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A COMPREHENSIVE REVIEW ON PHARMACOLOGICAL IMPORTANCE OF COUMARIN AND ITS DERIVATIVES

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ABSTRACT

Coumarins are a well-known group of naturally occurring benzopyrone compounds that are widely present in plants, microorganisms, and some marine environments, and they have gained significant importance as versatile frameworks in medicinal chemistry. Their basic structure, consisting of a fused benzene ring and an α-pyrone moiety, offers considerable flexibility for chemical modification, allowing the development of a wide variety of biologically active derivatives. In recent years, coumarins and their analogues have been extensively investigated due to their diverse pharmacological properties, such as antioxidant, antimicrobial, anti-inflammatory, anticoagulant, antiviral, antidiabetic, neuroprotective, and anticancer activities. These effects are mainly attributed to their ability to neutralize reactive oxygen species, inhibit key enzymes, regulate important cellular signaling pathways, and interact with nucleic acids, thereby contributing to their therapeutic potential in multiple disease conditions. Beyond their medicinal applications, coumarin derivatives also exhibit significant value in diagnostic and analytical fields because of their strong photophysical and fluorescent characteristics, which make them suitable for bioimaging, chemical sensing, and monitoring applications. Recent progress in synthetic chemistry, including eco-friendly methods, microwave-assisted synthesis, and multicomponent reactions, has enabled the efficient production of structurally diverse compounds with improved biological activity and selectivity. Moreover, the use of computational approaches such as molecular docking, quantitative structure–activity relationship analysis, and prediction of absorption, distribution, metabolism, excretion, and toxicity properties has facilitated the rapid identification and optimization of potential drug candidates. However, certain limitations, including low aqueous solubility, rapid metabolic breakdown, and potential toxicity, still pose challenges for their clinical use. Overall, coumarins continue to represent important and adaptable pharmacophores with promising prospects for the development of novel therapeutic and diagnostic agents in modern drug discovery.

KEYWORDS: 7-hydroxy-4-methylcoumarin, coumarin derivatives, structure–activity relationship, pharmacological activities, antioxidant, antimicrobial, anticancer, antiviral, antifungal, anticoagulant, antibacterial, fluorescence applications.

INTRODUCTION

History and Background of Coumarins

Coumarins represent an important class of naturally occurring organic compounds with a long and fascinating history in natural product chemistry. The compound coumarin was first isolated in the early 19th century, around 1820, from tonka beans obtained from the plant *Dipteryx odorata*. At the time of its discovery, coumarin attracted attention primarily because of its distinctive sweet aroma, resembling freshly cut hay. This pleasant fragrance led to its widespread use in the perfume industry and, for a period, in flavoring agents.[1]

Natural occurrence

Coumarin is found naturally in many plants. Freshly ground plant parts contain higher amount of desired and undesired phytochemicals than powder. In addition, whole plant parts are harder to counterfeit; for example, one study showed that authentic Ceylon cinnamon bark contained 0.012 to 0.143 mg/g coumarin, but samples

purchased at markets contained up to 3.462 mg/g, possibly because those were mixed with other cinnamon varieties.[2,3]

- Vanilla grass (*Anthoxanthum odoratum*).[4]
- Sweet woodruff (*Galium odoratum*)
- Sweet grass (*Hierochloe odorata*)
- Sweet-clover (genus *Melilotus*).[5]
- Meranti trees (genus *Shorea*)
- Tonka bean (*Dipteryx odorata*)
- Fenugreek (*Trigonella foenum-graecum*).[6]
- Cinnamon; different varieties containing different levels of coumarin:
- Ceylon cinnamon or true cinnamon (*Cinnamomum verum*): 0.005 to 0.090 mg/g
- Chinese cinnamon or Chinese cassia (*C. cassia*): 1.74 to 7.67 mg/g
- Indonesian cinnamon or Padang cassia (*C. burmannii*): 2.14 to 9.30 mg/g
- Saigon cinnamon or Vietnamese cassia (*C. loureiroi*): 1.06 to 6.97 mg/g
- Deertongue (*Carphephorus odoratissimus*).[7]
- Tilo (*Justicia pectoralis*)
- Mullein (genus *Verbascum*)
- Many cherry blossom tree varieties (of the genus *Prunus*).
- Related compounds are found in some but not all specimens of genus *Glycyrrhiza*, from which the root and flavour licorice derives.[8]

Coumarin is found naturally also in many edible plants such as strawberries, black currants, apricots, and cherries.[9,10]

Coumarins were found to be uncommon but occasional components of propolis by Santos-Buelga and Gonzalez-Paramas 2017.

As scientific research progressed, the focus gradually shifted from its aromatic properties to its chemical composition and biological significance. Researchers discovered that coumarin is a type of secondary metabolite, meaning it is not directly involved in the basic metabolic processes of plants but plays a crucial role in their survival and adaptation.[11] It was subsequently identified in a wide variety of plant species, including sweet clover, citrus fruits, cinnamon, and numerous medicinal herbs. In these plants, coumarins function as natural defense compounds, helping to protect against microbial infections, insect attacks, and environmental stress factors such as UV radiation.[12,13]

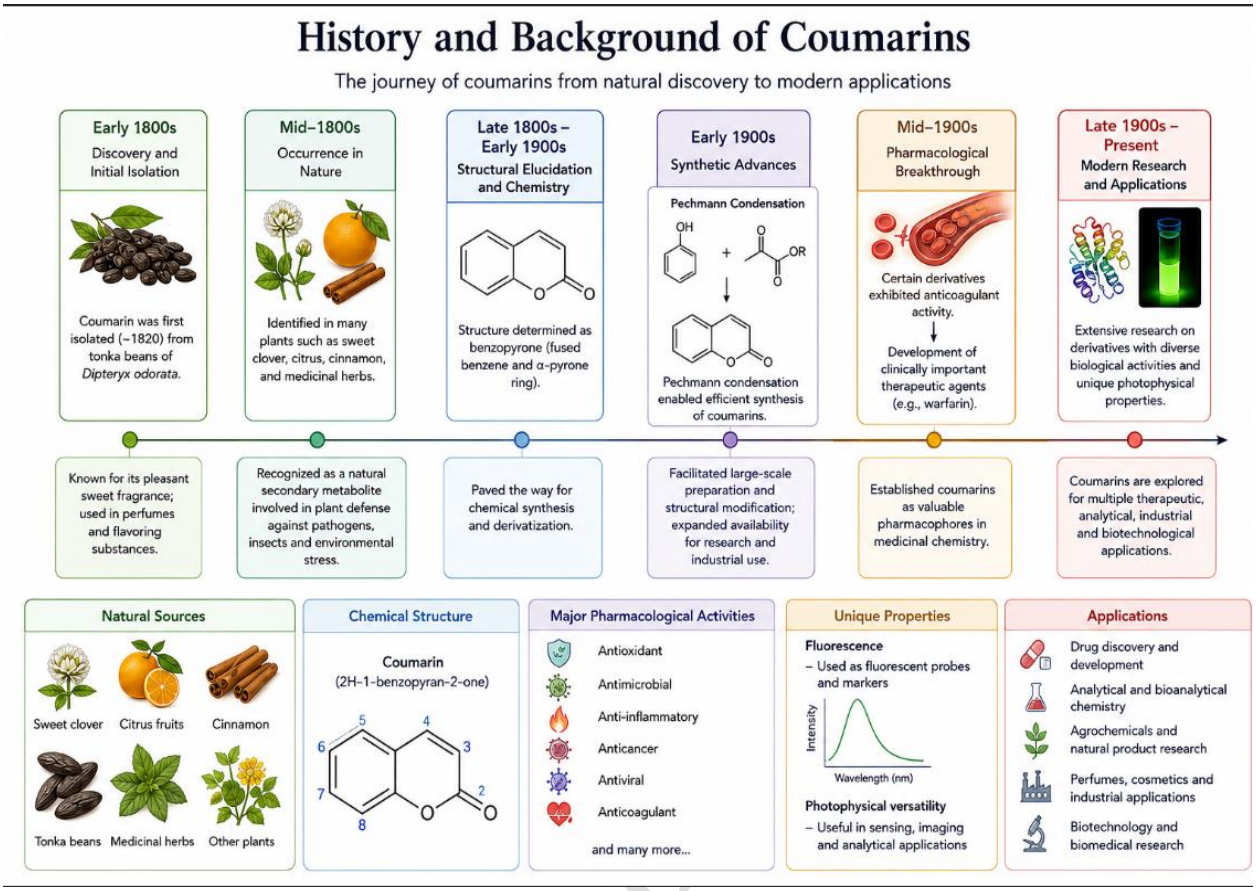
The advancement of organic chemistry during the late 19th and early 20th centuries marked a significant milestone in the study of coumarins. Scientists successfully determined its chemical structure, identifying it as a benzopyrone derivative, which consists of a benzene ring fused with an α-pyrone ring.[14,15] This structural elucidation opened the door for chemical synthesis and modification. One of the most important synthetic methods developed was the Pechmann condensation reaction, which allowed for the efficient laboratory preparation of coumarin and its derivatives. This development greatly increased the availability of coumarins for both scientific investigation and industrial applications.[16]

By the mid-20th century, coumarins gained considerable attention in the field of pharmacology. Certain synthetic derivatives were found to exhibit anticoagulant properties, leading to the development of clinically significant drugs used to prevent blood clot formation. This discovery marked a turning point, establishing coumarins as compounds of high medicinal value.[17,18]

In recent decades, research on coumarins has expanded extensively due to advances in medicinal chemistry and biotechnology. Modern studies have revealed that coumarin derivatives possess a broad spectrum of biological activities.[19,20] These include antioxidant, antimicrobial, anti-inflammatory, antiviral, and anticancer properties. Their versatility has made them promising candidates for drug development and therapeutic applications.

Additionally, coumarins exhibit notable fluorescent properties, which have led to their use in analytical chemistry, biochemical assays, and imaging techniques.[21] They are now commonly employed as fluorescent probes and markers in various scientific fields, including molecular biology and environmental analysis.

Overall, the development of coumarins has progressed from their initial discovery as natural aromatic compounds to their current status as important molecules in medicinal chemistry, industrial applications, and scientific research. Continued advancements are expected to further expand their potential in various fields.[22]



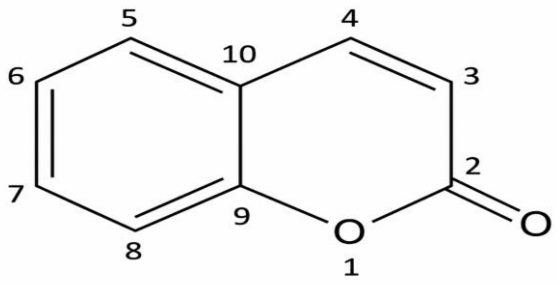
Introduction for coumarin and its derivatives

Coumarins are a group of benzopyrone derivatives characterized by a fused benzene and α-pyrone ring system. These compounds are widely distributed in nature and are present in higher plants, microorganisms such as bacteria, and certain fungi. As secondary metabolites, coumarins play an essential role in plant defense systems by protecting against microbial infections, herbivores, and environmental stress factors. They are particularly abundant in plant families like Apiaceae, Rutaceae, and Fabaceae.[23]

From a structural standpoint, coumarin consists of a benzene ring fused with an α-pyrone ring, forming a heterocyclic framework known as 2H-chromen-2-one. This structure possesses an extended conjugated π-electron system, which contributes to its stability as well as its ability to absorb ultraviolet radiation.[24] The presence of this conjugation is also responsible for the fluorescence exhibited by many coumarin derivatives, making them valuable in various scientific applications.

Chemically, coumarins display versatile reactivity due to the presence of both an aromatic ring and a lactone functional group. The aromatic portion readily undergoes electrophilic substitution reactions, while the lactone ring is susceptible to nucleophilic attack and hydrolysis under suitable conditions. This dual reactivity makes coumarins highly useful as intermediates in organic synthesis, enabling the preparation of a wide range of structurally diverse derivatives.[25,26]

Chemical Structure and Properties



The planar and conjugated structure of coumarin contributes significantly to its photophysical behavior. The molecule strongly absorbs ultraviolet light due to π-electron delocalization within the system.[27] Some important physicochemical properties of coumarin include:

- Molecular formula: $C_9H_6O_2$
- Molecular weight: 146.14 g/mol
- Physical state: Colorless crystalline solid
- Melting point: Approximately 68–70°C
- Solubility: Slightly soluble in water but readily soluble in organic solvents such as ethanol and ether.[28]

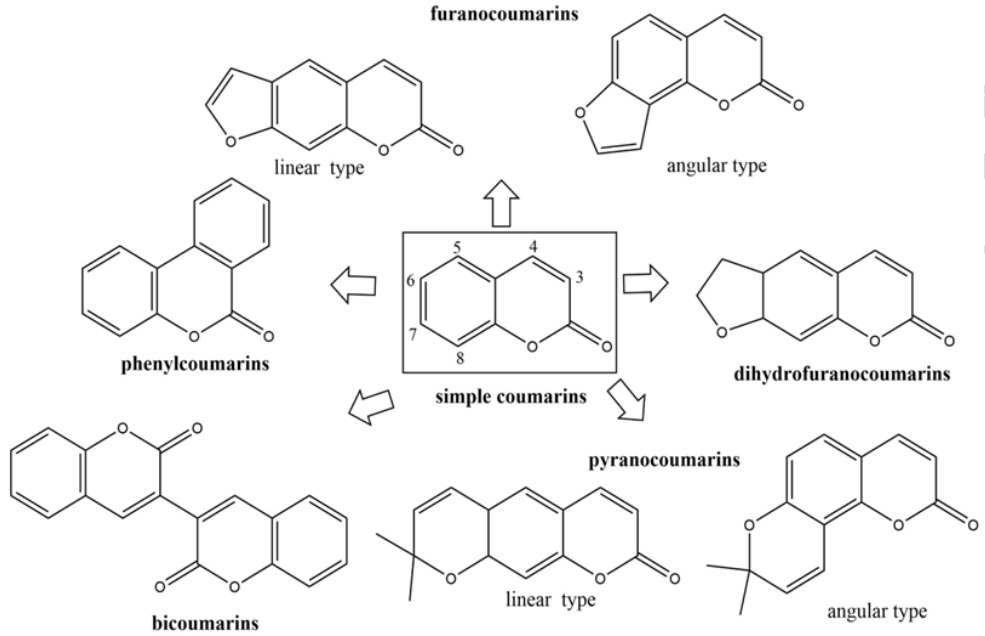
The lactone moiety plays a key role in chemical transformations, while substitutions on the aromatic ring influence both reactivity and biological function.

Classification of Coumarin Derivatives

Coumarin derivatives can be categorized based on their structural modifications into several groups:

- Simple coumarins
- Hydroxycoumarins
- Furanocoumarins
- Pyranocoumarins
- Substituted coumarins

Each category exhibits unique chemical characteristics and biological activities depending on the type and position of substituents attached to the coumarin core.[29]



Synthesis of Coumarin

A widely used method for synthesizing coumarins is the Pechmann condensation. This reaction involves the condensation of phenolic compounds with β-ketoesters in the presence of acidic catalysts.[30]

Pechmann Condensation Reaction (Coumarin Synthesis)

Phenol reacts with a β-ketoester under acidic conditions to form coumarin:

OH
|
Ar–OH + CH3–CO–CH2–COOR⟶(H2SO4/H3PO4, heat)⟶Coumarin + ROH (β-ketoester)

The mechanism generally proceeds through:

Step 1: Activation of β-ketoester (Protonation)

Acid protonates the carbonyl group, increasing electrophilicity:

CH3–CO–CH2–COOR + H+ → Activated β-keto ester.[31]

Step 2: Electrophilic Substitution (on Phenol)

The activated β-ketoester attacks the aromatic ring (ortho/para to –OH):

OH
|
Ar–H + Activated β-ketoester → Substituted intermediate

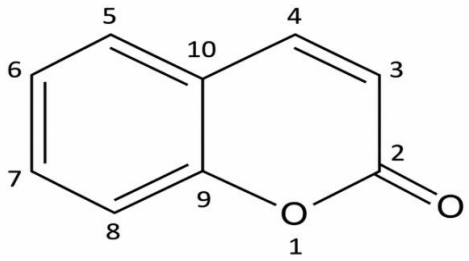
Step 3: Intramolecular Cyclization

The –OH group attacks the ester group forming a **lactone ring**

Intermediate → Cyclic intermediate (lactone formation)

Different catalysts such as sulfuric acid, phosphoric acid, and Lewis acids are commonly employed to improve the efficiency of the reaction. Modern techniques, including microwave-assisted synthesis and environmentally friendly (green) methods, are increasingly being used to enhance yield while reducing environmental impact.[32,33]

Structure–Activity Relationship (SAR) of Coumarin



Coumarin (1,2-benzopyrone) is a naturally occurring oxygen heterocyclic compound consisting of a benzene ring fused to an α-pyrone ring. Its biological activities are highly dependent on substitutions on this core scaffold, particularly at positions C-3, C-4, C-6, C-7, and C-8.

1. Coumarin Core Structure (Benzopyrone System)

- Consists of a benzene ring fused with an alpha-pyrone (lactone) ring
- Acts as the fundamental pharmacophore required for activity
- Provides molecular planarity, enabling efficient binding with biological macromolecules
- Facilitates interaction with proteins and DNA through π–π stacking and van der Waals forces.[34,35]
- The carbonyl group of the lactone ring serves as a hydrogen bond acceptor
- Maintains electronic delocalization, which is important for stability and reactivity
- Disruption of lactone ring leads to loss of activity
- Also contributes to UV absorption and fluorescence properties, useful in diagnostics.[36]

2. Substitution at Position 7 (Hydroxyl Group)

- Hydroxyl group at position 7 is crucial for activity
- Enhances hydrogen bonding with enzymes and receptors
- Responsible for antioxidant activity by donating hydrogen atoms
- Plays a key role in free radical scavenging and oxidative stress reduction
- Improves water solubility and polarity of the molecule
- Conversion to methoxy group:
  - Reduces antioxidant activity
  - Increases lipophilicity and membrane permeability
- Ester or ether derivatives:
  - May improve pharmacokinetics
  - Reduce direct antioxidant effect
- Forms metal complexes, enhancing antimicrobial and anticancer activity
- Important for binding affinity and target selectivity.[37,38]

3. Substitution at Position 4.

- Alkyl groups (such as methyl) increase lipophilicity
- Improve membrane permeability and absorption
- Enhance hydrophobic interactions with enzyme binding pockets
- Contribute to better pharmacokinetic properties
- Small substituents provide optimal activity
- Bulky groups may cause steric hindrance
- Large groups reduce binding efficiency and may affect target specificity
- Helps in balancing hydrophilic–lipophilic properties.[39]

4. Substitution at Position 3

- Important site for modifying biological activity
- Highly flexible position for drug design and optimization
- Electron-withdrawing groups (nitro, cyano):
  - Enhance antimicrobial activity
  - Improve anticancer activity
  - Increase electrophilic interaction with targets
- Amino and amide groups:
  - Improve enzyme inhibition
  - Effective against enzymes like cyclooxygenase and monoamine oxidase
- Conjugated systems:
  - Increase protein binding
  - Improve cytotoxic effects
  - Enhance electronic delocalization
- Plays a role in target specificity and potency enhancement.[40]

5. Substitution at Positions 6 and 8

- Influence electronic distribution of the molecule
- Affect reactivity and binding interactions
- Halogen groups (chlorine, bromine):
  - Increase lipophilicity
  - Enhance antimicrobial activity
  - Improve membrane penetration
- Methoxy groups:
  - Improve antioxidant activity
  - Enhance anti-inflammatory effects
- Dual substitution increases selectivity and potency
- Helps in fine-tuning pharmacological profile

6. Electron Donating and Electron Withdrawing Groups

- Electron-donating groups (hydroxyl, methoxy):
  - Increase antioxidant activity
  - Enhance free radical scavenging
  - Increase electron density in the aromatic system
- Electron-withdrawing groups (nitro, halogens):
  - Improve antimicrobial activity
  - Enhance anticancer effects
  - Increase enzyme binding and electrophilic interactions
- Influence chemical reactivity and biological interactions
- Balanced substitution is required for optimal activity.[41]
- Important for designing selective and potent derivatives

7. Lipophilicity and Biological Activity

- Moderate lipophilicity gives best biological activity
- Ensures proper membrane permeability and drug absorption
- Highly hydrophilic compounds:
  - Poor membrane permeability
  - Reduced bioavailability
- Highly lipophilic compounds:
  - Poor solubility
  - Reduced bioavailability
- Affects distribution and drug transport across membranes
- Balance between water solubility and lipid solubility is essential
- Critical for drug-likeness and pharmacokinetics.[42,43]

8. Hybrid Coumarin Derivatives

- Coumarin combined with other pharmacophores forms hybrid molecules
- Strategy used to enhance biological activity and overcome resistance
- Coumarin–chalcone derivatives:
  - Strong anticancer activity
  - Affect cell cycle and apoptosis pathways
- Coumarin–triazole derivatives:
  - Antimicrobial and antifungal activity
  - Improve enzyme inhibition.[44]
- Hybridization improves:
  - Target specificity
  - Multi-target action
  - Biological potency
- Useful in developing multifunctional therapeutic agents

9. Mechanistic Insights

- Antioxidant activity depends on phenolic hydroxyl groups
- Involves neutralization of reactive oxygen species
- Anticancer activity depends on:
  - Molecular planarity
  - Substitution at positions 3, 6, and 7
  - Interaction with DNA and enzymes
- Antimicrobial activity increases with:
  - Halogen substitution
  - Increased lipophilicity
- Enzyme inhibition depends on:
  - Hydrogen bonding
  - Aromatic interactions
- Multi-mechanistic action contributes to broad pharmacological profile.[45]

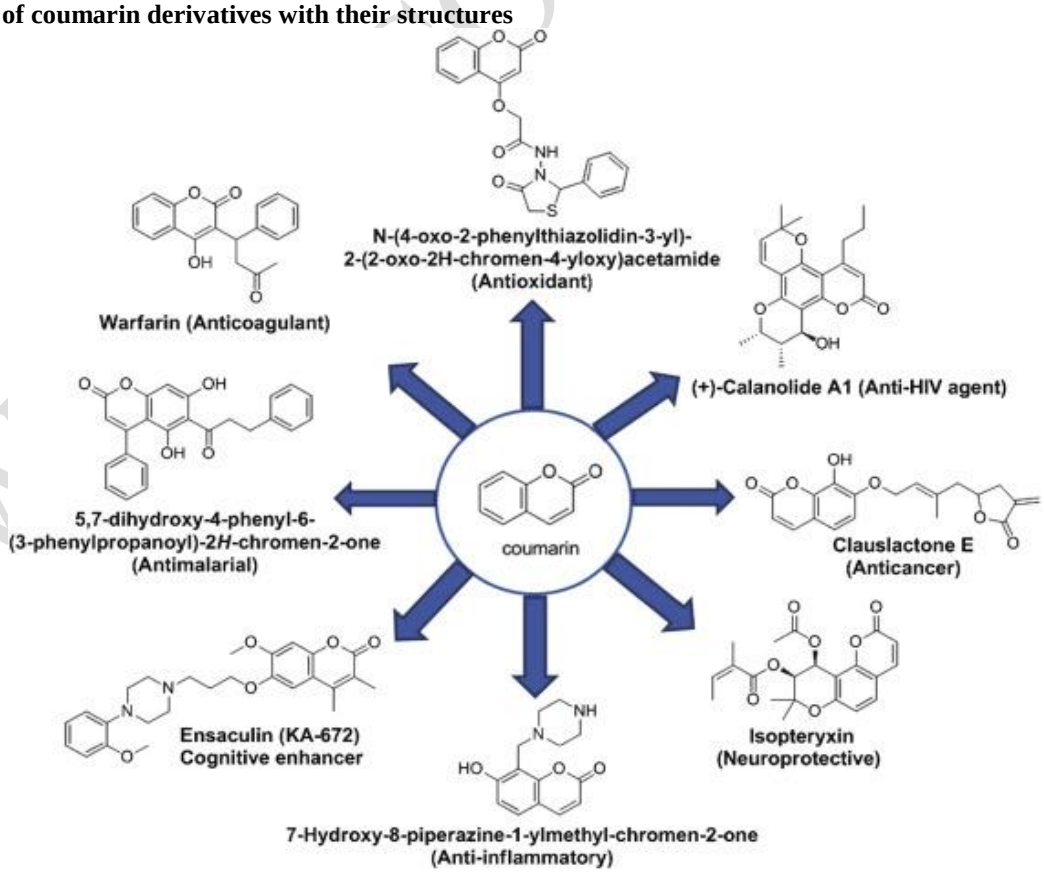
Dimerization and Fused Coumarins

- Dimeric coumarins (dicoumarols) show anticoagulant activity (e.g., warfarin-like effect).
- Fused coumarins (e.g., furocoumarins, pyranocoumarins):
  - Exhibit phototoxic, anticancer, and antimicrobial properties
  - Intercalate DNA upon UV activation

10. ADMET Considerations

- Hydroxyl groups may undergo rapid metabolism
- Reduces bioavailability through conjugation reactions
- Bulky groups:
  - Increase metabolic stability
  - May reduce solubility
- Lipophilicity affects absorption and distribution
- Important for drug transport and tissue penetration
- Structural modification required to:
  - Improve bioavailability
  - Reduce toxicity
  - Enhance stability
- Essential for successful drug development and clinical application

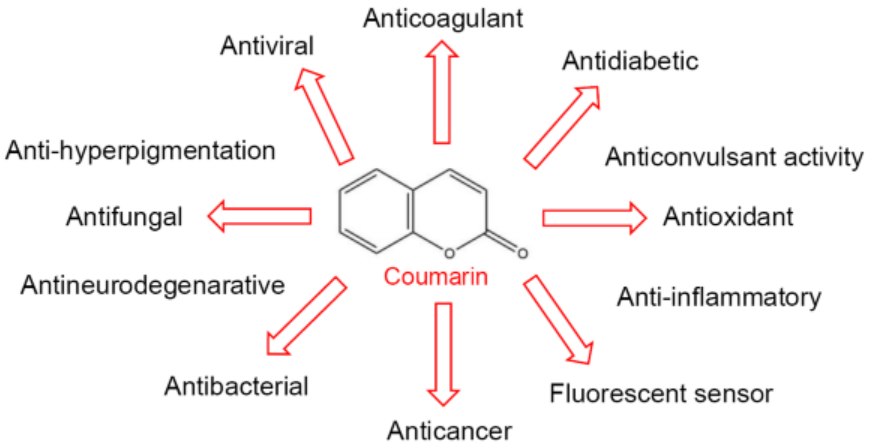
Examples of coumarin derivatives with their structures



Biological and Pharmacological Activities of Coumarin and their derivatives

Coumarins exhibit a diverse range of biological activities, which has attracted significant interest in medicinal chemistry. Some of their notable pharmacological effects include:

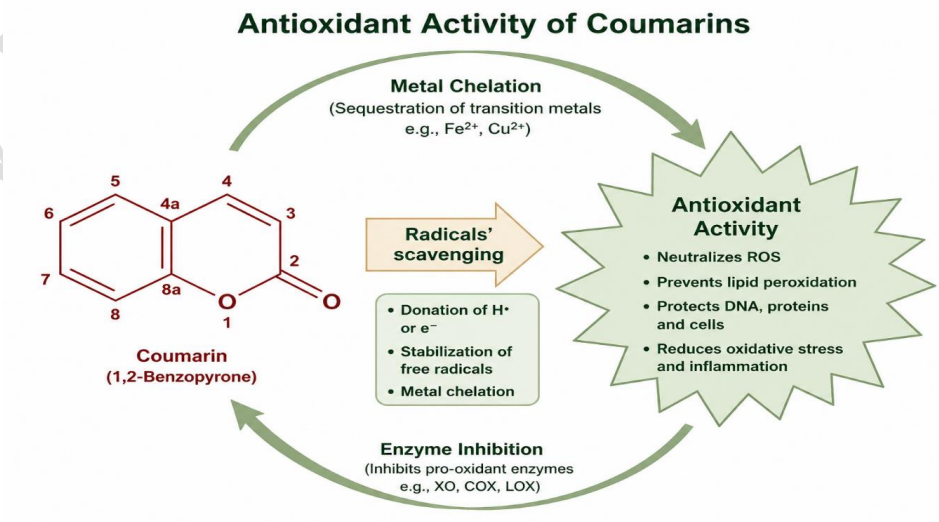
- Antioxidant activity through free radical scavenging
- Antimicrobial effects against bacteria and fungi
- Anti-inflammatory properties
- Anticoagulant activity, particularly in certain derivatives
- Potential anticancer effects.[46]



Anti oxidant activity

Coumarins exhibit significant antioxidant properties due to their conjugated π-electron system and phenolic structure. Their antioxidant activity is primarily attributed to their ability to neutralize reactive oxygen species (ROS) and free radicals such as superoxide, hydroxyl radicals, and hydrogen peroxide, which are involved in oxidative stress–related diseases.[47,48]

One of the principal mechanisms involves direct free radical scavenging**,** where coumarins donate hydrogen atoms or electrons to stabilize reactive species, converting them into less harmful molecules. Additionally, coumarins can act as metal chelators, binding transition metals like iron and copper, thereby preventing Fenton-type reactions that generate highly reactive radicals.[49] They also inhibit ROS-producing enzymes such as xanthine oxidase and lipoxygenase, further reducing oxidative damage. Structural features strongly influence antioxidant potential. Substituents such as hydroxyl (-OH) and methoxy (-OCH_3) groups enhance radical scavenging ability by increasing electron density and stabilizing phenoxyl radicals through resonance. Synthetic and semi-synthetic coumarin derivatives have been developed to optimize these properties, often showing improved antioxidant activity compared to natural counterparts. Overall, coumarins exhibit a multifunctional antioxidant mechanism**,** including radical scavenging, metal ion chelation, and enzyme inhibition, making them promising candidates for therapeutic applications in diseases associated with oxidative stress such as cancer, diabetes, and neurodegenerative disorders.[50,51]



Coumarins modulate several key signaling pathways associated with oxidative stress.

- **Nrf2 (Keap1–Nrf2 pathway):** Activation of Nrf2 enhances the expression of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase.
- **AhR:** Certain coumarins can modulate AhR-mediated gene expression involved in detoxification and oxidative stress.[52]
- **NF-κB:** Inhibition of NF-κB signaling reduces inflammation-associated oxidative damage.
- **PI3K/Akt pathway:** This pathway is modulated to support cell survival and indirectly enhance antioxidant defenses.[53]

Anti microbial activity

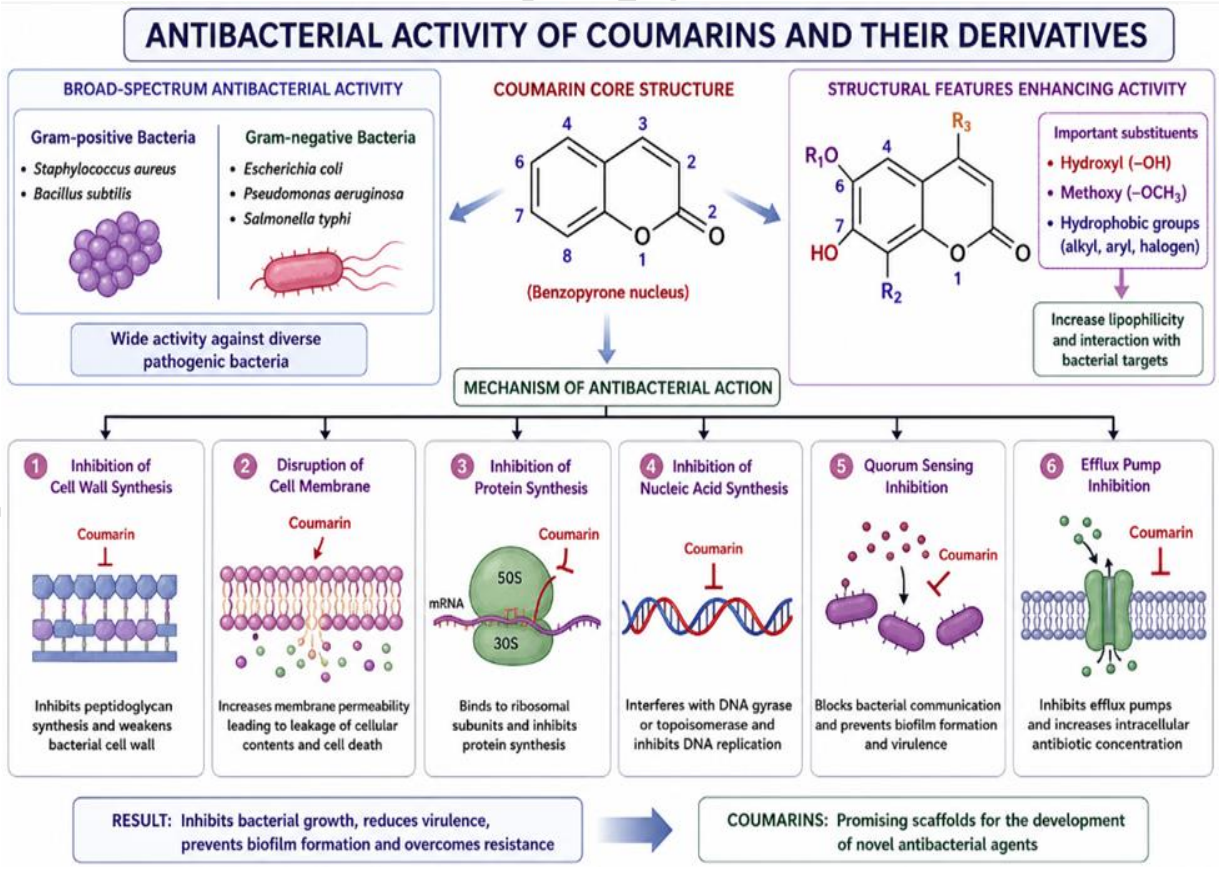
Coumarins and their derivatives possess considerable antimicrobial potential against a diverse range of microorganisms, including Gram-positive and Gram-negative bacteria as well as fungi. Both natural and synthetic forms have been reported to act against pathogens such as Staphylococcus aureus, Escherichia coli, and Salmonella typhi, reflecting their wide biological applicability.[54]

Their mechanism of action is multifaceted, involving disruption of membrane integrity, inhibition of nucleic acid synthesis, and suppression of essential enzymatic processes. Additionally, coumarins interfere with bacterial communication systems by blocking quorum sensing and limiting biofilm development, thereby reducing pathogenicity and resistance. Structural modifications within the coumarin framework strongly influence activity, where functional groups such as hydroxyl, methoxy, and hydrophobic substituents enhance lipophilicity and improve interaction with microbial targets. These combined effects make coumarins promising scaffolds for the development of novel antimicrobial agents, particularly in combating resistant microorganisms.[55]

Anti microbial targets of coumarins are

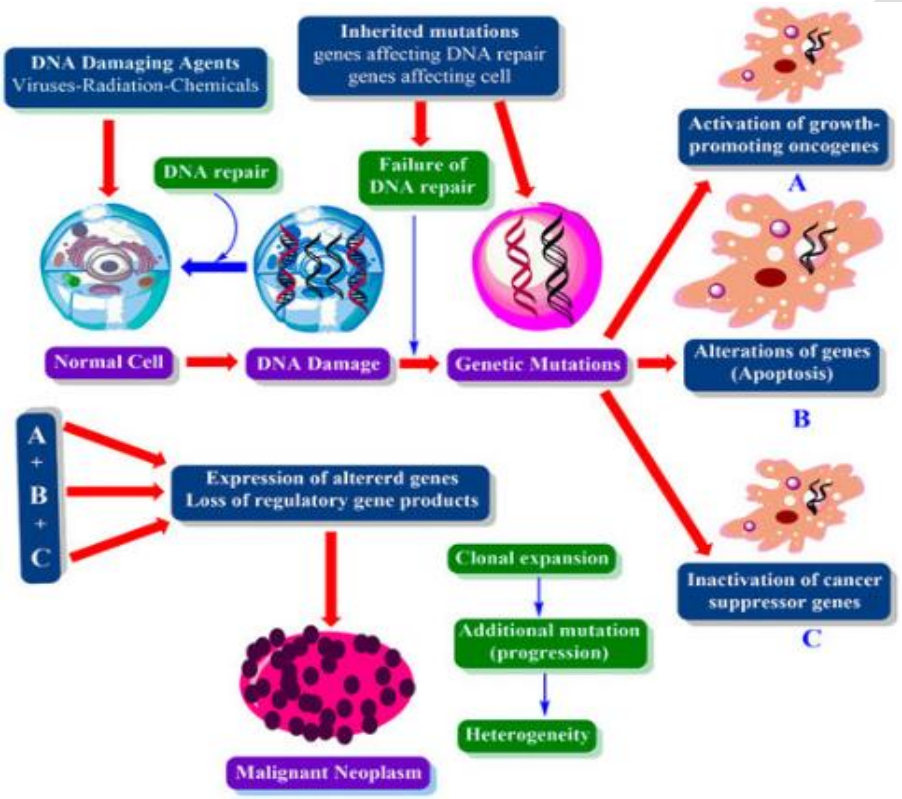
- **DNA gyrase (GyrB subunit):** Coumarins bind to the ATP-binding site and inhibit bacterial DNA replication.
- **Topoisomerase IV:** They block chromosome separation during bacterial cell division.
- **Efflux pumps (e.g., NorA):** They inhibit drug efflux, increasing intracellular antimicrobial concentration.
- **Quorum sensing receptors (LuxR-type):** They disrupt bacterial communication and biofilm formation.[56]
- **Cell membrane components:** They damage membrane integrity, causing leakage of cell contents.

Fungal CYP51 enzyme: They inhibit ergosterol synthesis, weakening fungal cell membranes.



Anticancer activity

Cancer remains a major global health concern, driving the search for new anticancer agents. Coumarin derivatives have shown strong potential, though their mechanisms are not fully understood.[57] The compound RKS262 inhibits ovarian cancer cell growth by inducing mitochondrial dysfunction, leading to loss of membrane potential and regulation of apoptosis-related proteins—upregulating pro-apoptotic factors (Bid, Bad, Bax) while downregulating anti-apoptotic proteins (Bcl-xL, Mcl-1). Similarly, dicoumarin polysulfide SV25 causes G2/M cell cycle arrest in HCT116 colon cancer cells and promotes apoptosis through increased Bax and cytochrome c expression along with activation of caspase-3 and caspase-7. Coumarin analogues Tr1 and Tr2 further show anticancer potential by binding and stabilizing G-quadruplex DNA structures, suggesting a novel therapeutic target. Another derivative, 7-diethylamino-3-(2′-benzoxazolyl)-coumarin (DBC), disrupts microtubule dynamics, resulting in mitotic arrest at the G2/M phase with selective toxicity toward cancer cells over normal fibroblasts. In addition, DMAC inhibits colon cancer cell proliferation by inducing apoptosis through Bak upregulation, caspase-3 activation, PARP cleavage, and typical apoptotic morphological changes such as chromatin condensation and cellshrinkage.[58,59]



Coumarin, as an anti cancer agent, binds to receptors such as

- Aryl hydrocarbon receptor – Coumarins modulate AhR to regulate gene expression and inhibit tumor growth.
- Estrogen receptor – They interact with estrogen receptors and may suppress hormone-dependent cancers.
- Topoisomerase I / II – Coumarins inhibit these enzymes, blocking DNA replication in cancer cells.
- PI3K / Akt – They suppress this pathway, reducing cell survival and proliferation.[60]
- NF-κB – Coumarins inhibit NF-κB, decreasing inflammation and tumor progression.
- VEGF – They inhibit VEGF signaling, preventing tumor angiogenesis.
- Cyclin-dependent kinases – Coumarins regulate CDKs, leading to cell cycle arrest.

Antiviral Activity

1. Overview of antiviral properties

Coumarins are a class of benzopyrone compounds widely recognized for their potential as antiviral agents. They occur naturally in plants, fungi, and microorganisms and have been extensively studied as promising scaffolds in antiviral drug development. Their effectiveness largely depends on structural modifications, which can significantly influence biological activity.

These compounds have demonstrated activity against several viruses, including HIV, influenza, hepatitis C virus (HCV), herpes simplex virus (HSV), and coronaviruses. Even small changes in their chemical structure can enhance or reduce their antiviral potency.[61,62]

2. Mechanism of antiviral action

Coumarin derivatives exert antiviral effects through multiple pathways, making them versatile therapeutic candidates:

- **Enzyme inhibition:** They can block key viral enzymes such as reverse transcriptase and integrase, particularly in HIV.
- **Inhibition of viral replication:** These compounds interfere with viral entry, replication, and protein synthesis.[63]
- **Host-target interaction:** Some derivatives affect host cell mechanisms that are essential for viral survival and propagation.

3. Examples from research studies

A. Anti-HIV activity

Certain natural and synthetic coumarin derivatives, such as pyranocoumarins (e.g., calanolides), have shown strong inhibitory effects on HIV-1 reverse transcriptase. Another compound, wedelolactone, has been reported to inhibit HIV integrase. These multi-target effects reduce the likelihood of resistance.[64]

B. Activity against coronaviruses

Recent studies have highlighted the antiviral potential of newly synthesized coumarin derivatives against coronaviruses, including SARS-CoV-2. These compounds are typically prepared through reactions such as esterification, hydrazination, and cyclization, and are being explored for their therapeutic potential in COVID-19 treatment.[65]

C. Broad-spectrum antiviral activity

Some coumarin derivatives have shown effectiveness against multiple viral strains, including drug-resistant HIV variants. For example, certain compounds exhibit inhibitory activity against viral enzymes like RNase H, demonstrating their broad-spectrum nature.[66]

D. Anti-chikungunya and anti-HCV activity

Hybrid molecules combining coumarin with other pharmacophores, such as quinazoline, have shown enhanced antiviral activity. These compounds exhibit significant effectiveness against chikungunya virus (CHIKV) and hepatitis C virus (HCV), highlighting the benefits of molecular hybridization.[67]

E. Activity against IHNV

Imidazole-containing coumarin derivatives have demonstrated potent antiviral effects against infectious hematopoietic necrosis virus (IHNV). These compounds reduce virus-induced cellular damage and inhibit apoptosis, making them potential candidates for further drug development.

F. Synthetic derivatives with modified functional groups

Coumarin derivatives containing functional groups like dithioacetals have shown promising antiviral activity in experimental models. Such structural modifications improve both the stability and biological activity of the compounds.[68]

4. Structure–Activity Relationship (SAR)

The antiviral activity of coumarins is strongly influenced by their chemical structure:

- The presence of hydroxyl groups enhances binding interactions.
- Fused ring systems (such as pyran or furan rings) increase biological activity.
- Incorporation of heterocycles (e.g., imidazole, quinazoline) improves selectivity.
- Hybrid compounds often show better potency due to multi-target action.
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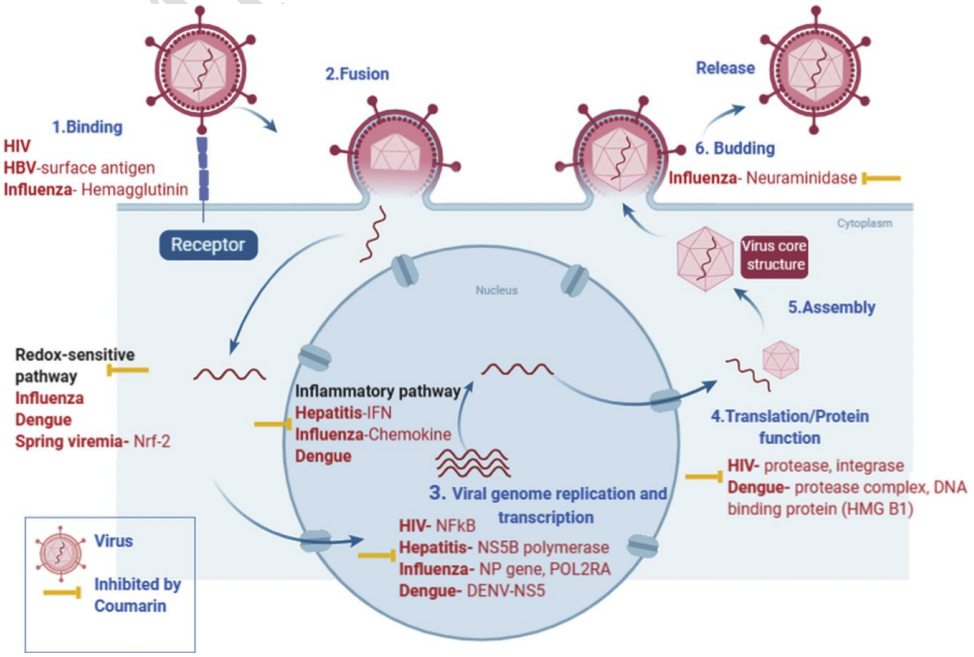


Antifungal Activity of Coumarin and Its Derivatives

1. Overview of antifungal properties

Coumarins are naturally occurring benzopyrone compounds widely distributed in plants and microorganisms. They have gained considerable attention due to their diverse biological activities, including significant antifungal potential. These compounds are being explored as alternatives to conventional antifungal agents, especially in response to increasing drug resistance.[69]

Coumarin derivatives have shown activity against a variety of fungal pathogens such as Candida albicans, Aspergillus niger, Aspergillus fumigatus, and Cryptococcus neoformans. Their antifungal effectiveness is highly dependent on structural modifications and functional group substitutions.

2. Mechanism of antifungal action

Coumarin derivatives exhibit antifungal effects through multiple mechanisms:

- **Disruption of fungal cell membrane:** They interfere with ergosterol biosynthesis, leading to increased membrane permeability.
- **Inhibition of fungal enzymes:** Certain derivatives inhibit key enzymes involved in fungal metabolism.[70]
- **Induction of oxidative stress:** They can generate reactive oxygen species (ROS), causing cellular damage.
- **Inhibition of biofilm formation:** Some compounds prevent fungal adhesion and biofilm development.

3. Examples from research studies

A. Activity against *Candida* species

Several natural and synthetic coumarins have demonstrated strong inhibitory effects against Candida albicans. Hydroxylated coumarin derivatives, in particular, show enhanced antifungal activity due to improved interaction with fungal targets.

B. Activity against Aspergillus species

Coumarin derivatives have been reported to inhibit the growth of Aspergillus niger and Aspergillus fumigatus. Substituted coumarins with electron-donating or withdrawing groups often exhibit improved antifungal potency.

C. Hybrid coumarin derivatives

Hybrid molecules combining coumarin with other pharmacologically active moieties (such as triazoles or imidazoles) show increased antifungal activity. These hybrids act on multiple targets, enhancing efficacy and reducing resistance.

D. Synthetic derivatives with enhanced activity

Newly synthesized coumarin derivatives, including Schiff bases and heterocyclic analogues, have shown promising antifungal activity in vitro. These compounds often display better stability and stronger activity compared to parent coumarins.

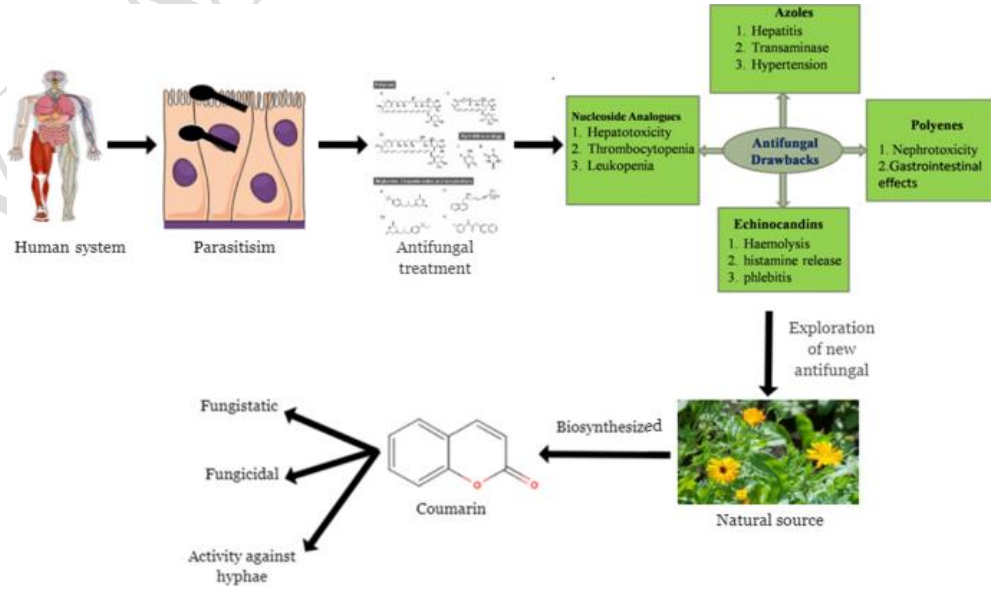
E. Agricultural antifungal applications

Coumarin derivatives have also been evaluated for controlling plant pathogenic fungi. Some compounds exhibit strong inhibitory effects against phytopathogens, making them useful in agricultural applications.[71]

4. Structure–Activity Relationship (SAR)

The antifungal activity of coumarins is influenced by several structural features:

- **Hydroxyl (-OH) groups** enhance antifungal potency.
- **Methoxy (-OCH_3) substitutions** can improve lipophilicity and membrane penetration.
- **Fused ring systems** increase biological activity.
- **Heterocyclic substitutions** (e.g., triazole, imidazole) enhance selectivity and efficacy.
- **Hybrid molecules** show improved multi-target action.[72]



Anticoagulant Activity of Coumarins, Their Mechanism and Derivatives

- Coumarins are an important class of benzopyrone derivatives known for their strong anticoagulant properties. Both naturally occurring and synthetic coumarin derivatives are widely used in medicine to prevent and manage thromboembolic disorders. Their activity is primarily associated with interference in the vitamin K–dependent blood coagulation pathway.
- **Mechanism of Anticoagulant Action:**

1. Inhibition of Vitamin K Epoxide Reductase (VKOR)

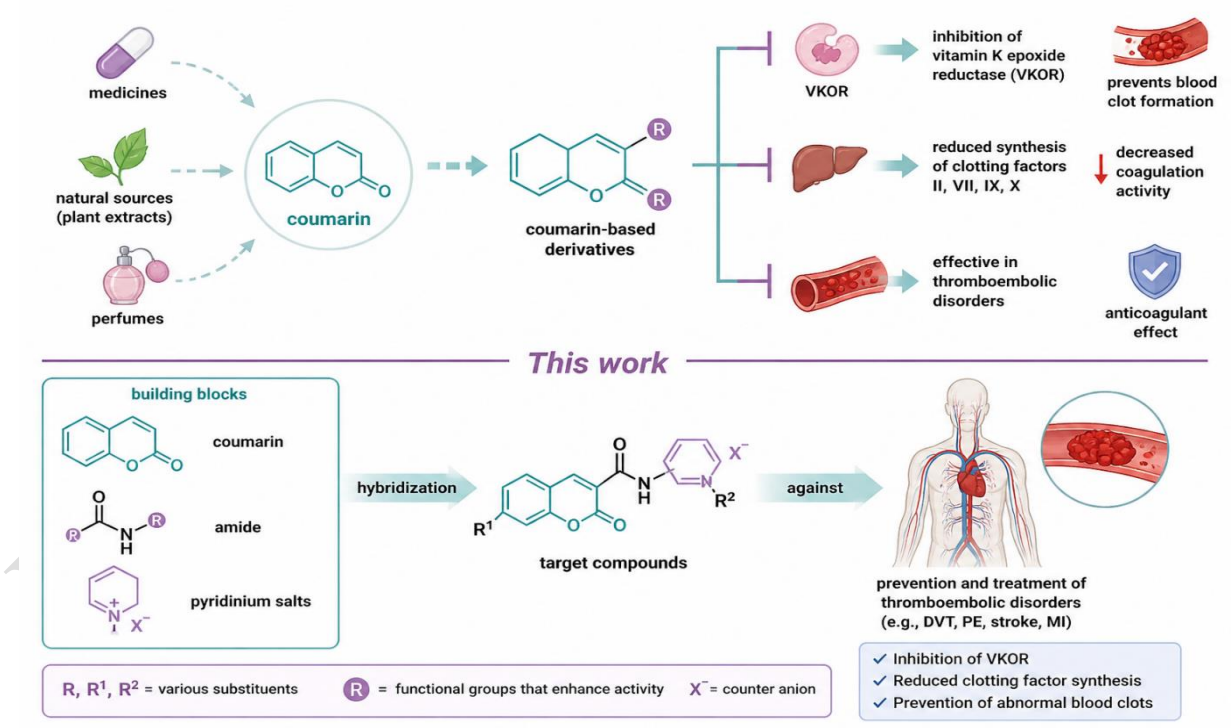
- The main mechanism involves inhibition of the enzyme vitamin K epoxide reductase (VKOR).
- This enzyme normally regenerates active (reduced) vitamin K from its inactive epoxide form.
- Coumarin derivatives block this recycling process, leading to depletion of active vitamin K in the liver.

2. Decreased Synthesis of Vitamin K–Dependent Clotting Factors

- Active vitamin K is essential for γ-carboxylation of specific clotting factors.
- Inhibition of vitamin K regeneration results in reduced production of functional clotting factors II (prothrombin), VII, IX, and X.
- These factors become biologically inactive due to lack of proper modification.

3. Interference with the Coagulation Cascade

- The deficiency of active clotting factors slows down the coagulation process.
- This leads to prolonged clotting time and prevents the formation of abnormal blood clots.
- **Examples of Coumarin Derivatives with Anticoagulant Activity**
- **Warfarin**
  A widely prescribed anticoagulant that effectively inhibits VKOR and is used to prevent thrombosis and embolism.
- **Dicoumarol**
  A naturally derived compound that was historically important in the development of anticoagulant therapy.
- **Acenocoumarol**
  A synthetic derivative with a shorter duration of action, commonly used as an alternative to warfarin.
- **Phenprocoumon**
  A long-acting coumarin derivative used in long-term anticoagulant therapy.[73,74]



Antibacterial Activity of Coumarins and Their Derivatives

Coumarins, which belong to the benzopyrone class of compounds, are naturally occurring as well as synthetically modified molecules known for a variety of biological properties, including strong antibacterial activity. Their effectiveness largely depends on structural modifications such as hydroxyl, methoxy, halogen, and heterocyclic substitutions, which improve their interaction with bacterial targets.[75]

These compounds exhibit activity against both Gram-positive bacteria like Staphylococcus aureus and Bacillus subtilis, and Gram-negative organisms such as Escherichia coli and Pseudomonas aeruginosa. Due to their broad-spectrum action, coumarins are considered promising candidates in the development of new antibacterial drugs, especially to address antibiotic resistance.[76]

Examples of Coumarin Derivatives with Antibacterial Activity

1. Basic Coumarins

Umbelliferone (7-hydroxycoumarin)

Displays moderate antibacterial effects against Escherichia coli and Staphylococcus aureus, mainly due to the presence of a hydroxyl group that enhances binding with bacterial enzymes.

Esculetin (6,7-dihydroxycoumarin)

Exhibits stronger antibacterial properties as the additional hydroxyl group increases its ability to interact with bacterial proteins and DNA.

2. 4-Methylcoumarin Derivatives

7-Hydroxy-4-methylcoumarin (4-methylumbelliferone)

Shows effective antibacterial activity against Bacillus subtilis and Staphylococcus aureus. Substitutions at specific positions enhance lipophilicity and facilitate better penetration into bacterial cells.[77]

3. Coumarin–Hydrazone Derivatives

These compounds are synthesized by reacting coumarins with hydrazine or related derivatives.

They demonstrate strong antibacterial activity, particularly against Mycobacterium tuberculosis and Staphylococcus aureus.

The hydrazone linkage improves binding affinity with bacterial enzymes.

4. Halogen-Substituted Coumarins

The introduction of halogen atoms such as chlorine, bromine, or fluorine enhances lipophilicity and chemical stability.

These modifications result in improved antibacterial activity, even against resistant strains.

Example

Chlorinated coumarin derivatives show increased effectiveness against *Escherichia coli*.[78]

5. Fused Coumarin Derivatives

Structurally fused coumarins, such as benzocoumarins, exhibit higher antibacterial potency due to increased rigidity and stronger interaction with bacterial targets.

6. Coumarin–Metal Complexes

Complexes formed with metals like copper and zinc often display greater antibacterial activity than the parent compounds.

Metal ions assist in better cellular penetration and may induce oxidative damage in bacteria.

Example

Copper–coumarin complexes are highly active against Staphylococcus aureus and Escherichia coli.[79]

Mechanisms of Antibacterial Action

1.Inhibition of DNA Gyrase (Topoisomerase 2)

A key antibacterial mechanism of coumarins involves targeting bacterial DNA gyrase, an enzyme required for DNA replication and supercoiling. Coumarins interact with the GyrB subunit of the enzyme.

This interaction inhibits ATP hydrolysis, thereby blocking DNA replication and transcription processes. Their mode of action is comparable to antibiotics such as novobiocin.

Example

Coumarin-based compounds similar to novobiocin are effective against Staphylococcus aureus and Escherichia coli.[80]

2. Disruption of Bacterial Cell Membrane

Lipophilic coumarin derivatives are capable of penetrating the bacterial lipid membrane.

They compromise membrane integrity, resulting in leakage of cellular contents.

This ultimately leads to cell lysis and bacterial death.

Example

Derivatives of 7-hydroxy-4-methylcoumarin exhibit membrane-disrupting activity against *Bacillus subtilis*.

3. Inhibition of Nucleic Acid Synthesis

Due to their planar aromatic structure, coumarins can insert between DNA base pairs (intercalation). This disrupts DNA and RNA synthesis, thereby inhibiting bacterial growth.

Example

Esculetin (6,7-dihydroxycoumarin) demonstrates DNA-binding properties that suppress bacterial proliferation.

4. Enzyme Inhibition

Coumarins can block essential bacterial enzymes involved in metabolic pathways and cell survival.

These include oxidoreductases and enzymes associated with fatty acid biosynthesis.

Example

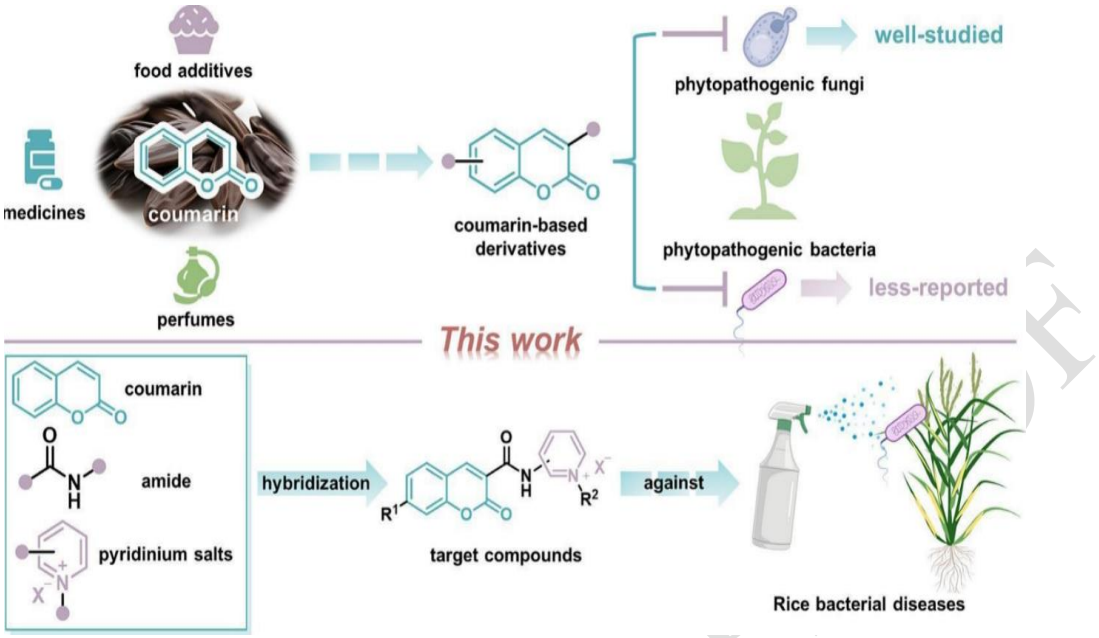
Coumarin–hydrazone derivatives show inhibitory effects on enzymes in *Mycobacterium tuberculosis*.

5. Generation of Reactive Oxygen Species (ROS)

Certain coumarins, particularly when complexed with metals, promote the formation of reactive oxygen species.

ROS cause oxidative damage to proteins, lipids, and DNA, leading to bacterial cell death.[81]

Example: Copper–coumarin complexes exhibit strong antibacterial effects through ROS-mediated mechanisms.[81,82]



FLUORESCENT ACTIVITIES OF COUMARIN

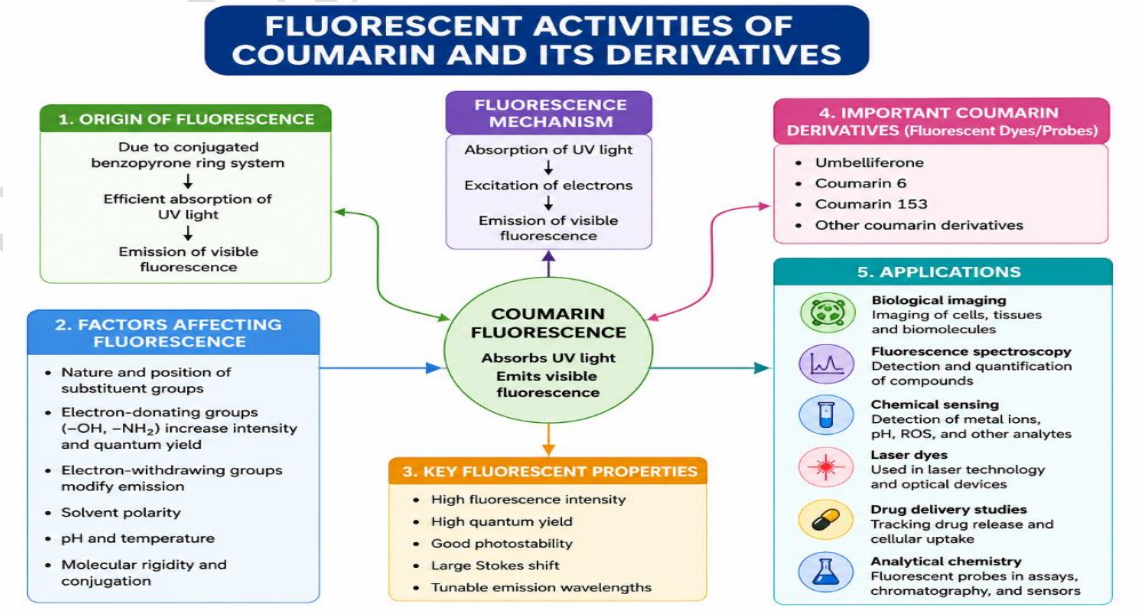
Coumarin and its derivatives are important fluorescent compounds widely used in medicinal chemistry, analytical science, and photochemistry. Their fluorescence is mainly due to the conjugated benzopyrone ring system, which absorbs ultraviolet (UV) light and emits visible fluorescence.[83]

The fluorescent activity of coumarins depends on the type and position of substituent groups attached to the coumarin nucleus. Electron-donating groups such as hydroxyl (–OH) and amino ($–NH_2$) groups generally increase fluorescence intensity and quantum yield. Coumarin derivatives also exhibit good photostability, large Stokes shift, and tunable emission wavelengths.[84]

Several coumarin derivatives, including Umbelliferone, Coumarin 6, and Coumarin 153, are widely used as fluorescent dyes and probes. These compounds have applications in:

- Biological imaging
- Fluorescence spectroscopy
- Chemical sensing
- Laser dyes
- Drug delivery studies
- Analytical chemistry

Because of their strong fluorescence, low toxicity, and easy structural modification, coumarin derivatives are considered valuable fluorophores in modern biomedical and material science research.[85]



CONCLUSION

Coumarin and its derivatives have gained considerable attention in scientific and pharmaceutical research because of their diverse chemical structures and wide range of biological activities. Numerous studies have shown that coumarin-based compounds exhibit significant anticoagulant, anti-inflammatory, antimicrobial, antioxidant, antiviral, anticancer, antidiabetic, neuroprotective, and cardioprotective effects. Their capability to interact with various biological targets has established coumarins as an important group of heterocyclic compounds in contemporary medicinal chemistry.

The clinical effectiveness of well-known coumarin derivatives, especially anticoagulant drugs such as Warfarin, demonstrates the therapeutic importance of the coumarin scaffold and supports the ongoing development of new analogues with enhanced safety and efficacy. Progress in synthetic methodologies, molecular docking techniques, computational drug discovery, and structure–activity relationship (SAR) studies has significantly contributed to the design of coumarin-based drug candidates with greater selectivity and lower toxicity.

Although coumarins show promising pharmacological potential, certain limitations still exist, including poor bioavailability, possible drug–drug interactions, toxicity at elevated doses, and limited clinical evidence for several newly developed derivatives. Consequently, future studies should emphasize improving pharmacokinetic characteristics, understanding detailed molecular mechanisms, performing extensive toxicological assessments, and broadening clinical research.

Overall, coumarin remains a highly versatile and valuable pharmacophore in the field of drug discovery and development. Continued multidisciplinary research involving medicinal chemistry, pharmacology, biotechnology, and nanotechnology may contribute to the development of safer and more efficient coumarin-derived therapies for the management of various human diseases.

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