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A Comprehensive Review on Pharmacological Properties of Coumarins

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Abstract

Coumarins are a diverse group of secondary metabolites found in a variety of plant species (over 1200 different coumarins have been identified from natural sources, especially plants), as well as in fungi and microorganisms. Coumarin is a simple, widely occurring chemical structure in nature, present in many plants, fungi, and bacteria. In recent years, these natural compounds have attracted growing interest from the scientific community due to their broad spectrum of biological activities, primarily because of their ability to interact with various enzymes and receptors in living organisms. Furthermore, the coumarin structure is easy to synthesize and modify, offering opportunities to design new coumarin-based compounds and explore their potential in treating various diseases. The flexibility of the coumarin scaffold makes it useful not only in medicinal chemistry but also in the agrochemical industry and the cosmetics and fragrance sectors. Coumarins possess several advantageous properties, such as low molecular weight, a simple structure, high bioavailability, excellent solubility in most organic solvents, and low toxicity. These features, combined with their wide-ranging biological effects, make them promising lead compounds in drug discovery. Coumarins demonstrate a variety of pharmacological effects, including antimicrobial, anticoagulant, neuroprotective, anti-inflammatory, antidiabetic, and anticonvulsant properties. They are also valuable in the food industry, where their fungicidal and antioxidant activities are being explored and utilized.

Keywords: Coumarins, biological activity, metabolites, natural sources, synthesis

INTRODUCTION

Secondary metabolites are a broad category of natural compounds that are produced by plants [1]. Secondary metabolites have a variety of uses in human medicine, aromatization, flavoring, and other applications. The last few decades have seen a significant amount of phytochemical and pharmacological research on natural compounds called coumarins. The polyphenolic substances known as coumarins, are a class of crystalline, colorless, oxygenated heterocyclic chemicals that were initially separated from the tonka bean (Dipteryx odorata wild). Comprising four primary subtypes, coumarins are classified as simple, furanocoumarin, pyranocoumarin, and pyrone-substituted coumarins. Along with its glycosides, the hydroxylated, alkoxylated, and alkylated derivatives of the parent molecule, coumarin, are known as simple coumarins, and they include coumarin [2], 7-hydroxycoumarin, and 6,7-dihydroxycoumarin. The five-membered furan ring that makes up furanocoumarins is joined to the coumarin nucleus and can be either linear or angular, with substitution occurring at either or both remaining benzoid sites. Like furanocoumarins, pyranocoumarin members have a ring with six

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members. The pyrone ring is substituted with coumarins, such as 4-hydroxycoumarin. This coumarin class includes the synthetic chemical warfarin. Although it is generally agreed upon that 7-hydroxycoumarin should be recognized as the parent chemical, coumarin has been assigned as the head of the benzo-alpha-pyrone due to its structural simplicity. A variety of plants contain coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) and its derivatives in both heteroside and free forms. There are currently 800 naturally existing coumarin constituent chemicals, derived from around 100 families and 600 genera, among which Rutaceae, Umbelliferon, Clusiaceae, Guttiferae, Caprifoliaceae, Oleaceae, Nyctaginaceae, and Apiaceae are a few major genera [3]. The overwhelming majority of coumarins are found in higher plants, and the Rutaceae and Umbelliferone families are the most significant sources. Coumarins are found in every part of the plant, but they have the greatest concentration in the fruits, with the roots, stems, and leaves having the highest percentages. The occurrence in different regions of the plant might be influenced by variations in the seasons and environmental factors. Natural biologically active compounds called coumarins are known for their pharmacological activities against diseases such as cancer, hypertension, tuberculosis, anticoagulants, antimicrobial, antifungal, antiviral, anti-inflammatory, anticonvulsant, anti adipogenic [4], and antihyperglycemic effects, in addition to their neuroprotective and antioxidant attributes. The current review seeks to investigate and examine structure-activity relationship studies on coumarin core and consolidate a wide range of research reports on natural and generated coumarin derivatives with anticancer activity. Determination of crucial structural characteristics around the coumarin core could enable researchers to design and create novel analogues with a potent cancer-fighting effect and minimize the potential adverse reactions of existing medical treatments [5].

Phytochemicals

Chemical compounds that are found normally within the Kingdom of plants are known as phytochemicals. Some of them oversee the organoleptic characteristics of the natural resources where they can be found. Although not all compounds are known to be necessary nutrients, the phrase is typically used to describe substances that may have biological relevance, such as carotenoids, flavonoids, coumarins [6], or chromones. They could be used as 4000 distinct phytochemicals with potential anti-disease properties, including those related to metabolism, degeneration, and cancer. Coumarins are a family of benzopyrones that are widely spread throughout nature [7]. They are a significant family of naturally occurring and synthesized oxygen-containing heterocysts with a characteristic benzopyrones framework [8]. The various coumarins are present in different plants and it show in Table 1.

Uses

The most common group of compounds found in many therapeutic plants comprises the benzopyrone family, which consists of coumarins. An extensive range of pharmacological activities have been demonstrated through natural coumarins, such as anti-inflammatory in nature anticoagulant medication, chemotherapy [9], antibacterial, antimalarial, antifungal, antiviral, neuroprotective, antiepileptic, phytoalexins, ulcerogenic, and antihypertensive properties. Modulating self-assembly mechanisms yields programmable and reversible material properties; this is made feasible by the incorporation of coumarin moieties into polymer chain structures [10]. Coumarin's effect on these polymers' reactivity to outside stimuli – especially light – has been examined. The exceptional characteristics of coumarin-based photo responsive polymers, that consist of dynamic changes in solubility, structure, and mechanical properties upon UV irradiation, have been successfully achieved through stringent research and development [11]. The crucial function of coumarins has been highlighted in natural products, organic chemistry, and medicinal chemistry. Coumarins are employed as industrial additives, fragrances, and cosmetics. Some of them and their derivatives have additionally been used as aroma enhancers in tobacco and some beverages containing alcohol.

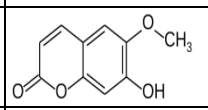
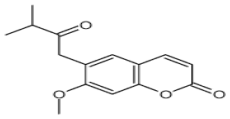
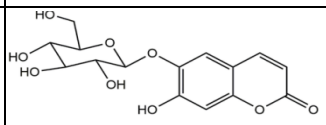
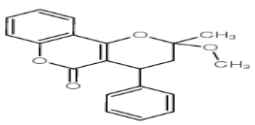
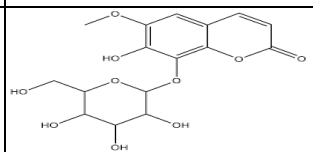
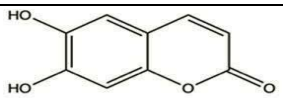
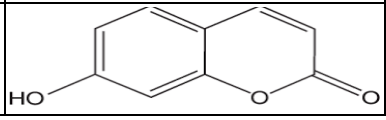
Pharmacological Activities

Anti-inflammatory Activity

An essential, immunologically protective physiological response to any form of assailant or aggression is inflammation. Inflammation can have a limited or an all-encompassing action, depending

on the extent to which the stimulation was. Many things can set off a response that is inflammatory [12]. Injury, trauma, exposure to poisons, microbial attacks, etc. are a few of these. When any form of inflammation takes place in our body, many kinds of immune cells operate together. During the process, many kinds of molecules. Some molecules, notably histamine and bradykinin, are released. The five primary indications of aggravation are torment, swelling, redness, warmth, and misfortune of work. These signs and symptoms lead to vascular permeability, leukocyte invasion, pain generation, local fluid retention, and necrosis. Many medical conditions, including atherosclerosis, osteoarthritis, and Alzheimer's, can be indicated by inflammation. Additionally, chronic inflammation has been associated with an assortment of cancer forms. Therefore, it is critical to combat inflammation before it worsens and constitutes a disease. Many plant species possess coumarin nuclei. Numerous phytoconstituents with powerful anti-inflammatory properties have been shown to be produced from the coumarin nucleus, as demonstrated by studies. Numerous phytocompounds produced from coumarins, such as the scopoletin, umbelliferone, marmin, columbiatnetin [13], and visniadin, have been suggested to possess anti-inflammatory properties. Along with their potential effectiveness as antioxidants and radical scavengers these synthetic compounds could possibly possess anti-inflammatory properties as well. One of its subordinates, imperatorin, has also been illustrated to have anti-inflammatory impacts in both in vivo carrageenan-induced rat paw swelling models and lipopolysaccharide-stimulated mouse macrophages (RAW264.7) [14–18]. In lipopolysaccharide-stimulated RAW264.7, it restrains the protein expression of NO synthase and inducible cyclooxygenase-2, though esculetin, an elective subsidiary, had anti-inflammatory exercises in rodent colitis created through trinitrobenzene sulfonic corrosive. A potential explanation for the anti-inflammatory advantages associated with coumarins is their antioxidant capabilities. It has long been recognized that shoulder lymphedema can be decreased gradually using coumarin 1,2-benzopyrone.

Table 1. Different types of coumarins.

S.N.	Name	Structure	Plant	Activity	References
1	Scopoloetina		*Cuminum cyminum*	Antioxidant	[17]
2	Ulopterol		*Toddalia aculeata*	Anti-bacterial	[14]
3	Aesculin		*Lactuca virosa*	Anti-inflammatory	[2]
4	Pyranocoumarins		*Apiaceae visnaga*	Anti-microbial	[6]
5	Fraxoside		*Fraxinus excelsior*	Anti-diarrheal	[11]
6	Esculetin		*Salvia officinalis*	Anti-diabetic	[16]
7	Umbelliferone		*Pimpinella anisum*	Anti-cancer	[10]

Anticoagulant Activity

In the human body, blood fluidity is tightly controlled by a multidimensional system. When confronted with injury, blood must clot efficiently and remain inside the vasculature. Vitamin K is classified as a blood anticoagulant, and it shares a lot of physiological characteristics with warfarin. Warfarin's structural and physiological in nature characteristics to vitamin K result in it being a vitamin K antagonist. Without impacting protein amalgamation, coumarin anticoagulants avoid vitamin K from freeing plasma clotting, calculate VII in liver cuts from creatures lacking in vitamin K. The inhibition goes away when the quantities of coumarin anticoagulant are elevated while retaining a fixed ratio of vitamin K to it. It can be inferred from this that the pharmacological activity of coumarin anticoagulants relies on a lifetime restriction of regular vitamin K transportation to the targeted area. Although the antioxidant vitamin K can enter the cell through a different pathway unobstructed by coumarin anticoagulants, the inhibition can be removed at higher concentrations of the vitamin [14]. Warfarin was originally used as a poison for poisoning rats in research experiments, however for over sixty years now, it has been widely regarded as an anticoagulant. By mechanism, it prevents the liver microsomal from producing vitamin K-dependent factors for coagulation (II, VII, IX, and X). The coagulation components (II, VII, IX, and X) that are dependent on vitamin K are sometimes stimulated by vitamin K; N-terminal glutamate is left behind to create γ-carboxyglutamate. Reduced vitamin K (Vit KH2) is involved in γ-carboxylation, and warfarin suppresses epoxide reductase, therefore inhibits Vit KH2 from generating.

Anticancer Activity

A group of cells dividing abnormally and having a likelihood for propagation to other bodily tissues through either immediate development within these tissues or cell migration (metastasis) to farther-off sites in the body are traits associated with cancers [15].Coumarin has been found amid a later examination as a defensive operator for the organs that create spit and epithelium in people getting head and neck radiation treatment As osthol is dynamic in directing the movement and invasion of breast cancer cells by implies of recuperating the wound or transwell tests, coumarin can moreover straightforwardly treat cancer. Through a huge number of components, such as the restraint of carbonic anhydrase, the PI3K/AKT/mTOR signaling pathway, microtubule polymerization, angiogenesis, monocarboxylate transporters, hypoxia-inducible factor-1, acting on apoptosis proteins and hindering tumor multidrug resistance, direction of ROS, and so forward, the compound coumarin substances may prevent the improvement, expansion, and cancer metastasis of different harmful tumor cells. For the development of cutting-edge anticancer medications, coumarin is a highly intriguing pharmacophore. Furthermore, this moiety's hybridization with other chemotherapeutic pharmacological agents has shown potential for minimizing side effects and enhancing the therapeutic efficacy of cancer treatment.

Antibacterial Activity

With an elevated mortality as well as morbidity rate, which serves as bacterial infections currently constitute significant dangers to health globally. It has been watched that pathogenic resistance against both characteristic and engineered antimicrobial specialists has been expanding essentially. To solve this problem, new prototype combinations are needed. In this sense, there has been considerable potential for the amalgamation of natural antibacterial agents derived from plants and pharmaceuticals [16]. It has been demonstrated that coumarins have efficacy against both Gram-positive and Gram-negative bacteria. Ammoresinol and ostruthin, two long-chain coumarin subsidiaries, illustrated more prominent viability against Staphylococcus aureus, Bacillus megaterium, Micrococcus luteus, and Micrococcus lysodeikticus. In any case, anthogenol, an elective frame of coumarin which has been found from Aegle marmelos, includes a solid anti-Enterococcus action. Additionally, Shigella dysenteriae' development and dissemination are hampered by the furanocoumarin compound imperatorin, which has been separated from Angelica dahurica and A. archangelica (Umbelliferon).

Anti-HIV Activity

Human immunodeficiency infection (HIV) contamination causes obtained immunodeficiency disorder (Helps), which may be a genuine worldwide wellbeing issue due to a noteworthy diminish of

resistant capacities [17]. The development of innovative anti-HIV agents is urgently needed since the creation of mutations in the virus and the severe adverse reactions of anti-HIV agents represent significant obstacles to the treatment of HIV infection [18]. However, anti-HIV drugs are essential for HIV/AIDS therapy. Plant-derived compounds exhibit a wide range of structural and mechanistic properties. Among them, derivatives based on coumarins have the capacity to inhibit distinct stages of the HIV replication cycle, such as attachment of the virus to the host cell, fusion of the cell membrane, integration, and assembly, in addition to the more common focuses on, such as enzymes, such as reverse transcriptase, protease and integrase. Furthermore, a natural substance based on the coumarins called (+)-calanolide A. Coumarins is a potential anti-HIV agent. Consequently, compounds based on coumarins are effective as foundations for the manufacturing of drugs against HIV.

CONCLUSIONS

In conclusion, the heterocyclic compounds known as coumarins are found in numerous plants, including tonka beans, and they belong to the benzopyrone class. All three of these roles are served by coumarin, a naturally occurring benzo-pyrone molecule that is most frequently utilized as a component in fragrances. In a wide range of concentrations, from 0.01% to 2.4%, coumarin is utilized in lotions, detergents, fragrances, and hand soaps. Numerous pharmacological characteristics, including anticoagulants, antibacterial, anti-inflammatory, antioxidant, anticancer, antiviral, and chemical restraint, are displayed by coumarins and their subsidiaries. Although higher dosages of coumarin have appeared to be hepatotoxic, they have positive benefits by bringing down the hazard of cardiovascular and neurological illnesses as well as cancer. The rummaging of free radicals is mindful for most of these impacts. Certain coumarins, such quercetin, esculetin, and umbelliferone, show antioxidant qualities and protect cellular DNA from oxidative harm. By blocking the impacts of vitamin K, dicumarol has anticoagulant qualities, while angelmarin has appeared to be cytotoxic in pancreatic cancer.

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