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Research Article

Coumarin Derivatives: A Systematic Review Of Their Biological And Pharmacological Activities

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ABSTRACT

Coumarin belongs to benzopyrones group, in which a benzene ring is attached to a pyrone nucleus. In the present study, data is collected to demonstrate the biological and pharmacological activities (like anticancer, anticoagulant, antimicrobial, anti-inflammatory, Antioxidant etc.) of coumarin derivatives. On the evidence of various researches, we found that Coumarin derivatives perform the valuable function as therapeutic agents in a range of diseases.

Keywords: Coumarin, Butyrylcholinesterase, Apoptosis, Cancer,

Introduction

Numerous plants can yield chemicals known as coumarins (2H-1-benzopyran-2-one). These substances are known by the term "coumarin" because they were initially identified from the seeds of Coumarouna odorata Aube (Diptryx odorata). [1] A heterocyclic molecule, coumarin belongs to the benzopyrone chemical family. 2H-1-benzopyran-2-one, often known as chromen-2-one, is its IUPAC name (Fig. 1). Chroman and chromones are members of the same chemical family as coumarins. Coumarins are essentially made up of a benzene molecule fused with a pyrone ring. Using UV spectrophotometry, conjugated molecules such as coumarins can be identified. Their blue fluorescence is a distinguishing characteristic in UV. Coumarin structures the majority of coumarins have natural origins. Vogel extracted the first coumarin molecule in 1820 from the tonka bean (Dipteryx odorata Wild). [2] Numerous green plants, as well as other creatures like animals, microorganisms [3], and clover leaves, contain them. [4, 5] The Perkin, Pechmann, Knovenagel, Wittig, Kostanecki-Robinson, and Reformatsky reactions can be used to create coumarin scaffold. [6]

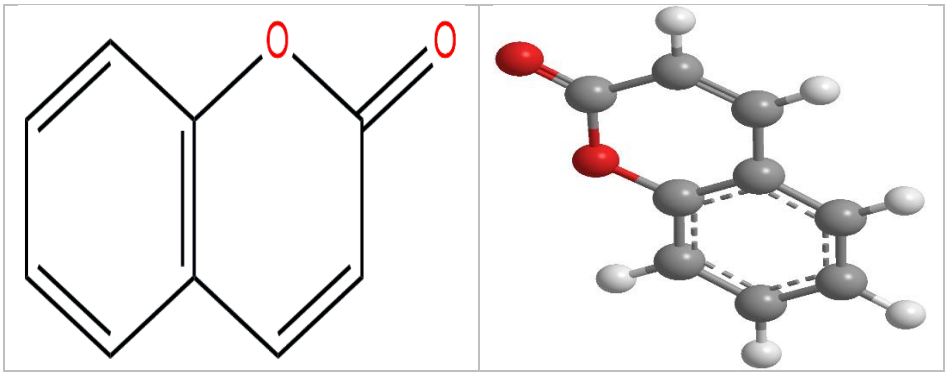
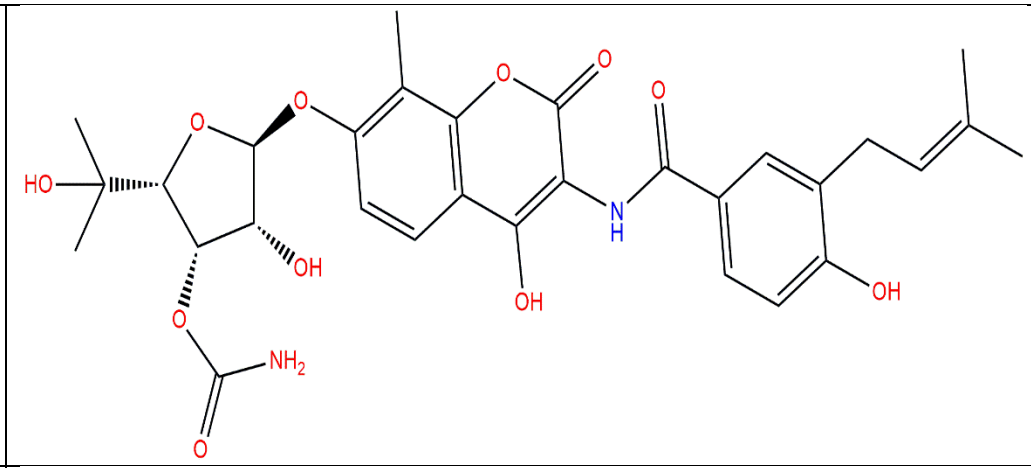
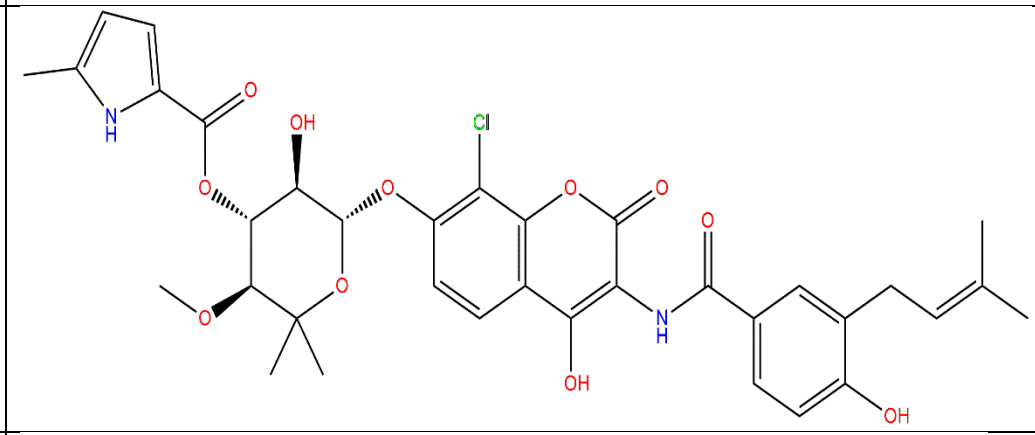
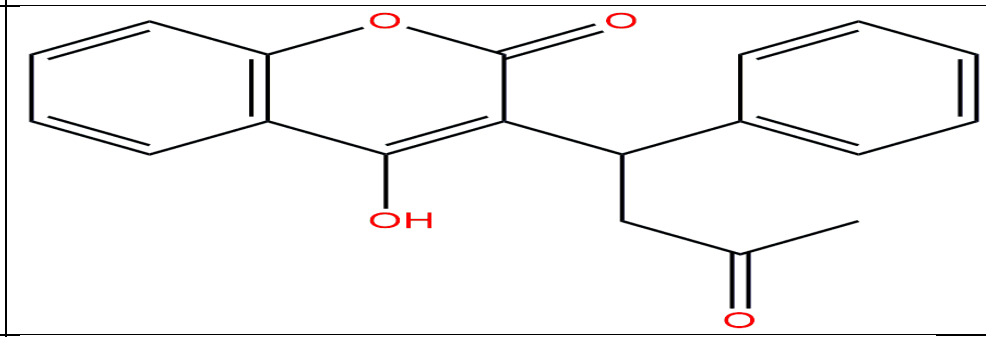
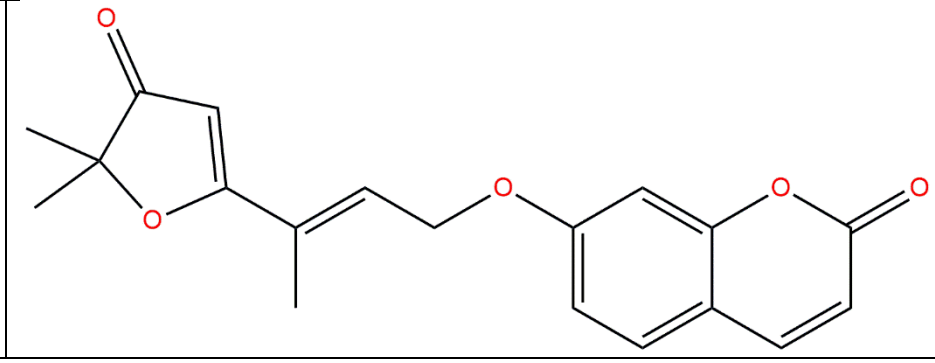


Fig. 1: Chemical structure of coumarin

The coumarin structure is present in a wide variety of medications that are sold today. For example, warfarin is frequently used as an anticoagulant in conditions affecting the cardiovascular system. [6] Another significant coumarin derivative finds application as an antibiotic. The antibiotics Novobiocin and Chlorobiocin are the most well-known coumarin-derived drugs. Because they prevent the DNA gyrase enzyme from working, they are very effective against Gram-positive bacteria. [7, 8] Several of geiparvarin derivatives have been synthesised

and shown to have strong cytotoxic activity. Geiparvarin is also obtained from plants that have the coumarin structure (Table 1). [9]

Table 1: Chemical structure of some coumarin derivatives

Novibiocin	
Chlorobiocin	
Warfarin	
Geiparvarin	

Biological and pharmacological activities

Because of their wide spectrum of biological functions, coumarins have been a popular choice among scientists as compounds. A variety of pharmacological characteristics, including antibacterial, neuroprotective, anticancer, antidepressant, anti-inflammatory, antioxidant, and anticoagulant effects, may be exhibited by coumarin derivatives. Coumarins are also industrial additives that are utilised in tobacco, cosmetics, and perfumes. [10, 11]

In a 2014 paper, Sandhu et al. evaluated coumarin derivatives, categorising compounds and their bioactivities based on the location at which the coumarin structure was derivatized. The compounds' antiviral, anticancer,

anti-inflammatory, and antioxidant properties were the ones that the authors found to be most frequently reported (Fig. 2). [12] The review also emphasised the significance of derivatization from carbon 3 and 4, as these locations were primarily responsible for the production of the bioactive chemicals. Only a small number of publications highlight the anti-inflammatory and anticancer properties of these coumarin derivatives, and derivatization from the eighth position was found to be restricted.

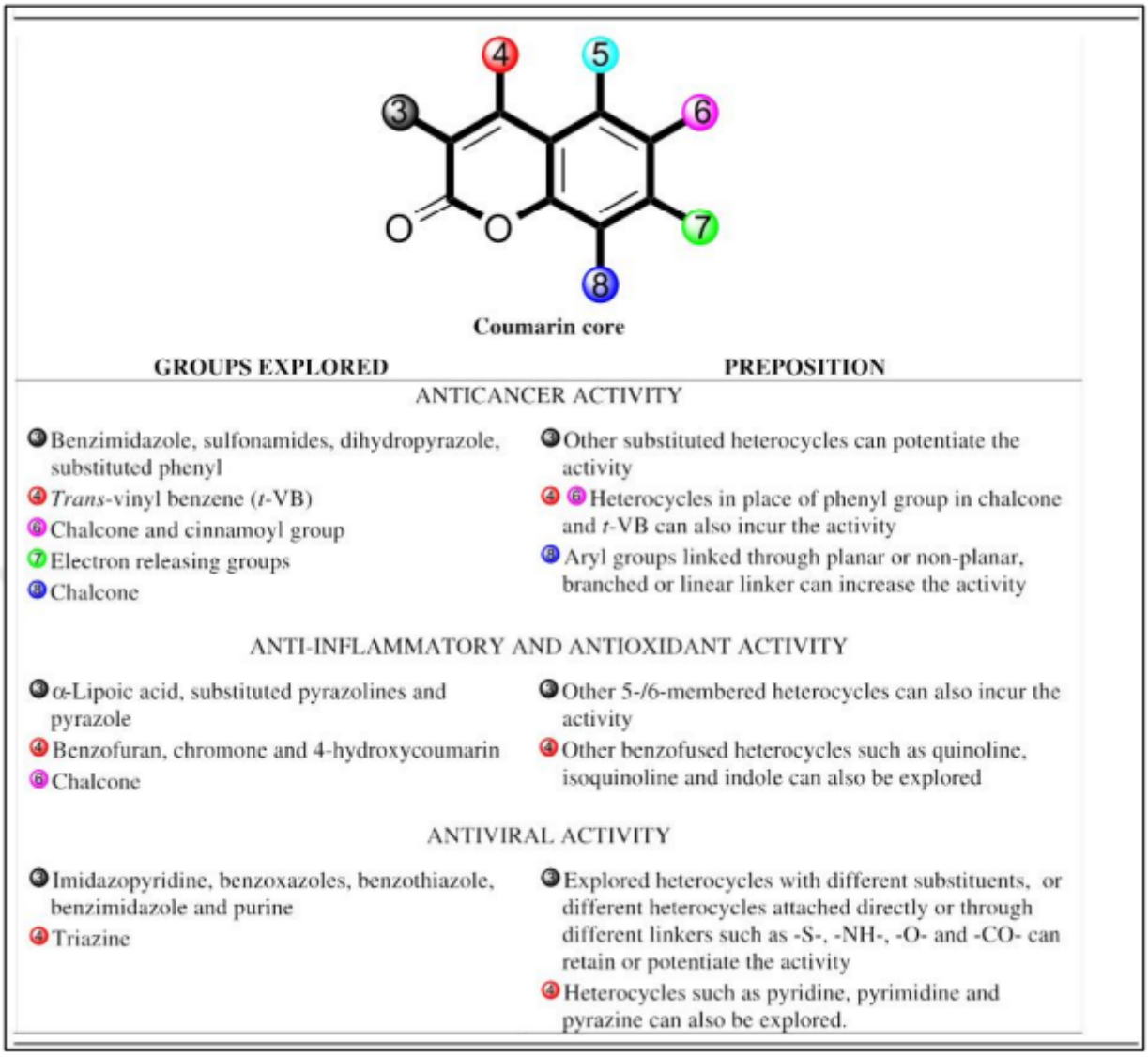


Fig. 2: Correlation between derivatization position and biologic activity of coumarin derivatives.

Anticancer Activity

The term "cancer" refers to a wide variety of incurable illnesses in which cells divide uncontrollably and invade other tissues. The World Health Organisation (WHO) states that cancer is the leading cause of death worldwide, and that within the next ten years, more cases of the disease are expected than expected. [13] Although several cancer treatment approaches have been studied, chemotherapy is still the most effective course of action at this time. Thus, it is still essential to develop cytotoxic agents. Accordingly, coumarin derivatives hold great promise as cytotoxic agents for the treatment of cancer. Their anticancer bioactivity is ascribed to inhibition of kinase, cell cycle arrest, angiogenesis, heat shock protein (HSP90) inhibition, telomerase inhibition, antimitotic activity, inhibition of carbonic anhydrase, inhibition of mono-carboxylate transporters, inhibition of aromatase, and inhibition of sulfatase (Fig.3).[14-16]

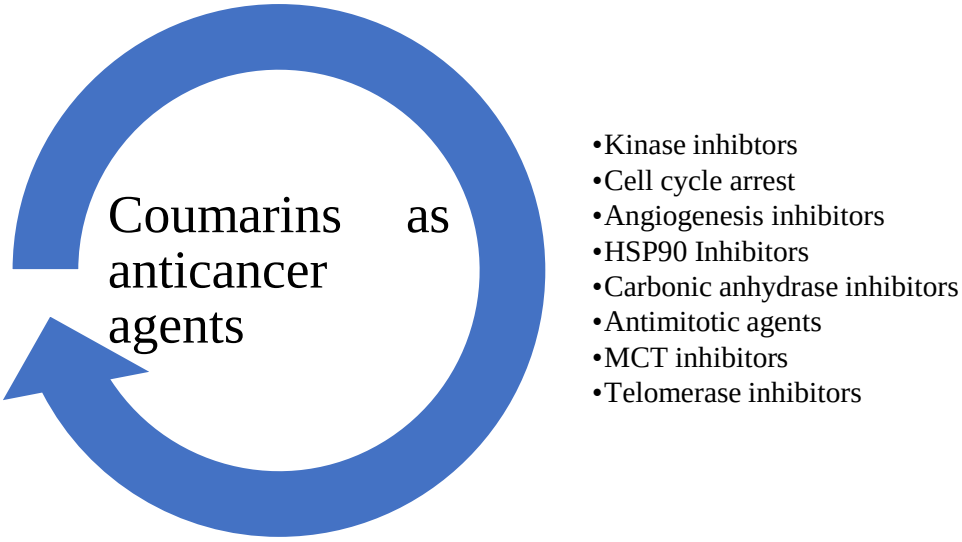


Fig.3: Mechanism of action of coumarin derivatives as anticancer agents

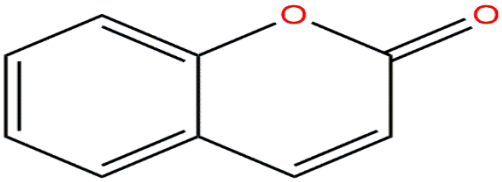
Kinase Inhibitors

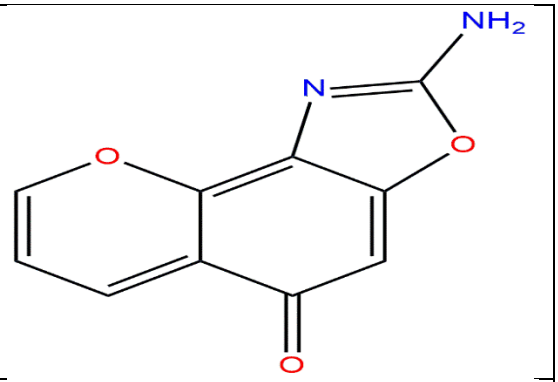
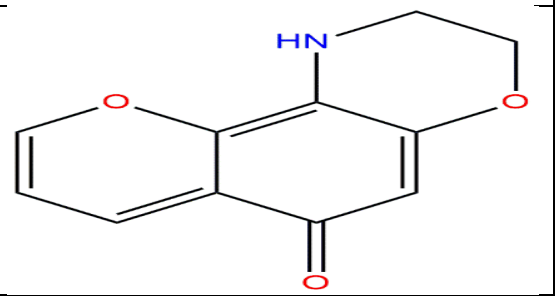
The process of phosphorylation, which involves adding a phosphate group from ATP to a protein, is carried out by proteins called protein kinases. Numerous cellular processes, including signalling, division, growth, and proliferation, are mediated by kinases. Therefore, in many cancer types, active versions of kinases enhance angiogenesis and block apoptosis. In addition, phosphorylation plays a role in the mechanisms that cause inflammation. Thus, it is imperative to inhibit kinases in order to prevent cancer and various other diseases, and numerous coumarin derivatives have been identified as kinase inhibitors. Nasr et al. conducted research on coumarin compounds in 2014, which shown efficacy against drug-fragile Hep-G2 and CCRF cells as well as resistant pancreatic cells. They produced derivatives of coumarins replaced with hydrazine and hydrozone. Their findings indicated that while both coumarin and hydrazine-hydrazone by themselves did not exhibit good biological activity, coumarin derivatives that had hydrazine-hydrozone substituted exhibited even greater activity than the reference drug doxorubicin. [17-19]

The Src kinase inhibitory activity of six distinct series of anticancer drugs was studied in 2011 by Kathuria et al. They produced quaternary ammonium coumarins, pyranocoumarins, coumarin carboxamides, 3-alkyl-4-methyl-coumarins, 7-aminocoumarins, and 4-aminocoumarins throughout their investigation, however they found only a weak relationship between the antiproliferative effect and the Src kinase inhibitory action. The compounds that were synthesised with hexyl and decyl groups exhibited low antiproliferative activity and substantial inhibitory activity of Src kinase, respectively. [20]

A docking investigation of coumarin derivatives was carried out by El-Ansary et al. in 2014. Fourteen new coumarin derivatives, substituted amino-5H-pyrano[6,5-e], and substituted-1Hbenzopyran-2-ones were found based on their findings.1,6-dihydropyrano and benzoxazol-5-ones substituted[6,5-f]It was possible to synthesise 1,4-benzoxazin-6-ones (Table 2). Tests were conducted on CCR-CEM, HL-60, HOP-92, NCI-H460, HCT116, and SF-295 cancer cell lines using the synthesised chemicals. The findings demonstrated the prospective anticancer action of a coumarin scaffold including a thiadiazole or dihydropyrazole ring. [21]

Table 2: Chemical structures of coumarin derivatives

1Hbenzopyran-2-one	

Amino-5H-pyrano[6,5-e] benzoxazol-5-one	
2,6-dihydropyrano[6,5-f]-1,4- benzoxazin-6-one	

Cell Cycle Arrest

All cell types require apoptosis, which is a sort of controlled cell death. It has to do with how multicellular creatures evolve. Several forms of cancer are also treated with this natural dying mechanism. Thus, inducing apoptosis is an effective cancer treatment strategy. Many kinds of chemicals that cause apoptosis have been created for this purpose. Coumarins are one of the more promising families of compounds. The cell cycle can be stopped by coumarins at the Go, G1, S, or M stages. This stoppage of the cell cycle causes apoptosis. [22] When mitochondria release cytochrome c, metalloproteinase levels drop and caspase9's initiator is activated. This in turn triggers caspases-3/7, which ultimately results in cell death (Fig.3).

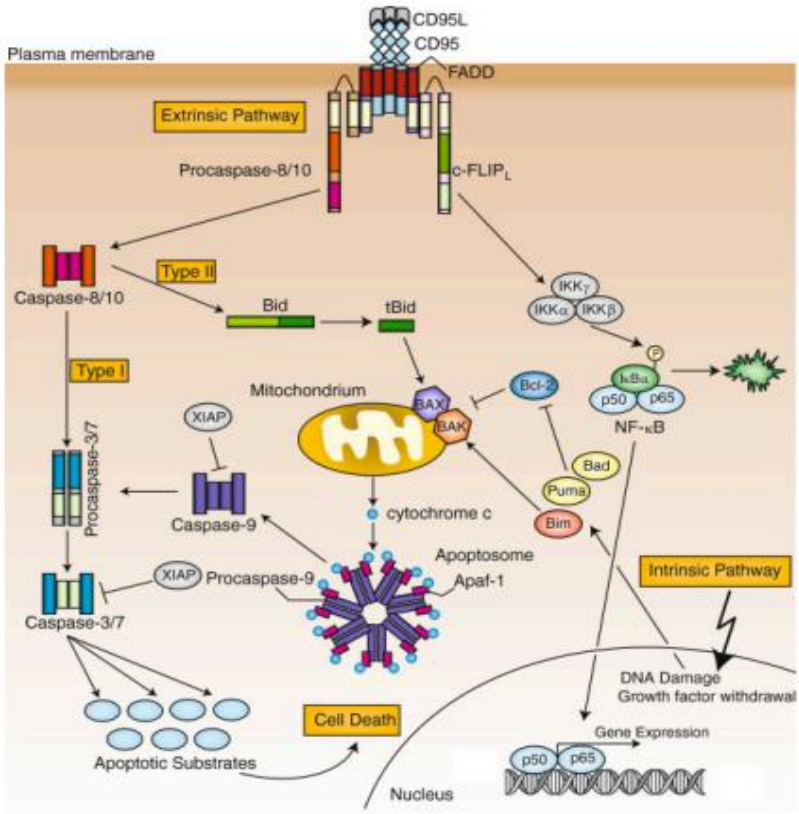


Fig.4: Apoptosis cascade

Kumar et al. synthesised 3-(4,5-Dihydro-1-phenyl-5-substituted phenyl-1H pyrazol-3-yl)-2H-chromen-2-one derivatives in 2013. Investigations into the anticancer properties of these substances revealed that they had anticancer properties against sixty distinct cancer cell lines. They then discovered these compounds' mode of action. Molecules exhibited antitumor action through G1 phase arrest. Hydrolysis of the coumarin derivatives was stopped until they reached the target tissue in order to determine the effect of the coumarin scaffold on the anticancer activity. Then, cell cycle arrest was solely elicited by conserved coumarin derivatives. This indicates that the coumarin scaffold was essentially necessary for anticancer action. [23]

Angiogenesis Inhibitors

Angiogenesis is the process by which preexisting blood arteries grow new ones. That is a dynamic and intricate process that happens when endothelial cells are activated during their lifetime. Because endothelial cells are generally dormant, they play a crucial role in angiogenesis. However, in pathological circumstances including cancer, rheumatoid arthritis, and chronic ischemia, these cells divide from their neighbours and multiply. New boats are created as a result. [24] Angiogenesis is induced by many growth factors in vascular endothelial cells. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and mitogen that is specific to vascular endothelial cells, making it stand out among the others. [25] VEGF attaches to receptors such as VEGFR-1 and VEGFR-2 to activate them. Endothelial cells have these receptors on their surface. [26] Because VEGF and its receptors are important players in pathological angiogenesis, blocking VEGF or its receptor's activity is essential for the treatment of cancer. [27] Numerous coumarin-based inhibitors of angiogenesis have been synthesised recently. One of the angiogenesis inhibitors with promising action is scopoletin (6-methoxy-7-hydroxycoumarin) (Fig. 4). R. Pan et al.'s study [28] found that scopoletin inhibited the creation of new blood vessels in the synovium of rats given an adjuvant-induced arthritic.

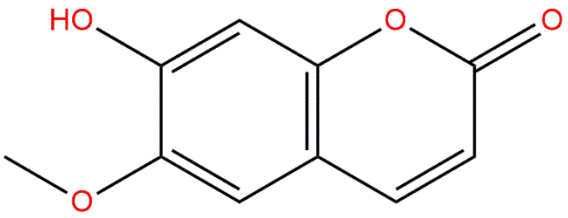


Fig.5: 6-methoxy-7- hydroxycoumarin

Hsp90 Inhibitors

One of the essential components of the chaperone machinery, which is in charge of protein folding, stability, and activation, is Hsp90. Protein conformational changes are used by Hsp90 to drive all of these processes. With the assistance of co-chaperones and Hsp90, ATP is bound and hydrolyzed to cause conformational changes. [29] Because Hsp90 is intimately related to eight cancer hallmarks, inhibiting Hsp90 has gained importance as a target for cancer treatment. [30] Coumarins are a promising class of Hsp90 inhibitors because they have the ability to directly bind to Hsp90, degrade co-chaperone and client proteins, and ultimately stop the growth of cancer cells. Neckers et al. looked at the binding aspects and characteristics of Hsp90 in 2000. This study indicates that Hsp90's amino and carboxyl terminals can interact with tiny compounds. Novobiocin was tried to inhibit Hsp90, and it was found that in addition to novobiocin, clorobiocin, and coumermycin also exhibited inhibitory effect against Hsp90. [30,31]

Antimitotic Agents

Normal and tumour cells both go through the process of mitosis, a form of cell division. Two identical daughter cells are created when a parent cell divides. The prophase, prometaphase, metaphase, anaphase, and telophase are the five phases of mitosis. Strategies for treating cancer can focus on any phase, as each plays a significant role in the division. [30] Allylpolyalkoxybenzenes, which are members of the umbelliferae family and are biologically active compounds, include myristicin and apiol. Tsyganov et al. synthesised polyalkoxy-3(4-methoxyphenyl)coumarins derived from plants in 2013 and examined their potential antimitotic properties. Sea urchin embryos were utilised to investigate the antimitotic activity, and SAR analyses showed that the three methoxy groups at carbons C5, C6, and C7 are necessary for maximum activity. The most effective polyalkoxy-3(4-methoxyphenyl) coumarin was antimitotic. Its interaction with tubulin and/or microtubules was linked to its antiproliferative activity. [32] Since microtubules are essential for both healthy and malignant cell division, their inhibition has grown in importance in the field of cancer treatment. The development of the mitotic spindle is necessary for cell division, and microtubule modifications that occur dynamically are what separate the chromosomes. [33]

Carbonic Anhydrase Inhibitors

Carbonic anhydrases (CAs) are metalloenzymes found in both prokaryotes and eukaryotes that are classified as having a zinc ion (Zn+2). In physiological and pathological processes, CA enzymes are required for the conversion of CO2 into the bicarbonate ion. They control the secretion of electrolytes in tissues and organs;

they balance pH and CO2 concentration; they regulate the transport of CO2 and bicarbonate; they regulate ureagenesis, glucogenesis, lipogenesis; calcification and tumorigenicity; and so they are important targets for the treatment of glaucoma, obesity, epilepsy, and cancer. Hypoxia is a characteristic of cancer. It is caused by tissues not receiving enough oxygen. Hypoxia leads to some genes expression like CAs. For example, in many tumors such as papillary/follicular carcinomas [34], gliomas/ependymomas [34], uterine cervix [35,36] , breast [34, 37,38] cancers CA IX expression is highly increased. Recently, a coumarin molecule was identified as a new CA inhibitor (CAI) through screening of natural product extracts. 6-(1S-hydroxy-3-methylbutyl)-7-methoxy-2H-chromen-2-one (Fig. 5) Since the isolated coumarin did not exhibit any interaction with the zinc-binding domain, the (CAI) isolated from Leionemaellipticum (Rutaceae) has been reported to have distinct inhibitory capabilities when compared to other known CAIs. [39] As a result, for this molecule to function, it needs a distinct binding mechanism.

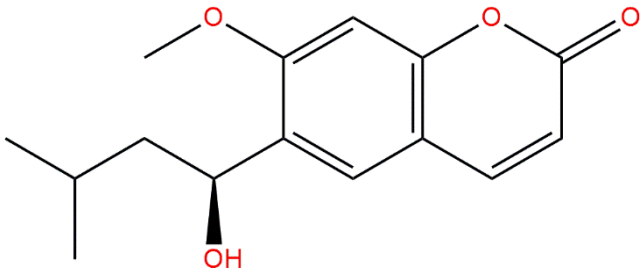


Fig.6: 6-(1S-hydroxy-3-methylbutyl)-7- methoxy-2H-chromen-2- one

Monocarboxylate Transporters (MCT) Inhibitors

The metabolic characteristics of tumour types can be used to categorise them into subgroups. Treatment options for certain tumours, such gliomas and triple negative breast cancer, are limited by their metabolic characteristics. Because hypoxic and non-hypoxic tumour features differ in their metabolism, they require distinct treatments. Targeted therapies should be created since hypoxia tumours are resistant to conventional treatments; hence, it is necessary to examine the metabolic pathways of hypoxic tumour cells. It has been discovered that monocarboxylate transporters (MCTs) are engaged in the metabolic pathways of hypoxic cells, making them a crucial target. In fact, cell function is compromised when lactate transfer is hindered. [40] Since coumarins have previously been shown to impede lactate transportation, Draoui et al. (2014) examined the lactate transport inhibitory action of 7-aminocarboxycoumarins. They demonstrated that the coumarin scaffold was required to achieve an acceptable inhibitory effect based on the findings of their SAR analysis. The authors observed that the inhibitory effect of coumarin was eliminated when the oxygen atom was swapped out for a nitrogen atom. They also demonstrated how the bioacitivity was being lost as a result of the ester being substituted for the acid group at position C3. It was discovered that the activity's other significant substitution occurred on coumarin's C7. It was discovered that methyl, lactone, or lactam groups reduced the inhibitory effects, but O-benzyl and substituted amine groups increased the activity. [40]

Anti-Inflammatory Activity of Simple Coumarin

Several natural and synthetic coumarin compounds have so far been reported in the literature to have potential anti-inflammatory properties, but none of them have resulted in the creation of a commercially available medication. The process of inflammation is the body's immune system's reaction to damage or external intruders like germs and viruses. [41] Five key symptoms are indicative of inflammation: pain, swelling, heat, redness, and altered function. Four main players are involved in inflammatory pathways: sensors, inflammatory mediators, inflammatory inducers, and target tissues (Fig. 6). Initiators of inflammation, including as infections, are first identified by sensors such as Toll-like receptors (TLRs). Sentinel cells, which include mast cells, dendritic cells, and macrophages, are influenced by sensors. These cells generate mediators, including chemokines, cytokines, eicosanoids, and bioactive amines. Mediators' primary function is to modify target tissues in response to inflammatory conditions. [42]

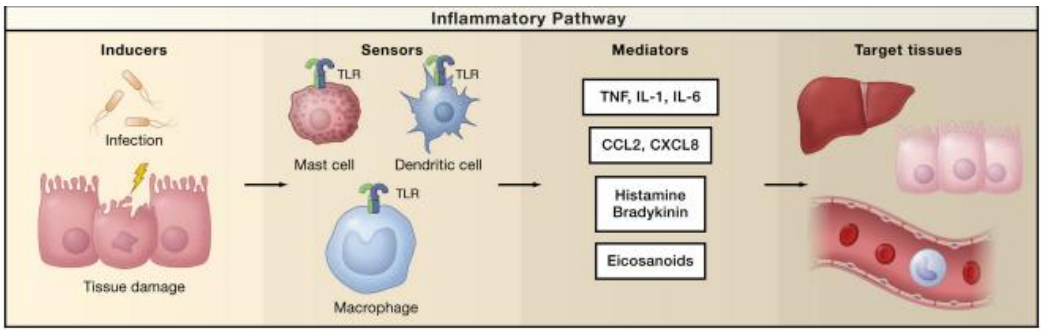


Fig.7: Inflammatory pathways constituents

Inhibiting inducers, sensors, and inflammatory mediators (plasma proteases) can stop the inflammatory process. [43] Additionally, for the development of successful anti-inflammatory therapies, the involvement of mediators such PGE2, leukotrienes (metabolites of arachidonic acid), serotonin, histamine, nitric oxide, cytokines, and chemokines have been studied. [44] Thus far, a multitude of derivatives of heterocyclic compounds have been synthesised for their anti-inflammatory properties, and several mechanisms of inflammation reduction have been documented for coumarin derivatives (Fig. 7). The two types of coumarin derivatives that are studied are synthetic and natural (derived from plants). Their SAR research and anti-inflammatory properties are also covered.

Table.3: Effects of coumarins on inflammation

Coumarins		
Sensor Level	**Mediator Level**	**Protection**
MAP Kinases	Prostaglandins inhibitor	Atherosclerosis
	Leukotrienes inhibitor	Rheumatoid arthritis
	TNF-α inhibitor	
	iNOS inhibitor	
	NF-kB inhibitor	

Anti-Inflammatory Activity of Natural Coumarins

Coumarins derived from plants are significant phytonutrients. They can be found in fruits, green tea, and essential oils. The groups Rutaceae and Umbelliferae are recognised for having the largest concentrations of compounds based on coumarins. [41] Numerous plant-derived coumarin compounds have been reported to have anti-inflammatory properties. They reduce tissue edoema, prevent the production of free radicals, or inhibit enzymes like lipoxygenase and cyclooxygenase. A succinct SAR model was created based on the anti-inflammatory properties of coumarin derivatives. It has been demonstrated that increasing the activity involves attaching a hydroxyl or bunsaturated carbonyl group to the coumarin ring's C8 position. It was also said that maintaining bioactivity required the substitution of the C6 and C7 locations. It has been demonstrated that oxygen-containing groups, either in monosubstitution or disubstitution, are suitable for the anti-inflammatory activity of these locations. The observation that all naturally occurring coumarins have an unsubstituted C4 position is an intriguing one. Lastly, it was also noted that good activity may be achieved by substituting saturated long chains for the C3 position. [41] In addition to coumarins found in nature, many synthesised coumarins have also been studied for their potential anti-inflammatory properties.

Antimicrobial agents

In order to prepare new compounds with strong antibacterial action, like derivatives of thiazolidin-4-one, thiosemicarbazones play a crucial role as an intermediary. When these thiazolidine-4-one derivatives were added to 25 μg/ml, they showed activity that was similar to that of ampicillin and chloramphenicol. The 4-methylcoumarinthiazolidine-4-one hybrids were also reported to have good antimicrobial activity; the thiazolidine-4-one, at 10 μg/ml, had activity similar to that of ciprofloxacin and griseofulvin, and the 4-methylcoumarin-thiazolidine-4-one, at a minimum inhibitory concentration value of 0.10 μg/ml, had strong antifungal activity. Thus, the goal of this work was to investigate the effects of hybridising various N4-substituted thiosemicarbazones that were cyclized into the C5-substituted-thiazolidine-4-one ring with 7-hydroxy-4-methylcoumarin and their 7-alkoxy analogues. New compounds' antibacterial activity was assessed. [45]

Anticoagulant activity

The function of vitamin K in blood coagulation is significant. Warfarin shares a structure with vitamin K and functions as a vitamin K antagonist in terms of anticoagulant activity, as illustrated in Fig. 8. Warfarin was first used as a poison to eradicate rats, then for the next nearly 60 years, it was used as an anticoagulant medication. By preventing the hepatic microsomal production of vitamin K-dependent coagulation factors (II, VII, IX, and X), warfarin demonstrates its anticoagulant action. The N-terminal glutamate residues of the vitamin K-dependent coagulation factors (II, VII, IX, and X) can produce γcarboxyglutamates when stimulated by vitamin K. [46] Reduced vitamin K (Vit KH2) is involved in γ-carboxylation, and Warfarin prevents the synthesis of Vit KH2 by inhibiting epoxide reductase.

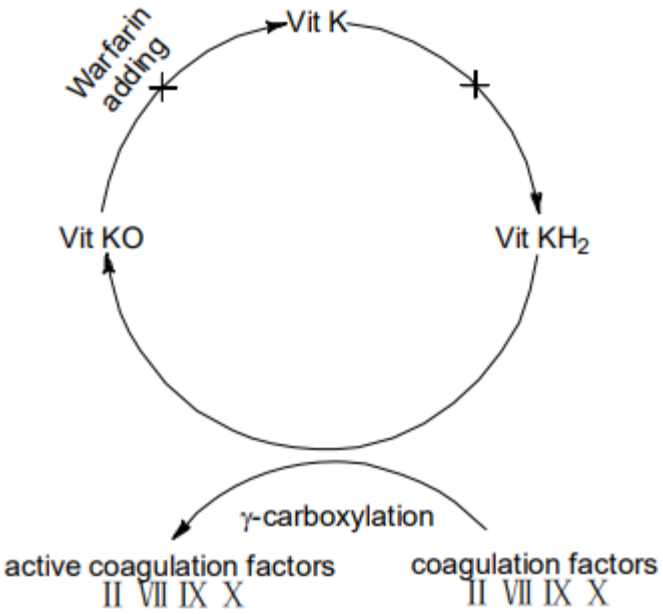


Fig.8: Mechanism of action of warfarin

Alzheimer's disease Inhibition

Alzheimer's disease (AD) is a degenerative condition of the central nervous system that causes changes in personality, language barrier, and memory. [47] AD is the most prevalent disease among the aged, and its prevalence is rising at an alarming rate. Although the exact cause of AD is unknown, numerous studies have revealed that patients have decreased levels of acetylcholine (ACh), amyloid-β (Aβ) forms, and oxidative stress. [48–50] According to recent studies, coumarin derivatives can reduce AD. The Maria Joao Matos group created and synthesised a range of 3-substituted coumarin derivatives. The results of their biological evaluation show that these compounds have the ability to micromolar inhibit the isoforms of monoamine oxidase A and B as well as acetylcholinesterase AChE. The Xiao-Bing Wang group designed and synthesised a series of tacrine-coumarin hybrids that demonstrated a significant ability against AD by inhibiting cholinesterase (ChE) and causing β-amyloid (Aβ) aggregation. One compound in particular has the best activity for inhibiting AChE, with an IC50 of 0.092 μM, and also very effectively inhibiting butyrylcholinesterase (BuChE), with an IC50 of 0.234 μM. Additionally, the compound exhibits its activity by binding and activating the AChE peripheral and midgorge sites. [51-52]

Antioxidant Activity

A combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2Hchromene-2-thiones was created by Singh OM et al. in a simple, practical, and highly yielding manner. The compounds were evaluated for their ability to scavenge radicals, namely the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), and it was discovered that these compounds were effective at doing so. Significant antioxidant activity was shown by the recently created substances. Five particular substances have the ability to shield curcumin from sulphur free radical damage caused by glutathione (GSH) radiolysis. [53]

A number of coumarin derivative compounds were synthesised by Maja M et al. The in-vitro antioxidant activity of these substances was assessed.42 With these substituents, these compounds have 3,4-dihydroxyphenyl and 2,5-dihydroxyphenyl rings (Fig.9). Given that hydrogen donation results in the creation of a stable quinoid structure, the compounds were predicted to have antioxidant action. Two hydroxyl groups in the orthogonal orientation have been found to be crucial for antioxidant action. [54-56]

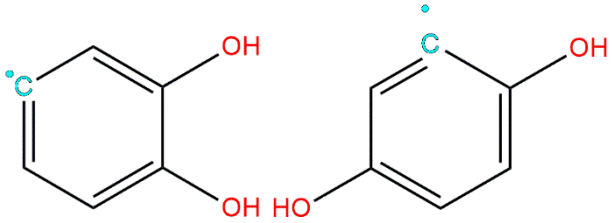


Fig.9: 3,4-dihydroxyphenyl and 2,5-dihydroxyphenyl

According to Chang et al., 7-hydroxyl coumarin, also known as umbelliferone, is crucial for XO inhibition. Moreover, at low concentrations (20 mM), certain 5,7-dihydroxycoumarins were able to effectively reduce

signals produced by the X/XO system; the most effective radical scavenger was 5,7-dihydroxy-6-(3-methyl-butyryl)-4-ethyl-chromen2-one (Fig.10). [57]

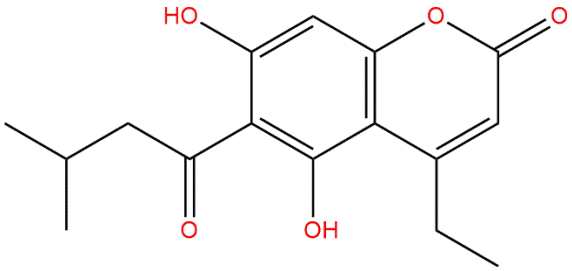


Fig.10: 5,7-dihydroxy-6-(3-methyl-butyryl)-4-ethyl-chromen2-one

According to Yang et al., the majority of hydroxylated 3-phenyl coumarins, often known as stilbene-coumarin hybrids, are potent antioxidants that prevent pBR322 DNA strand breakage caused by AAPH. [58]

Conclusion

This review has thoroughly explored the wide array of biological and pharmacological activities exhibited by coumarins, including their antibacterial, anticancer, antidepressant, anti-inflammatory, antioxidant, and anticoagulant effects. The evidence consistently demonstrates the desirable efficacy of coumarins across these various therapeutic areas. These findings highlight the significant potential of coumarins as versatile agents in the development of novel treatments for a range of diseases.

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