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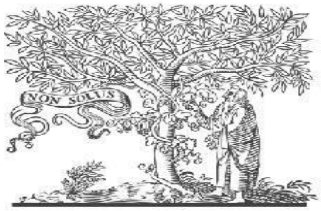

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A STUDY OF CHARACTERIZATION AND BIOLOGICAL APPLICATION OF COUMARIN

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ABSTRACT
These computational simulations explore the interactions between coumarin derivatives and key biomolecular targets, such as enzymes and receptors, providing valuable insights into the binding affinities and modes of action. Furthermore, the investigation investigates the impact of coumarin on other biological processes, including its potential as an enzyme inhibitor and its role in modulating various cellular signaling pathways. The results obtained from these experiments offer valuable information that can aid in the development of novel therapeutic agents. Overall, this research contributes to the expanding knowledge of coumarin and its biological applications. The findings not only provide a detailed understanding of the compound's physicochemical properties but also establish its potential as a promising candidate for pharmaceutical and medicinal applications. The insights gained from this study may pave the way for the development of new coumarin-based drugs targeting various diseases, thus enriching the fields of medicinal chemistry, pharmacology, and drug development.

KEYWORDS: Biological Application, Coumarin, computational simulations, biological processes, physicochemical properties

INTRODUCTION

Coumarins are polyphenolic compounds belonging a group of colorless and crystalline oxygenated heterocyclic compounds first isolated from the plant named Dipteryx odorata Willd. (Fabaceae) known locally as “coumaroun” by Vogel in 1820. Oxygenated heterocyclic compounds are furan derivatives with 4C atoms or pyran derivatives with 5C atoms. Although furan derivatives are rarely present in plants, pyran derivatives forming the structure of various compounds are encountered more frequently. The pyran derivatives are ketonic compounds that in the form of α-pyron or γ-pyron. Secondary metabolites called benzo-α-pyrone (coumarin) and benzo-γpyrone (chromone) occur due to condensation of pyron derivatives with benzene in plants. Coumarin (1,2-benzopyrone or 2H-1-benzopyran-2-one) and coumarin derivatives are natural compounds that are widely available in plants as a heteroside or free form. A total of 800 coumarin derivative compounds that naturally found were obtained from about 600 genera of 100 families to date [5,6]. Coumarin and its derivatives are frequently found in the seeds, roots and leaves of many plant species belonging to families (especially Rutaceae and Apiaceae) in the Dicotyledonae class of the division of Spermatophyta. Although most natural coumarins are isolated from vascular plants, some coumarins such as novobiocin, coumermycin and aflatoxin are isolated from microbial sources. These compounds have become of importance in recent years due to their various biological

activities. Previous biological activity studies performed on coumarin derivatives revealed that these compounds have antitumor photochemotherapy, anti-HIV, antibacterial and antifungal, anti-inflammatory, anticoagulant [inhibitors of the enzyme VKOR, triglycerides lowering and central nervous system stimulant effects However, a strong antioxidant and protective effect against oxidative stress by scavenging the reactive oxygen species has also been reported for hydroxycoumarins. In addition, the discovery of coumarins with weak estrogenic activity has enabled the usage of this type of coumarins in the prevention of menopausal distress. On the other hand, the usage of some coumarin derivatives as a tobacco flavor, which are used as fixative and flavoring agents, has been regulated by the FDA because of its negative effects, such as mild nausea, diarrhea and hepatotoxicity. Besides their medical use, coumarins are also used in the cosmetic industry and agrochemical industry, as well as optical brightening agents . Both natural and synthetic coumarin derivatives draw attention due to their photochemotherapy and therapeutic applications in cancer. It has been reported that substitution patterns can affect the therapeutic, pharmacological and biochemical properties of coumarins in a positive way. For instance, the substitution of a methoxy group at the 7-position and a 3-methyl 2-butenyl group at the 8-position of the osthol leads to a strong reduction of plasma alkaline transferase (ALT) level in hepatitis and inhibition of caspase-3 activation. Some coumarins have cytostatic effect, while others have cytotoxic activity. It has been revealed to show cytostatic activity of coumarin and its active metabolite, 7-hydroxycoumarin, on human cancer cell lines such as HL60 (leukemia), MCF-7 (breast), A549 and H727 (lung) and ACHN (kidney). Moreover, cytostatic activity of these compounds against prostate cancer, malignant melanoma and metastatic kidney cell carcinoma has also been reported in clinical studies. Compounds of 3 and 4-hydroxycoumarin structure were determined to inhibit cell proliferation in the gastric carcinoma cell line.

Occurence

Coumarins are classified in four groups: simple coumarins, furanocoumarines, pyranocoumarins and pyrone-substituted coumarins. Simple coumarins: these are composed of hydroxylated, alkoxylated and alkylated derivatives of coumarin and their glycosides (e.g., Umbelliferone, skimmin, limettin, herniarin, esculetin, esculin, daphnetin and daphnin (Figure 1)).

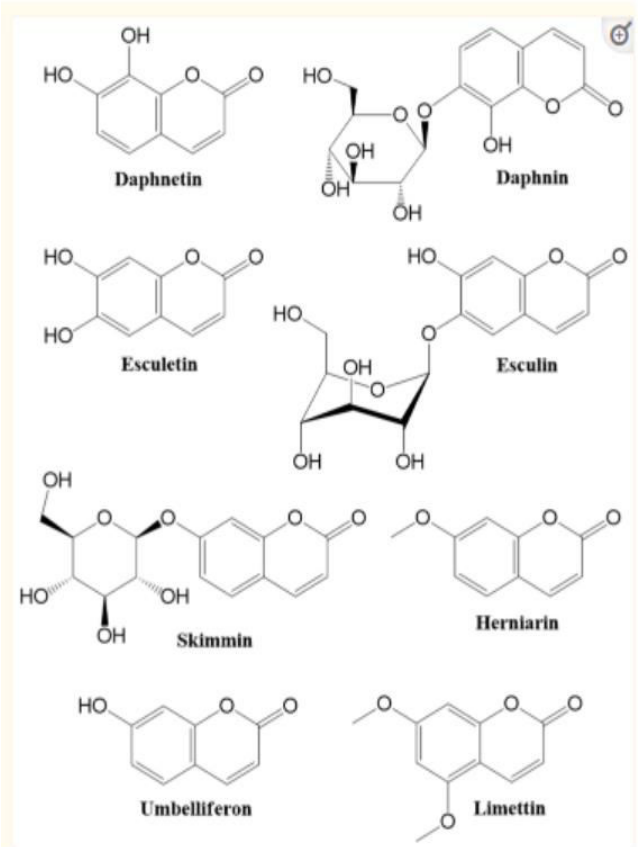

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Figure 1. chemical structures of some simple coumarins

Furanocoumarins: This group of coumarins consists of a furan ring fused with a coumarin. They are divided into two groups as C6/C7 (linear) type, C7/C8 (angular) type according to the attachment place of the furan ring. (e.g., psoralen, xanthotoxin, bergapten, imperatorin, isopimpinellin, anjelisin, isobergapten and pimpinellin (Figure 2)).

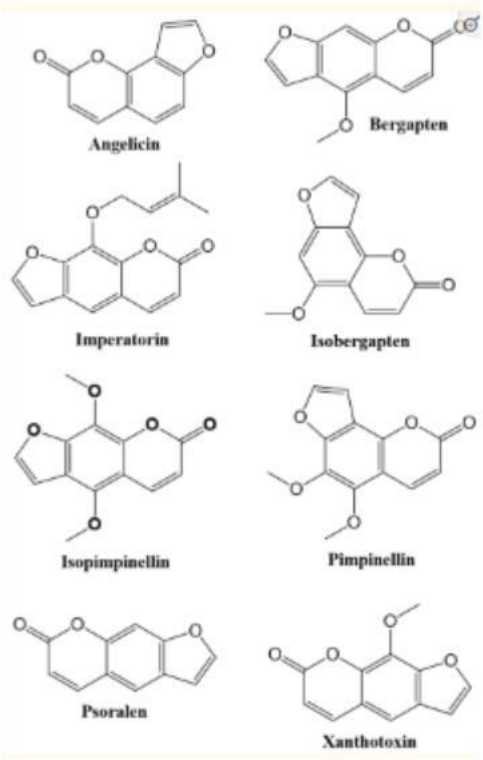

Figure 2 chemical structures of some furanocoumarins.

Pyranocoumarins: six-membered pyran ring is fused with the benzene ring via C6-7 (linear) or C7–8 (angular) (e.g., visnadin, xanthyletin and seselin)

Multi-target compounds are recently being searched for and these compounds are thought to be promising compounds for the treatment of several disorders, including cancer and heart failure. In this context, compounds observed from natural sources come into prominence due to their low toxicity, low drug resistance, low cost and high efficacy. Therefore, new compounds isolated from natural sources, such as plants and animals, and possible combination of these compounds with conventional chemotherapeutic agents seems to be important strategies to improve life quality, especially in cancer patients. Coumarin-based structure compounds constitute a major group of natural compounds with various pharmacological effects. These group of compounds can be isolated from different plants, including Achillea, Artemisia and Fraxinus genera, and also, they can be synthesized through various chemical reactions. Several strategies such as maceration, reflux, ultrasonic-assisted and microwave extraction methods are used for the isolation and purification of coumarin compounds. Perkin, Von Pechmann, Knoevenagel and Wittig organic reactions are some of reactions that coumarins can be synthesized. In the biosynthetic origin of coumarins, the shikimic acid pathway plays an important role. In this pathway, there are several enzymatic steps leading to occur chorismic acid, cinnamic acid, p-coumaric acid and umbelliferone. Moreover, the cytochrome P450 enzymes have a crucial role in the ortho-hydroxylation of cinnamic acid leading to occur umbelliferone, scopoletin and isofraxidin .

COUMARIN AND ITS DERIVATIVES

The potential therapeutic value of coumarin (2), which combines benzene and pyrone ring systems, has prompted research in the biological sciences. Depending on the changes made to the basic moiety, it has tremendous anticancer potential with few side effects. Coumarins

have an outstanding capacity to normalize broad variety of cellular processes that may be studied for specific anticancer efficacy [38]. As cancer is the second leading cause of death globally, many studies have been conducted to develop chemicals with little or no adverse effects; coumarins were found to have only mild to moderate effects. Tonka bean camphor, or coumarin, is a member of a large family of chemicals found in plants, fungi, and bacteria. Other names for this substance include 1,2-benzopyrone, 2H-1-benzopyran-2-one, phenylpropanoids, cis-ocoumarinic acid lactone, and coumarinic anhydride. Its name comes from the French term "Coumarou," which is used as a common name for tonka beans (family Fabaceae).

The largest concentrations of coumarins are found in the fruits (Aegle marmeleos), seeds (Calophylluminophyllum Linn), roots (Ferulago campestris), and leaves (Murraya paniculata) of various plants. Although coumarins have often been categorized as benzoic acid derivatives, Perkin, Sr.'s conventional approach instead places them in the category of oxygenated heterocycles. Various biological activities of coumarins basically depends on the type of coumarin nucleus which includes antibacterial scavanging of reactive oxygen species (ROS) antiinflammatory cycloxygenase inhibition lipoxygenase, antithrombotic vasodilatory antimutagenic CNS stimulants and anticancer activity, the coumarin scaffold is present in a number of therapeutically relevant natural and synthesized medications. All of them have been widely utilized in clinical settings and have shown pharmacological activity.

4-Methylumbelliferone (hymecromone), for instance, was used as a choleretic and antispasmodic drug. Antioxidant, hepatoprotective, antiinflammatory, and antifungal activities have been attributed to scopoletin, also known as 6-methoxy-7-hydroxycoumarin (32). The impact of carbochromen (33) on coronary disease is beneficial. Anticoagulant drugs that function as vitamin K antagonists include acenocoumarol (or a 4-hydroxycoumarin derivative, 334), phenprocoumon (or coumarin, 35), warfarin (or Coumadin, 36), difenacoum (37), and brodifacoum (38). Antibiotics include armillarisin A (39), novobiocin (40), monoamine oxidase inhibitor (antiproliferative) geiparvarin (41), dementia therapy ensaculin (42), and chemoprotective drug auraptene (43). Moreover, coumarins are a part of flavonoid group of plant secondary metabolite, that exhibited versatile pharmacological activities including antiinflammatory , antioxidant, antinociceptive, hepatoprotective, antithrombotic, antiviral, antimicrobial, antituberculosis anti-carcinogenic, antidepressant, antihyperlipidemic and anticholinesterase activities.

Synthesis of coumarin and its derivatives

In 1868, coumarin (2) was first artificially produced. As a precursor reagent, it is utilized in the pharmaceutical industry to create synthetic anticoagulant medications similar to dicoumarol. These include the well-known drug warfarin and several even more powerful rodenticides that use the same anticoagulant action. The research of sweet clover sickness led to the development of pharmacological coumarins, which are a form of vitamin K

antagonists. Claisen rearrangement, Perkin reaction, Pechmann reaction, Witting reaction, Knoevnagel condensation, and Witting reaction are all examples of synthetic techniques for coumarin analogs. Scheme 1.6 shows the general chemistry involved in the synthesis of substituted coumarin analogs from phenols and ethyl acetoacetate or methyl acetoacetate through Pechmann condensation under various catalytic and reaction conditions.

Biological applications of coumarin and its derivatives

The vast array of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems has been suggested to be due to the extremely long association of plant coumarins with various animal species and other organisms throughout evolution. The researched coumarins exhibit a wide range of pharmacological characteristics and impacts on distinct cellular mechanisms. A multitude of pharmacological factors should be investigated to expand our knowledge of the processes by which these coumarins function. As antioxidants, enzyme inhibitors, and toxicant precursors, coumarins play a significant role in plant biochemistry and physiology. The regulation of respiration, photosynthesis, and infection resistance are all processes that are linked to the presence of these substances, as are the effects of plant growth hormones and growth regulators. Anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral, and anticarcinogenic properties have long been attributed to coumarins. Because of their phenolic nature, hydroxycoumarins are effective metal chelators and free radical scavengers. Furthermore, they are potent free radical scavengers. The coumarins have a wide variety of biochemical and pharmacological effects, some of which indicate that certain coumarins may have major effects on the operation of specific mammalian cellular systems. The coumarins' pharmacological activity may be affected by the many different sorts of substitutions that can be made to their fundamental structure. Recent reports from a large number of studies indicate that the coumarin moiety's pattern of substitution determines the coumarin's biological features and therapeutic uses.

Anti-inflammatory and analgesic activities

Khode et al. [109] developed coumarin analogs after reviewing the literature and testing them for anti-inflammatory and pain-relieving properties in living animals. Among the series, compounds having 4-Cl-C6H4, 2,4-(Cl)2-C6H3, 3-OMe-C6H4 and 4- F-C6H4 showed noteworthy antiinflammatory activity in models of acute inflammation such as carrageenan-induced rat paw edema while compound (53) having 4-Cl-C6H4 showed substantial activity in a model of chronic inflammation such as adjuvant induced arthritis and was compared with diclofenac as a standard drug. In addition to having a low ulcerogenic index, this chemical was shown to be significantly analgesic in an acetic acid-induced writhing paradigm and antipyretic in a yeast-induced pyrexia model.

BIOLOGICAL EFFECTS OF COUMARINS

Coumarins are a class of organic compounds with a distinct bicyclic

structure consisting of a benzene ring fused with an alpha-pyrone ring. They are widely distributed in the plant kingdom and are often found in various natural sources such as fruits, vegetables, herbs, and essential oils. Over the years, coumarins have garnered significant attention due to their diverse pharmacological properties, ranging from their role as anticoagulants to their potential as anticancer agents. This article delves into the biological effects of coumarins, highlighting their impact on human health and their therapeutic applications.

Anticoagulant and Antithrombotic Activities: One of the most well-known effects of coumarins is their anticoagulant and antithrombotic activities. Compounds like warfarin and acenocoumarol, derived from coumarin, are commonly used clinical anticoagulants. They exert their effect by inhibiting the synthesis of vitamin K-dependent clotting factors in the liver, thereby prolonging the clotting time and reducing the risk of thrombosis. However, the therapeutic use of these coumarin derivatives requires careful monitoring due to their narrow therapeutic window and potential interactions with other drugs and dietary factors.

Vasodilation and Cardiovascular Effects:

Certain coumarins exhibit vasodilatory effects, which mean they can relax blood vessels, leading to improved blood flow. This property can be valuable in managing cardiovascular conditions like hypertension. For instance, scopoletin, a natural coumarin found in plants like Artemisia capillaris, has been shown to possess vasodilatory properties by promoting the release of nitric oxide (NO) and inhibiting vasoconstrictive factors. This effect contributes to the overall cardiovascular health by reducing blood pressure and preventing endothelial dysfunction.

Anti-Inflammatory and Immunomodulatory Activities:

Coumarins have demonstrated anti-inflammatory and immunomodulatory effects in various experimental models. These properties are attributed to their ability to inhibit pro-inflammatory cytokines, enzymes (such as cyclooxygenases and lipoxygenases), and other mediators of inflammation. By modulating immune responses, coumarins can potentially be utilized in conditions characterized by excessive inflammation, such as autoimmune diseases and chronic inflammatory disorders.

Antioxidant Effects:

Several coumarins possess antioxidant properties, which make them valuable in combating oxidative stress and its associated detrimental effects on cells and tissues. Through scavenging reactive oxygen species (ROS) and enhancing the cellular antioxidant defense system, coumarins contribute to reducing oxidative damage and protecting cellular components like DNA, lipids, and proteins. By doing so, they potentially play a role in preventing various chronic diseases, including neurodegenerative disorders and cancer.

CONCLUSION

The scope of future research in the field of coumarins is vast and exciting, offering numerous opportunities for exploration, innovation, and advancement in various scientific disciplines. Here are some

potential areas of focus for future research on coumarins:

Novel Coumarin Derivatives: Researchers can continue to synthesize and characterize new coumarin derivatives with modified structures, functional groups, and substituents. These derivatives could exhibit enhanced biological activities, improved pharmacokinetic properties, and reduced side effects, making them potential candidates for drug development. Structure-Activity Relationship (SAR) Studies: Further investigations into the relationship between the structure of coumarin derivatives and their biological activities could provide valuable insights. Understanding how specific structural features influence their interactions with target molecules and cellular processes can guide the rational design of more potent and selective compounds.

Target Identification and Mechanism of Action: In-depth studies are needed to identify specific molecular targets and unravel the precise mechanisms of action through which coumarins exert their diverse biological effects. Advanced techniques like proteomics, genomics, and molecular modeling can aid in elucidating these interactions and pathways. • Multidisciplinary Approaches: Collaborative research efforts that combine expertise from different fields—such as chemistry, biology, pharmacology, and computational science—can lead to more comprehensive investigations. Integrating various techniques and perspectives can yield a deeper understanding of coumarins' potential applications. • Drug Delivery and Formulation: Developing efficient drug delivery systems for coumarin derivatives can enhance their therapeutic efficacy, bioavailability, and targeted delivery to specific tissues or cells. Nanoparticles, liposomes, and other delivery platforms can improve the stability and controlled release of coumarins.

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