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A Comprehensive Review on Coumarin Derivatives

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Abstract

Coumarins are naturally occurring compounds found in plants, fungi, and microorganisms with diverse bioactivities. They have antithrombotic, anti-inflammatory, antioxidant, antimicrobial, antiviral, anticancer, and neuroprotective properties. Extracting coumarins, using methods like maceration and microwave-assisted extraction, is crucial for their applications. However, safety and toxicology are important, especially in pharmaceuticals, cosmetics, and food additives. Consuming moderate amounts of coumarin-rich foods is generally safe, but excessive intake raises concerns about hepatotoxicity and photosensitivity. Specific coumarin derivatives, like warfarin, require precise dosing and monitoring to prevent bleeding complications. The safety and toxicity profiles of coumarins depend on factors like compound type, dosage, and individual susceptibility.

Keywords: Coumarins, synthesis, extraction, biological applications, Coumarin around Odorata

INTRODUCTION

Coumarins, derived from the tonka bean, are a class of compounds with four main sub-types: simple coumarins, furanocoumarins, pyranocoumarins, and pyrone-substituted coumarins. Simple coumarins are derivatives of coumarin and their glycosides, while furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus [1]. Pyranocoumarins have a six-membered ring, and 4-hydroxycoumarin is substituted in the pyrone ring. Warfarin, a synthetic compound, belongs to this subtype. Coumarin is considered the head of the benzo-alpha-pyrone, although 7-hydroxycoumarin is considered the parent compound of more complex coumarins. Genistein, an isoflavone, belongs to the benzo-gamapyrones and it is a natural component of soy. It has been extensively investigated as a chemotherapy agent against hormonally regulated breast and prostate cancers in animal models [2].

Coumarins are secondary metabolites found in plants and fungi microorganisms. They are derived from the plant *Coumarin around odorata*, which was isolated by Vogel in 1820. Coumarins are chemical heterocycles with a nucleus represented by benzo-pyrone (2H1benzopiran2one). The main pathway of coumarin biosynthesis is through the shikimic acid route, cinnamic acid, and phenylalanine metabolism. The systematic nomenclature was established by the International Union of Pure and Applied Chemistry (IUPAC) [3].

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STRUCTURE OF COUMARIN

- *Synonyms:* 1, 2-benzopyrone; 5, 6-benzo-2-pyrone; benzo-□-pyrone; Cis-o-coumarinic acid lactone; coumarinic anhydride.
- *Chemical Name:* 1-benzopyran-2-one.
- *Molecular formula:* $C_9H_6O_2$.
- *Physical Form:* Yellowish white crystals, flakes or powder.
- *Molecular Weight:* 146.
- *Solubility:* Soluble in alcohol, ether, chloroform and fixed volatile oils; slightly soluble in water.

Additional Physical and Chemical Specifications

- *Organoleptic Properties:* Fragrant odor like vanilla.
- *Melting Point:* 69°C.
- *Boiling Point:* 290°C.

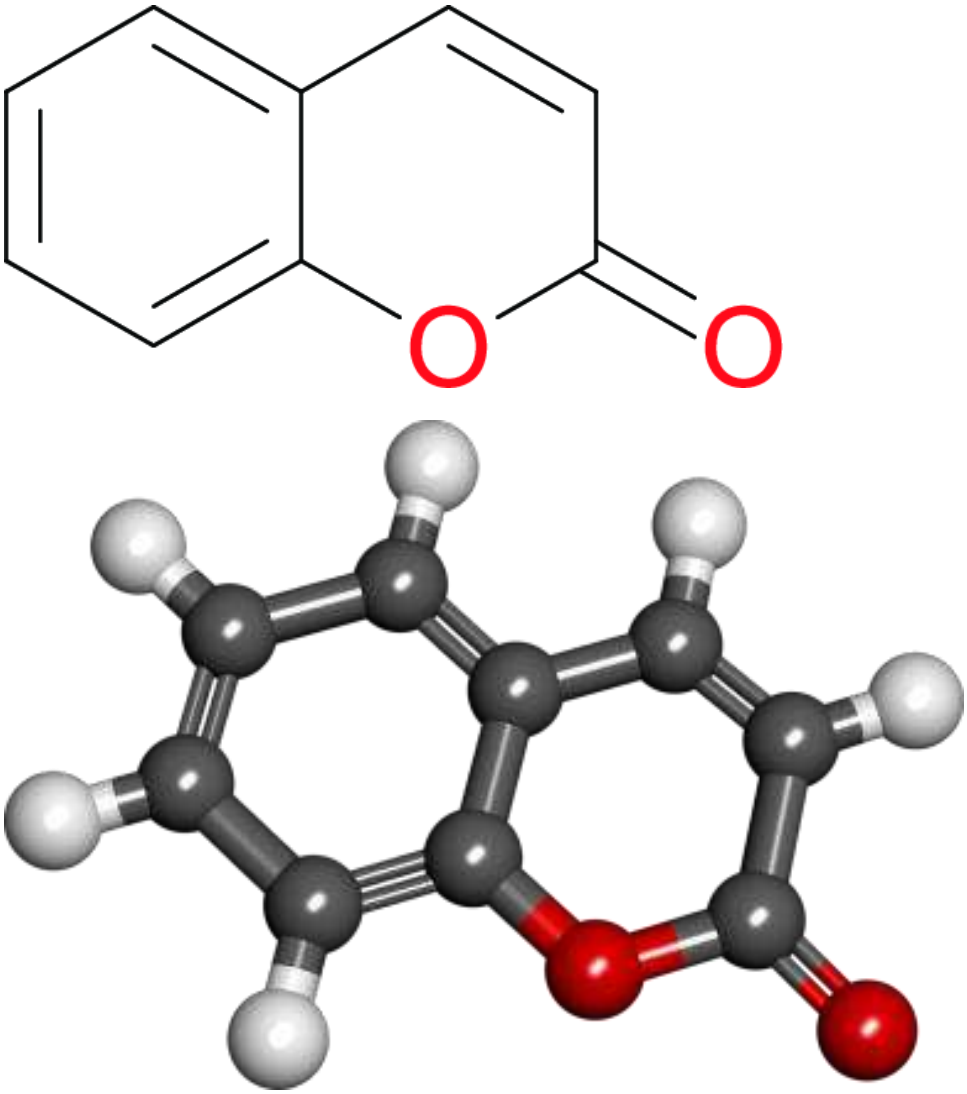

Figure. 1(a) Coumarin.

SYNTHESIS OF COUMARIN

Coumarin derivatives are synthesized using various routes, such as Pechmann reaction, Knoevenagel condensation, Perkin condensation, and catalyzed cyclization, primarily starting from salicylaldehydes or phenols, which are major classes of compounds [4].

Coumarin derivatives can be synthesized directly by electrophilic substitution of phenol with β-ketoesters, followed by cyclization (the top route in Figure 1(b)). The reaction involves electrophiles in Bronsted or Lewis acid, with a modified method enabling metal-catalyzed aryl C-H functionalization of alkynoates. From salicylaldehydes, condensation with malonate ester or similar compound is followed by intramolecular cyclization to produce coumarin structure (Figure 2) [4].

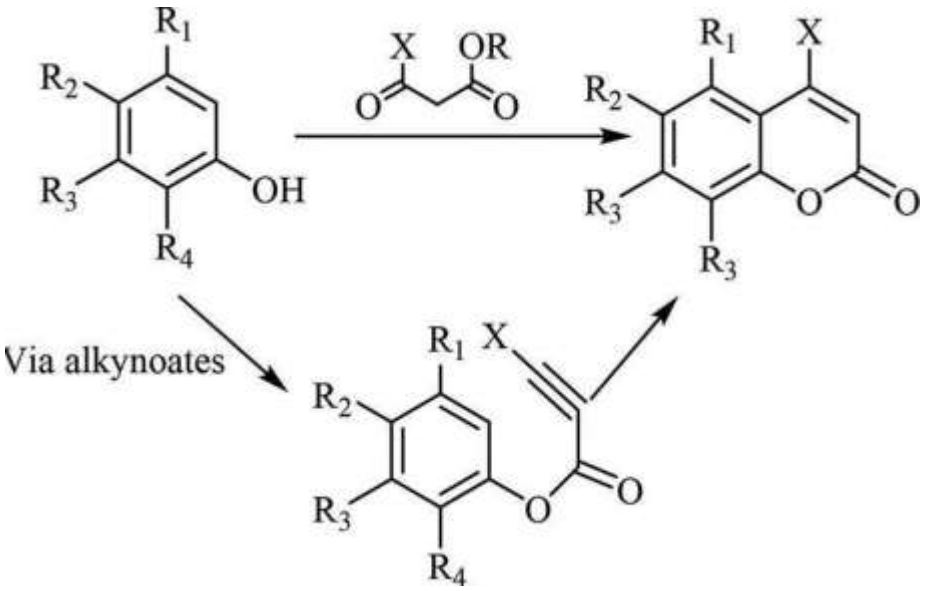

Figure 1(b). Transformation of phenols into coumarins.

SYNTHESIS THROUGH THE PECHMANN REACTION

The Pechmann condensation reaction, first reported in 1883 by Pechmann and Duisberg, is a simple and inexpensive method for synthesizing coumarin, involving the reaction of phenol 1 and β-keto ester 2 with H_2SO_4 as a catalyst (Figure 3) [4].

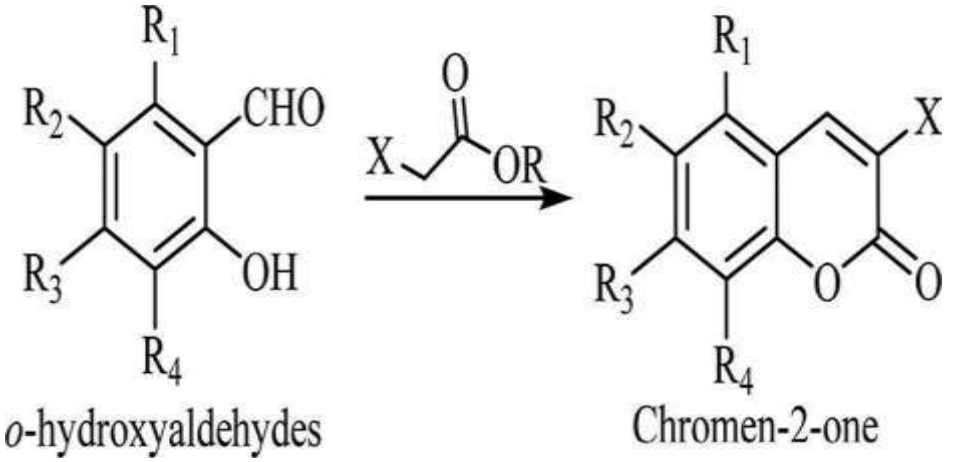

Figure 2. Transformation of salicylaldehydes into coumarins.

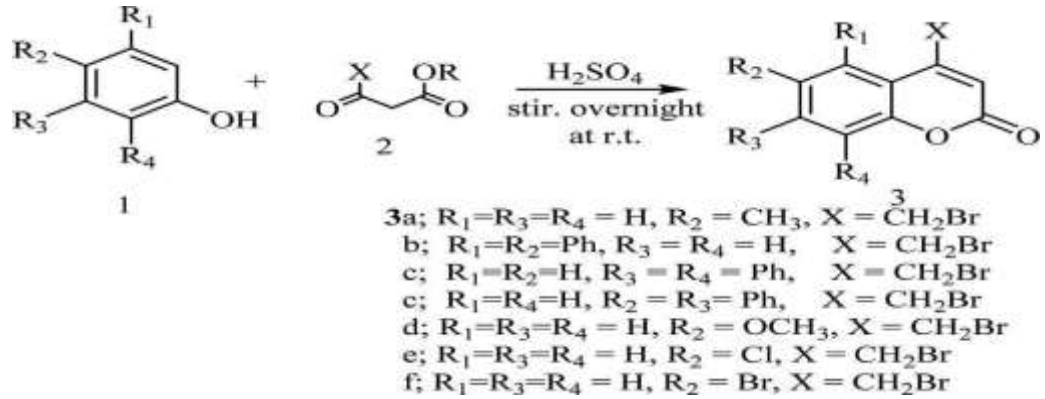

Figure 3. Synthesis of coumarins catalyzed by H_2SO_4.

SYNTHESIS THROUGH THE KNOEVENAGEL CONDENSATION

Coumarins can be prepared from salicylaldehydes through tandem Knoevenagel condensation and intramolecular cyclization with ethyl acetoacetate or dialkyl malonate. 2H-chromene-3-carboxylate can be obtained through refluxing salicylaldehydes with diethylmalonate in the presence of piperidine as a catalyst. Ethyl acetoacetate can also be used as an active methylene compound in Knoevenagel condensation with salicylaldehydes to generate 3-acetylcoumarins. Modifications have been made to increase the Knoevenagel synthetic of 3-acetylcoumarin under moderate reaction conditions. Diethyl amine as a dehydrating catalyst in Knoevenagel synthetic of 3-acetyl-2H-chromen-2-one is highly efficient under stirring conditions (Figures 4 and 5) [4].

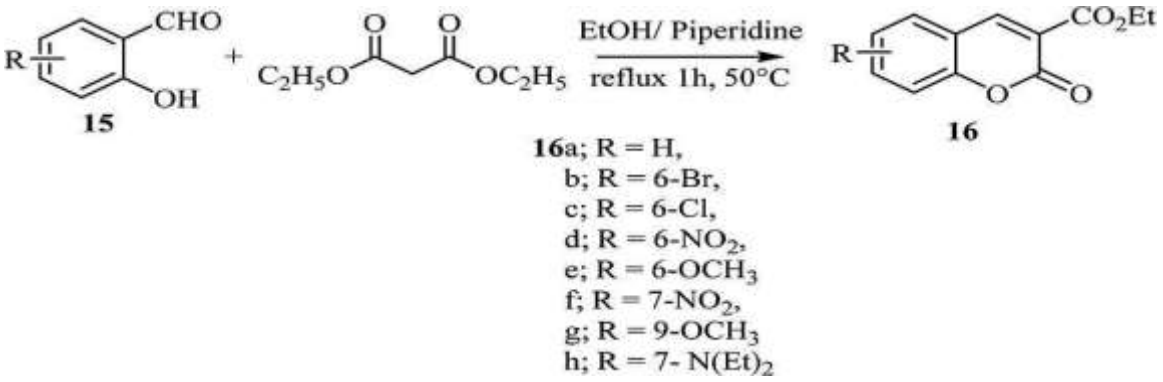

Figure 4. Synthesis of coumarin-3-carboxylates.

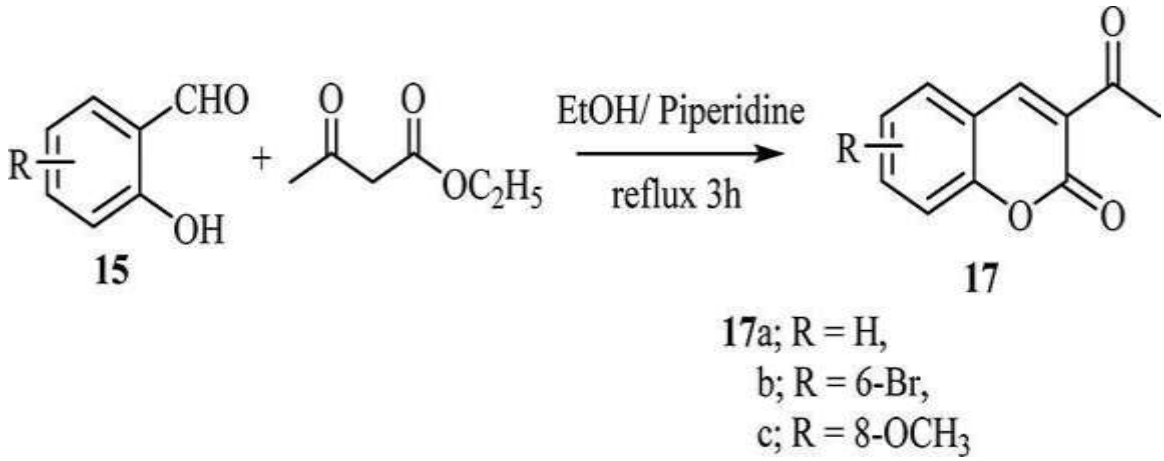

Figure 5. Synthesis of 3-acetylcoumarins catalyzed by piperidine.

SYNTHESIS OF COUMARINS CATALYZED BY PIPERIDINE

Watson et al. discovered a simple, solid-phase, and mild synthesis of substituted coumarin-3-carboxylic acid derivatives using the Knoevenagel condensation reaction, involving ethyl malonate and orthohydroxy Benz aldehydes in room temperature (Figure 6) [5].

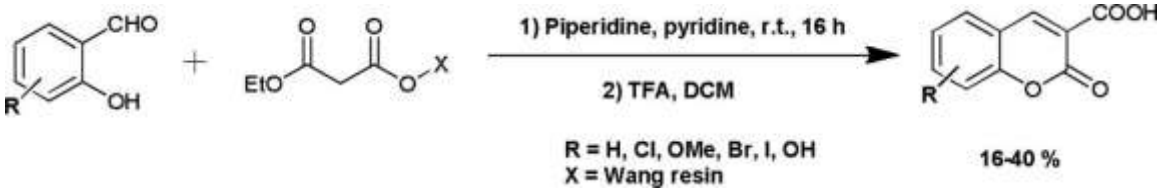

Figure 6. Synthesis of coumarin-3-carboxylic acid.

The protocol used Wang resin, a commonly used resin for peptide synthesis with C terminal

carboxylic acids, to obtain a high-purity product in good yield. The resin was bound with ethyl malonate, reacted with ortho-hydroxy benzaldehydes, and cleaved using trifluoroacetic acid in dichloromethane, resulting in pure coumarin-3-carboxylic acid derivatives [5].

CLASSIFICATION OF COUMARIN

Simple Coumarin

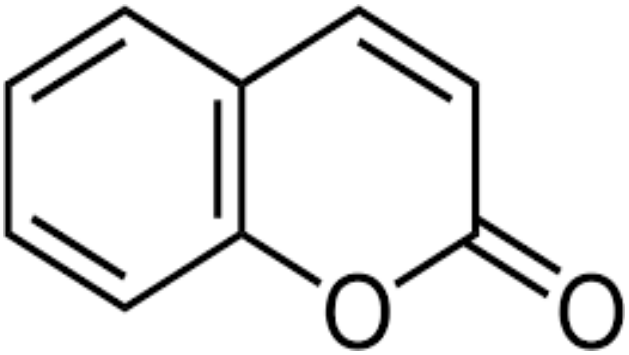

Figure 7(a). Simple Coumarin.

Example

*2H-**Chromen-2-One***

- Coumarin – Anti-inflammatory
- Esculetin – Antiadipogenic
- Ammoresinol – Antibacterial
- Ostruthin – Antifungal
- Osthole – Anticancer

Furanocoumarin

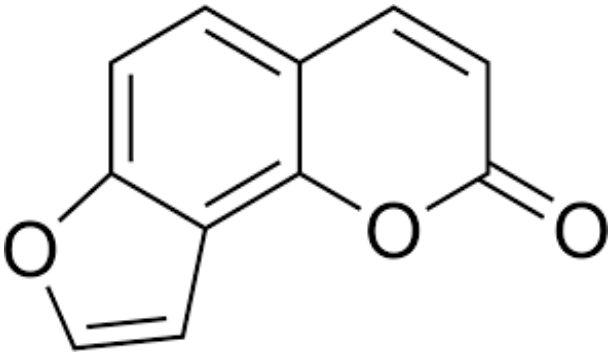

Figure 7(b). Furanocoumarin.

Methoxyfuro [2, 3-H] Chromen-2-One

Example

- *Imperatorin:* Anticancer.
- *Psoralen:* Antifungal.
- *Bergapten:* Antitubercular.
- *Methoxsalen:* Cy P450 inhibitor.
- *Marmalde:* Antibacterial.

Biscoumarin

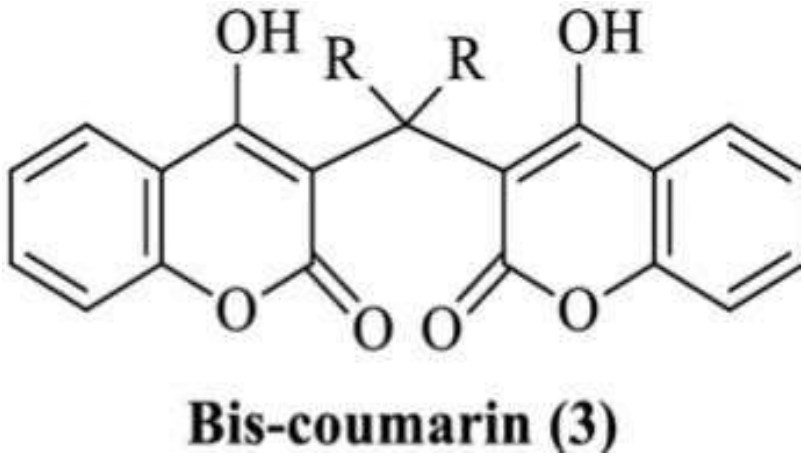

Figure 7(c). Biscoumarin.

Example

- *Disparpropylinol B:* Anti-inflammatory.
- *Dicoumarol:* Anticoagulant.

Pyranocoumarins

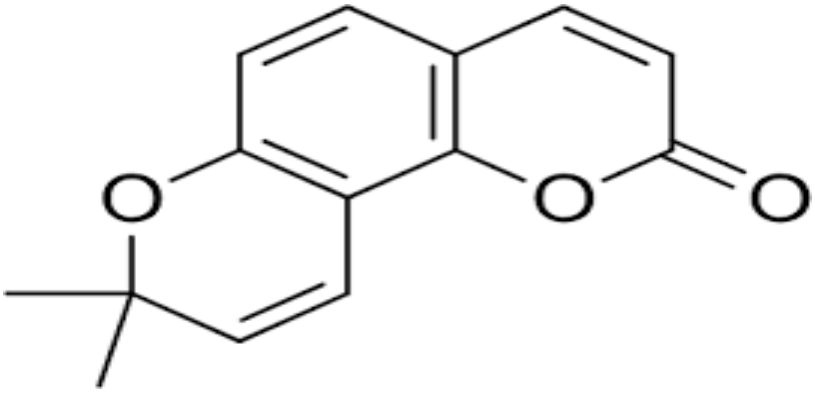

Figure 7(d). Pyranocoumarins.

Methoxy-2-Methyl-4-Phenyl-3,4-Dihydropyrano(3,2-C) Chromen-5-One

Example

- *Grandivittin:* Antibacterial.
- *Agasyllin:* Antibacterial.
- *Aegelinol benzoate:* Antibacterial.
- *Xanthyletin:* Antitubercular.
- *Inophyllum A, B, C, E, P, G1, and G2:* Antiviral [6].

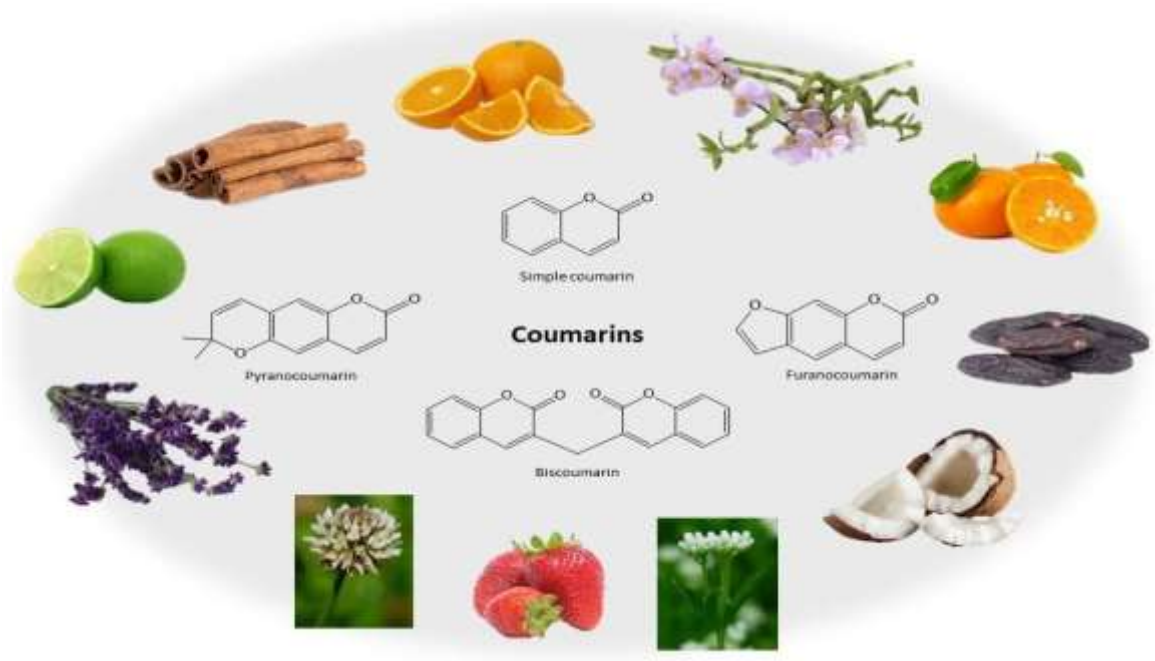

Figure 7(e). Classification of Coumarins.

Structure-Activity Relationship (Sar) of Coumarin Derivatives

Stereochemistry

Stereochemistry of substituents significantly impacts biological activity and receptor binding. The spatial orientation of groups at C-3 and C-4 positions affects anticoagulant activity, with S-configuration at C-4 resulting in higher potency. Conformational flexibility of side chains affects binding affinity and pharmacological properties. Natural coumarins often have specific stereochemistry

Hydrophobic Interaction

The drug-like characteristics of a drug are significantly influenced by the balance of hydrophobic and hydrophilic properties. Lipophilic substituents improve membrane permeability and tissue distribution, while aromatic rings increase binding affinity. The optimal balance depends on the therapeutic target and desired pharmacokinetic properties.

Hydrogen Bonding

Hydrogen bond donors and acceptors significantly influence binding interactions, with hydroxyl and amino groups being key donors and carbonyl and ether groups as acceptors. The spatial arrangement of these groups determines receptor binding specificity. Strategic substitution can fine-tune biological activities, while the number and positioning of hydrogen bonding sites correlate with solubility and absorption properties.

Molecular Dimensions

Molecular dimensions and shape significantly impact receptor fit and binding characteristics. Bulky substituents can affect target protein activity, and the spatial arrangement of functional groups affects biological target recognition. Studies suggest optimal size ranges for different biological activities, with excessive bulk often decreasing activity. Shape complementarity determines specificity and potency.

Electronic Density

The distribution of electron density in molecules impacts interaction with biological targets, and conjugated systems influence electronic properties and reactivity patterns. Electron-rich or electron-deficient regions determine binding interactions and understanding electronic effects aids in rational

design of new derivatives [7].

BIOLOGICAL ACTIVITY

Antifungal Activity

Fungal infections, such as ringworm and athlete's foot, are commonly found in hair, nails, and skin. Antifungal drugs, which include certain coumarins, are used to treat these infections.

Anti-Coagulant and Cardiovascular Activity

Coumarin derivatives, including Warfarin, are known for their cardiovascular and anticoagulant properties. Warfarin, a synthetic coumarin analogue, is used as an anticoagulant and is known as Coumadin. Coumarins, including phenprocoumon, acenocumarol, and warfarin, are vitamin K antagonists used in many countries. Warfarin is used more frequently than acenocoumarol due to its longer half-life, stable anticoagulation, and avoidance of factor VII fluctuations. The structure and anticoagulant activity of warfarin are also described in literature.

Anticancer Activity

Cancer is a global health issue, with the United States being the second leading cause of death. It involves abnormal cell growth and can spread through circulation. Caused by factors, like radiant energy, chemical substances, and genetics, anticancer drugs modify or kill cancer cells. Geiparvarin, a natural coumarin derivative, has been found to have anticancer activity, as detailed in literature.

Antiadipogenic Activity

Natural compounds effectively reduced triglycerides, boost lipolysis, and induce apoptosis [8].

EXTRACTION METHODS

The extraction of coumarins from natural sources is crucial for their potential applications in pharmaceuticals, food additives, and cosmetics. The choice of extraction method determines the yield and purity of the extracted coumarins. Common extraction techniques include.

- *Reflux Method:* The reflux method involves heating a mixture of coumarin-rich source material and solvent in a flask with a condenser, allowing the solvent to vaporize and condense, facilitating the extraction of coumarins. After refluxing for a specified time, the extract is collected [9].
- *Soxhlet Extraction:* Soxhlet extraction is a continuous method that uses solvent reflux to extract raw materials. The material is placed in a porous thimble and a Soxhlet extractor is used. The solvent is continuously boiled, evaporated, and condensed, ensuring efficient extraction. This technique is ideal for low coumarin content samples [10].
- *Maceration:* Maceration is a widely used extraction technique for extracting coumarins from dried plant material. It involves soaking the coumarin-rich source in a solvent for at least 3 days, allowing the solvent to absorb the coumarins. The resulting extract is then filtered and evaporated to obtain the coumarin-rich extract. Maceration is gentle and suitable for heat-sensitive compounds.
- *Infusion Method:* The infusion method involves soaking coumarin-rich source material in a solvent, which absorbs coumarins over time. After extraction, the mixture is filtered and evaporated to obtain the coumarin-rich infusion, typically at room temperature or slightly elevated. The method is comparable to maceration but differs in the duration and temperature of the solvent [1].

CONCLUSIONS

In this review we observed that coumarin is more potent and provides greater efficacy. Their unique chemical structure and broad spectrum of biological activities have established themselves as an invaluable class of natural and synthetic compounds. Their natural abundance, coupled with ease of chemical modification, makes them highly versatile for applicant ion in medicine, agriculture, and

industry.

The reactions proceeded in a few steps under mild conditions and usually gave good to excellent yields, overcoming current limitations would further expand their utility in diverse fields, and we hope to have conveyed to the readers of this review the current interest of the synthetic community in the synthesis of coumarin.

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