biosynthesis presents a promising and potentially sustainable route to discovering pharmacologically valuable agents[201]. Yet, unsustainable harvesting practices threaten this potential by endangering the very plant species that harbor unexplored therapeutic compounds. Alarmingly, global assessments suggest that approximately 20% of plant species face extinction, largely driven by overexploitation for commercial gain, particularly in tropical and subtropical regions where plant use is most intensive[202].

The rising demand for plant-based products, driven by population growth and a global pursuit of health and well-being, has intensified pressure on wild botanical resources. This dynamic raises critical concerns regarding the sustainability and ethics of current harvesting methods[203]. Overharvesting not only compromises ecological balance but may also impact the chemical integrity, therapeutic efficacy, and safety of plant-derived compounds such as coumarins. Ensuring the sustainable use of plant resources is essential, not only for preserving biodiversity but also for maintaining the quality of natural products in pharmaceutical applications[204]. Applying the principles of the circular economy, including waste reduction and resource efficiency, should be an integral part of processing coumarin-containing plants to meet modern pharmaceutical standards. While coumarin-based drugs have already secured a place in the therapeutic market, countless other plants remain underexplored, awaiting discovery through environmentally responsible and scientifically guided harvesting approaches. Preserving this natural heritage is not only an ethical imperative but also a strategic necessity for future drug discovery[205].

### 9.1. Ethical sourcing

Plants, especially those historically utilized in ethnomedicine, continue to serve as a cornerstone in modern drug discovery. With growing global recognition of traditional knowledge systems, there is an increasing emphasis on the ethical sourcing and sustainable use of medicinal plants. According to global health estimates, approximately 80% of the world's population relies, wholly or in part, on herbal remedies, often as their sole form of healthcare, particularly in underserved and rural communities[206]. As the commercial value of medicinal plants rises sharply, so too does the risk of unsustainable harvesting and socio-economic exploitation. This poses a dual threat: it endangers both the cultural communities that have stewarded these botanical resources for generations and the survival of plant species shaped by long-standing ecological and human interactions[207]. History has shown that traditional knowledge alone is insufficient to ensure conservation. However, when such knowledge is consciously passed down through generations, it can reinforce cultural identity and inspire active efforts to preserve these valuable resources[208].

The commercialization of plant-based bioactives has not been without controversy. Numerous legal disputes have emerged over the misappropriation of traditional knowledge, with indigenous communities often excluded from both recognition and benefit-sharing[209]. One of the most notable cases involved a contraceptive derived from knowledge attributed to indigenous communities in Puerto Rico. Although the inventors initially secured U.S. patent rights in 1994, the U.S. Patent Office later intervened in 1996 with a cease-and-desist order, acknowledging the ethical and cultural implications of the case. This example underscores the critical importance of equitable collaboration, transparent communication, and ethical compliance in bioprospecting[210]. It highlights the need for robust international guidelines to govern the interface between

patent authorities, scientific researchers, and indigenous knowledge holders. Developing clear frameworks for prior informed consent and benefit-sharing is essential to ensure that traditional communities are respected as rightful stakeholders in the global pursuit of natural product innovation[211].

### 9.2. Conservation efforts

Significant efforts are currently being made to promote the conservation of pharmacologically important plant species and to raise awareness among communities about the ecological threats these plants face. One effective initiative involves the deployment of "plant rangers"—specialized personnel dedicated to safeguarding endangered flora[212]. Educational outreach, such as distributing informational pamphlets, plays a crucial role in these efforts. These materials typically outline how to recognize threatened species, identify plants commonly used in traditional medicine, and report illegal harvesting to the appropriate authorities. Evidence suggests that such targeted educational campaigns have successfully contributed to reducing incidents of plant poaching[213].

A noteworthy example comes from a botanical survey in Lesotho, which highlighted several plant species requiring urgent conservation—species that are notably absent from South African floristic inventories. One such plant is *Gnaphalium polycaulon*, a member of the Asteraceae family, which has been identified in trade markets around Johannesburg[214]. Clearly, accurate regional identification of at-risk species is vital for implementing localized educational programs and guiding sustainable harvesting practices. This not only raises public awareness about plant endangerment but also helps protect human and animal health by ensuring that herbal products are harvested responsibly and safely[215].

Sustainable harvesting aims to allow for the continuous use of plant resources without compromising their long-term survival, an especially critical concern for small or fragmented populations. Unsustainable practices, such as indiscriminate or excessive harvesting, can significantly harm these plants, particularly when no species-specific guidelines are followed. Developing and disseminating detailed harvesting protocols, including when and how to collect plant parts and in which locations, can mitigate ecological damage while preserving the plants' medicinal value. Reducing illegal harvesting hinges largely on improving public understanding of which species are under threat and why. Building sustainable management frameworks for these plants requires collaborative input across stakeholders, from local harvesters and traditional healers to policymakers and conservationists. Establishing harmonized, science-based guidelines for sustainable use could ensure that pharmacologically valuable species are protected for future generations[216].

## 10. Challenges in coumarin research

The ongoing pursuit of novel, naturally occurring coumarins should not be seen as a futile or overly demanding endeavor. On the contrary, the continuous discovery of structurally diverse coumarins underscores the untapped potential within this class of compounds. For pharmacognosists and clinical pharmacologists who value alternative strategies beyond high-throughput screening or purely *in silico* methods, the exploration of coumarins remains a rewarding scientific pursuit[217]. Many lesser-studied plant genera offer promising sources of unique coumarins, especially when explored through interdisciplinary collaboration with natural product chemists. These unexplored natural reservoirs may yield coumarins with unprecedented structural motifs or stereochemical features, positioning them as valuable candidates for drug development—especially in the face of rising antimicrobial resistance and diminishing efficacy of current therapeutics[218].

Despite the appeal of synthetic and commercial libraries, these often provide only limited structural variation, typically achieved through simple modifications such as ortho-substitution. While such strategies offer convenience, they may fall short of addressing more complex pharmacological challenges, including solubility optimization, target selectivity, and resistance circumvention[219]. Natural coumarins, on the other hand, embody chemicogeographical signatures that influence their pharmacokinetic and safety profiles. These

intrinsic properties, shaped by evolutionary and environmental factors, may offer more favorable therapeutic indices and reduced toxicity profiles. Therefore, rediscovering coumarins from underexplored botanical sources is not merely a nostalgic scientific exercise, but a rational, forward-looking approach to identifying next-generation bioactive compounds with improved clinical potential[220].

## 10.1. Regulatory issues

The well-documented pharmacological properties of naturally occurring coumarins, combined with their long-standing use in traditional medicine, have sparked significant interest in their potential as lead compounds in drug discovery. In light of the growing global concern over treatment-resistant infections, there has been a renewed urgency to identify novel therapeutic agents. The escalating prevalence of bacterial and viral diseases, particularly HIV, tuberculosis, malaria, and various cancers, has driven substantial investments into the development of innovative pharmaceuticals[221]. To overcome limitations associated with conventional drug discovery, many life science companies and research institutions are increasingly turning to ethnopharmacology and traditional knowledge systems. This shift has intensified exploration into medicinal plants and the bioactive compounds they produce, with coumarins emerging as particularly promising candidates[222].

To ensure consumer safety and regulatory compliance, it is essential that these natural products undergo thorough safety and efficacy evaluations. This includes generating robust preclinical data and conducting systematic toxicological assessments[223]. Furthermore, developers must adhere to regulatory guidelines by preparing comprehensive product dossiers. These should encompass historical and ethnomedical usage, safety records, intended therapeutic indications, dosage recommendations, duration of use, proposed mechanisms of action, and scientific justification for use. Establishing this foundation is critical for the continued integration of coumarin-based products into modern healthcare and commercial markets[224].

## 10.2. Market access

The market access considerations must be focused primarily at the early stages of drug discovery and development, rather than delving into aspects related to regulatory approval or post-approval market limitations. At these initial phases, several critical factors influence decisions to invest in pharmaceutical research or advance a novel compound toward commercialization[225]. These include the perceived medical or commercial importance of the compound, projected market size, competitive positioning, estimated time to market, expected market penetration, and the anticipated return on investment. Additionally, aspects such as opportunity cost, technical hurdles in development, manufacturing feasibility, and financial sustainability are taken into account. These considerations are equally applicable to coumarin-based compounds[226].

The evaluation of candidate products typically follows a staged process. This begins with identifying and validating bioactive compounds, followed by optimizing their biological profiles and lead-like characteristics. Subsequent steps involve preclinical and early clinical development, scale-up for manufacturing, regulatory planning, and strategies for market introduction and expansion. For natural product-based drug candidates such as coumarins, securing a reliable and sufficient supply of the active ingredient at therapeutically effective and safe doses is essential, especially for advancing into clinical trials and regulatory evaluation[227]. From a commercial standpoint, the feasibility of large-scale production depends on either economically viable synthetic routes or efficient extraction from natural sources. However, the composition of plant-derived extracts can be influenced by numerous factors, including the plant's developmental stage, harvest timing, soil composition, and extraction methods; therefore, sustainable sourcing is a crucial consideration. This involves either controlled harvesting practices or cultivating medicinal plants under regulated conditions to ensure long-term availability and environmental responsibility[228].

# 11. Future directions in coumarin research

## 11.1. Innovative extraction techniques

Driven by the principles of green analytical chemistry, there has been a dual movement: the advancement of novel extraction methodologies and the refinement of conventional techniques that offer high yield and improved sustainability. Coumarin-rich plants also serve industrial purposes, imparting sweet, vanilla-like fragrances that are valued in perfumery, flavoring, cosmetics, and household products[229]. Traditional extraction of coumarins from aromatic plant materials frequently relies on methods such as Soxhlet extraction and continuous hydrodistillation. These approaches, while effective, are often time-consuming and require substantial quantities of water or organic solvents. In response, innovative macro- and micro-extraction techniques, combined with advanced chromatographic separations, are providing new insights into the composition and quantification of coumarin compounds[230].

Modern extraction technologies, such as solid-phase microextraction and dispersive liquid-liquid microextraction, have demonstrated high selectivity and sensitivity for isolating trace levels of coumarins from complex polyphenolic matrices. These methods are gaining traction not only for their analytical precision but also for their alignment with green chemistry principles. Furthermore, they offer promising alternatives for the selective recovery of plant phenolics, including coumarins[231]. On the other hand, validation studies are also of primary importance, including the quantification of specific coumarins such as osthole and xanthotoxin in *Plantago* species, as well as umbellin and co-occurring flavonoids—quercetin and luteolin—in *Nella*, a *Hypericum*-rich plant[232]. Finally, emerging trends in coupling selective extraction technologies with green and bio-responsive analytical systems are explored, underscoring their potential to enhance the efficiency, precision, and environmental compatibility of natural product research[233].

## 11.2. Synthetic biology approaches

In addition to optimizing extraction techniques, recent advances in synthetic biology are increasingly closing the gap between laboratory-scale production and industrial demands for coumarins, particularly in terms of sustainability and process efficiency. Metabolic engineering offers powerful strategies to manipulate biosynthetic pathways and significantly enhance coumarin yields. Moreover, the use of non-native microbial hosts expands both the scope of coumarin applications and their scalable production potential[234]. When considering the natural availability of 7,8-dihydroxycoumarins, certain plant species do produce these compounds selectively. However, the limited biomass of fruit and root tissues often restricts their utility for large-scale extraction, falling short of market demand. Synthetic biology provides a promising alternative by enabling the rational design of microbial systems capable of producing coumarin backbones at commercially viable levels[235].

Through the integration of bioinformatics and experimental biology, the engineering of cytochrome P450 enzymes has shown promise in tailoring the biosynthesis of structurally diverse coumarin derivatives. Simultaneously, incorporating well-characterized enzymatic modules and optimized metabolic pathways is crucial to avoid yield losses due to accumulation of intermediate compounds[236]. This is particularly relevant because many existing approaches to increasing natural coumarin production have relied on manipulating poorly understood or uncharacterized enzymes. Therefore, the iterative "design-build-test-learn" cycle inherent to synthetic biology holds significant potential in accelerating access to coumarin derivatives, especially those that are rare in nature or challenging to synthesize via traditional organic chemistry[237].

# 12. Case studies of coumarin derivatives

This section presents two illustrative case studies that showcase the clinical and preclinical development of coumarin derivatives. These examples were selected not only for their therapeutic potential but also for their

ability to represent distinct facets of coumarin's pharmacological versatility. In addition to exploring purposefully designed analogs, these case studies underscore the diverse mechanisms and applications associated with coumarin-based compounds. The latter part of the section shifts focus to research on coumarin-derived antioxidants. Unlike polyketide-inspired coumarin scaffolds, which often exhibit broad or non-specific activity, antioxidant derivatives are typically engineered to directly neutralize free radicals at their source. This functional divergence highlights the multifaceted nature of coumarin chemistry and its adaptability across different therapeutic domains.

## 12.1. Warfarin

Warfarin (**Figure 3**) is a widely prescribed oral anticoagulant, extensively used across the globe for the prevention and treatment of thromboembolic disorders. Its origins date back to the 1940s, when it was initially developed as a rodenticide following reports that cattle had died after ingesting spoiled sweet clover hay. This hay contained dicoumarol, a natural anticoagulant formed through microbial action. The active compound was later modified, giving rise to warfarin, which entered clinical use shortly thereafter as an effective inhibitor of blood clot formation[238]. A rare hereditary disorder characterized by the complete absence of measurable prothrombin and other vitamin K-dependent clotting factors has been linked to mutations in the VKORC1 gene. This gene encodes the enzyme vitamin K epoxide reductase complex subunit 1, the pharmacological target of warfarin and other vitamin K antagonists. Variations in this gene significantly affect warfarin sensitivity and dosing requirements among individuals[239].

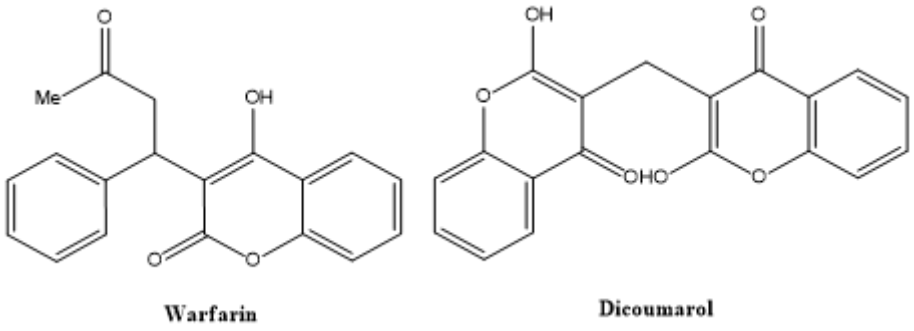


**Figure 3**. The chemical structures of warfarin and dicoumarol.

Despite the extensive characterization of warfarin, its structural behavior remains complex. Over the years, multiple conformations have been reported under varying experimental conditions. However, no single definitive structure has been universally accepted. This ambiguity is primarily attributed to the flexibility of the warfarin molecule, especially the rotational freedom between its aromatic rings and the carbomethoxy group. Even X-ray crystallographic studies have revealed different spatial arrangements, reflecting its conformational plasticity. Among the proposed forms, the oxime tautomer featuring an intramolecular N–O interaction involving the C3-H atom has gained widespread acceptance. Still, it remains uncertain whether this specific tautomer predominates in solution[240]. The high Lewis acidity of the carbonyl carbon at position C2 enhances the reactivity of the keto and enol tautomers toward biological nucleophiles, contributing to its pharmacological action. Interestingly, while many naturally occurring coumarins exhibit only mild anticoagulant effects, warfarin and structurally related compounds stand out due to their pronounced potency[241]. One exception is *Escherichia coli*, which can biosynthesize 7-hydroxycoumarin and warfarin analogs, underscoring the unique enzymatic adaptations of some microorganisms in utilizing coumarin scaffolds for bioactive molecule production[242].

## 12.2. Coumarin-based antioxidants

The increasing incidence of diseases associated with oxidative stress has intensified the search for novel compounds with antioxidant potential. Among naturally occurring substances produced through plant

secondary metabolism, polyphenols and phenolic derivatives have demonstrated strong capabilities for neutralizing free radicals. In this context, many research groups have focused on coumarins, particularly simple coumarin derivatives, due to their inherent structural features, such as aromatic rings and hydroxyl groups, which are known to facilitate interactions with reactive oxygen species[243]. Recent investigations have shown that certain simple coumarins, either isolated from tropical hardwoods or chemically modified to include functional groups such as alkyl, adduct, ether, acetal, carbonyl, or sulfhydryl moieties, as well as their sulfur- and nitrogen-containing analogues, exhibit notable antioxidant activity as evidenced by DPPH radical scavenging assays. In this regard, a series of coumarin derivatives featuring a pyrazole ring at the C-3 position, including both 3-pyrazolyl coumarins and their alkylated thiocarbamoyl analogues have been synthesized. These compounds were evaluated using the DPPH and ABTS radical cation assays, as well as a lipid peroxidation inhibition assay conducted on rat brain homogenates. Notably, 3-pyrazolylquercetin and 3-(phenyl)-pyrazolo-4-thienylquercetin demonstrated significant dual scavenging activity against both DPPH and ABTS radicals and were the most effective in inhibiting lipid peroxidation[244–246].

# 13. Coumarins and drug discovery

Coumarins continue to be a rich source for drug discovery due to their favorable characteristics. Their accessibility—whether through natural extraction or total synthesis—their broad structural diversity, and cost-effective production make them attractive scaffolds for developing small-molecule therapeutics and bioisosteric replacements[247]. This section aims to shed light on the pathway from high-throughput screening and computational modeling to the design and refinement of lead compounds. It explores how modern data integration, cheminformatics, and predictive algorithms contribute to the rational development of coumarin-based drug candidates.

Structurally, coumarins are particularly amenable to chemical modification, which enables fine-tuning of their pharmacological properties. Whether used as standalone agents or as part of hybrid molecules, coumarins demonstrate significant potential across various therapeutic areas. The integration of new computational tools and expansive chemical databases allows for more targeted structural modifications, helping researchers design compounds that fulfill specific biological roles[248]. In this context, the coumarin scaffold stands out as exceptionally compatible with modern drug discovery pipelines. Its broad pharmacological spectrum, ease of functionalization, and membership in a chemically diverse and biologically active molecular family provide a robust foundation for innovation[249]. Coumarins exemplify how natural compound classes can be harnessed, refined, and repurposed using contemporary bioinformatics and medicinal chemistry strategies to address today's therapeutic challenges.

## 13.1. Screening methods

Plant-derived natural compounds have historically served as vital sources of drug leads. Biodiversity-rich ecosystems, combined with the empirical knowledge embedded in traditional medicine, offer a vast reservoir of structurally unique and biologically active molecules. Many natural products exhibit novel modes of action distinct from synthetic agents. Advances in modern analytical and pharmacological technologies—such as bioassay-guided fractionation, high-resolution analytical techniques, pharmacokinetic modeling, and molecular mechanism elucidation—have bridged traditional medicine with contemporary drug discovery[250].

Coumarins, naturally present in a wide array of plant species, form a particularly promising class of bioactive molecules due to their structural diversity and broad pharmacological spectrum. Their therapeutic potential can be explored further using high-throughput screening techniques, now standard in drug discovery pipelines[251]. Additionally, coumarins can be evaluated in whole-organism models, aligning with traditional medicine's integrative approach to dosage optimization and route of administration. The incorporation of other bioactive compounds may further enhance the therapeutic efficacy of coumarins by clarifying their

pharmacodynamic profiles. Given the structural flexibility of the coumarin scaffold and its responsiveness to chemical modifications, it remains a valuable platform for the rational design of new drug candidates[252].

### 13.2. Lead Optimization

Natural products have historically played a pivotal role in drug discovery, offering a rich reservoir of chemically diverse and biologically active compounds. Their intricate structures and potent bioactivities make them valuable starting points for the development of new therapeutics. However, many natural leads face critical limitations, particularly related to poor bioavailability and potential toxicity, which often hinder their direct advancement into clinical use[253]. To overcome these challenges, lead optimization becomes a crucial phase in the drug development pipeline. This process aims to enhance therapeutic efficacy and minimize adverse effects by strategically modifying the structure of the original compound while preserving its biological function[254]. Advances in computational chemistry, especially techniques that model receptor-ligand interactions and quantitative structure–activity relationships, have revolutionized this phase. These tools can streamline the identification of more selective and potent derivatives, thereby accelerating the design of safer and more effective drug candidates[255].

## 14. Conclusion

Coumarins stand at the crossroads of tradition and innovation, embodying the enduring legacy of natural medicine while propelling modern scientific exploration. Their structural diversity, broad pharmacological profile, and remarkable adaptability have secured their role as valuable bioactive compounds in drug discovery, cosmeceuticals, and agrochemistry. This review has illustrated that coumarins are not merely botanical curiosities but rather sophisticated molecular frameworks capable of addressing some of the most pressing health and environmental challenges of our time.

The journey of coumarins, from their roots in ancient remedies to their transformation through synthetic biology and green chemistry, highlights the evolving relationship between nature and science. As technologies advance, so too does our capacity to harness coumarins sustainably, refine their therapeutic profiles, and tailor their bioactivities to specific clinical needs. Emerging tools such as machine learning, high-throughput screening, and metabolic engineering are already accelerating the pace of discovery and optimization, ushering in a new era for coumarin-based innovation.

Yet, challenges remain. Ensuring equitable access, ethical sourcing, and environmental stewardship must accompany scientific breakthroughs to preserve biodiversity and honor traditional knowledge systems. The integration of coumarins into circular bioeconomy frameworks offers a promising path forward—one that values not only efficacy and scalability but also resilience and sustainability. In closing, coumarins exemplify the harmony between natural heritage and scientific advancement. As looking to the future, their continued exploration—guided by interdisciplinary collaboration, responsible innovation, and a commitment to planetary health—may well unlock new frontiers in medicine, biotechnology, and sustainable development.

## Conflict of Interest

The authors declare no conflict of interest.

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