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Metal Complexes of Coumarin Derivatives: An Extensive Review

Thehasis Sheikh[1], P.M. Ronad[1*], A.A. Ankalikar[1], Akshata Menasinakai[1], Pooja Gouda[1]

[1]Department of Pharm-Chemistry, KLE College of Pharmacy, Vidyanagar, Hubli, India.

***Corresponding Author E-mail: pmronad@kledeemeduniversity.edu.in**

Abstract:

The plant kingdom is known rich source of phytochemicals and many of them possess organoleptic properties of the natural sources in which they originate. Over 4000 distinct phytochemicals are known to the mankind which have promising activity against several diseases whether metabolic, degenerative or infectious. The Family of Benzopyrones which are also known as coumarins or as 2H-1-benzopyran-2-ones, which are abundantly found in nature have displayed promising pharmacological activity. They comprise of a significant class of oxygen-containing heterocycles that are both naturally occurring and/or synthesized, and they have a typical benzopyrone framework. This review gives a broad overview of the varied pharmacological uses of metal complexes and of coumarin compounds individually as well as several metal complexes fused with the coumarin compounds. A tumultuous rise in the interest and in the publication about coumarin based metal complexes explains the powerful impact this class of medicines is having in the research field. We anticipate that this evaluation will be beneficial for the continued development of metal complexes based on coumarin in the field of medication development.

Keywords: Benzopyran, Coumarins, Dipteryx odorata, coumarin-based analogues, pharmacological activities

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1. Introduction:

In the kingdom of plants, coumarins are a broad class of naturally occurring polyphenolic phytochemicals. Many organic and medicinal chemists are drawn to the isolation from natural sources, biological or chemical synthesis, and pharmacological and biological evaluation of their applications [1].

The plant kingdom is known rich source of phytochemicals and many of them possess organoleptic properties of the natural sources in which they originate. Over 4000 distinct phytochemicals are known to the mankind which have promising activity against several diseases whether metabolic, degenerative or infectious. The Family of Benzopyrones which are also known as coumarins or as 2H-1-benzopyran-2-ones, which are abundantly found in nature have displayed promising pharmacological activity. They comprise of a significant class of oxygen-containing heterocycles that are both naturally occurring and/or synthesized, and they have a typical benzopyrone framework.

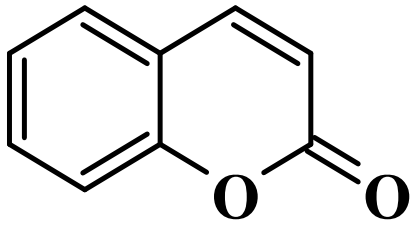


Figure 1: Chemical structure of Coumarin

The origin of the name coumarin is from a French word *coumarou*, seeds belonging to the plant *Dipteryx odorata* (*Coumarouna odorata*) (Fabaceae/Leguminosae), also termed as Tonka bean. The first time coumarin as natural product was isolated in 1820 and which has a sweet aroma similar to freshly mowed hay due to which it has been a part of perfume manufacturing since 1882. It is believed that plants produce this as a chemical defense against predators.

A typical structure of coumarinic compounds comprises of a benzene ring which is fused to a α-pyrone ring forming a conjugated system with strong transport of charge and rich electron characteristics. The coumarin structure framework is an extremely simple an exciting starting point for a variety of applications which is attributed to its simplicity and adaptability. Coumarins are used as fragrances, cosmetics, and industrial additives. Some of its compounds have been used to improve the aroma of tobacco products and some alcoholic beverages. However, their most important function is in natural products, organic chemistry, and medicinal chemistry. The extraction, synthesis, and evaluation of coumarins have developed into an extremely attractive and rapidly expanding area of science. Numerous coumarin compounds are also being significantly researched as potential medicines with potent pharmacological action, low toxicity and side effects, minimal drug resistance, high bioavailability, broad spectrum of activity, greater curative

benefits, etc. which find use in treating a variety of disorders. The major class of natural chemicals known as coumarins and its derivatives are found throughout the natural world. Although the biggest concentration is typically in fruits and flowers, they can also be found in the integument of seeds, fruits, flowers, roots, leaves, and stems. From hundreds of plant species in more than 40 different families, coumarins have been isolated. More than 1300 distinct coumarins were extracted, and they were widely dispersed across the Angiospermae, Monocotyledoneae, and Dicotyledoneae families. Araliales, Rutales, Asterales, Fabales, Oleales, Urticales, and Thymelaeales are the families which have more than 100 occurrences. The Apiaceae (Umbelliferae), Rutaceae, Asteraceae (Compositae), Fabaceae (Leguminosae), Oleaceae, Moraceae, and Thymelaeaceae families, in that order, are those having occurrence counts greater than 100. Coumarins are also found as secondary metabolites, in sponges, certain bacteria, and higher plants whose sole purpose is the defense against herbivores and microbial invasions. These families contain the most well-known and extensively studied coumarins in the fields of phytochemistry, pharmacology, medicinal chemistry, and food science. Initially, *D.odorata* seeds were used to isolate coumarin. The plant biosynthesises these substances by using shikimic acid and phenylalanine.

The first time coumarin was synthesized, in 1868, it was employed as a precursor in the pharmaceutical industry for producing a variety of synthetic anticoagulant drugs, starting with dicoumarol.

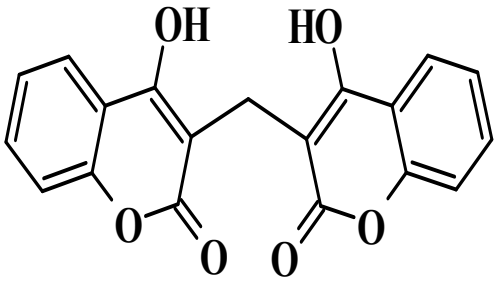


Figure 2: Chemical structure of dicoumarol

Several coumarin-based anticoagulant drugs have so far been widely used in clinics. The development of coumarin-based anticoagulant, antioxidant, antimicrobial (anti-viral, anti-fungal, and anti-parasitic), anticancer, anti-diabetic, analgesic, antineurodegenerative, anti-hypertensive, antitubercular, anticonvulsant, anti-adipogenic, Cytochrome P450 inhibiting, anti-hyperglycemic, antioxidant and anti-inflammatory medicines has received a lot of attention. Additionally, coumarin compounds play a significant role in medicinal chemistry due to their unique and adaptable oxygen-containing heterocyclic structure[2].

Since the majority of extracted coumarins are biologically active, coumarin derivatives are increasingly being synthesised since it takes long time and is expensive to extract coumarins from plants. There are numerous ways to make coumarins, including the Perkin reaction, the Vilsmeier-Haack-and-Suzuki cross-coupling process, the Knoevenagel condensation, the Pechmann

condensation, the Wittig reaction, the Baylis-Hillman reaction, and the Knoevenagel condensation[3].

2. Classification of Coumarin:

The coumarin derivatives are classified into various categories. They can generally be grouped chemically into three categories: simple coumarins, complex coumarins, and various coumarins. Usually, more advanced coumarins are combined with other heterocycles. Because of this, they can be divided into several categories, including simple coumarins, furocoumarins, dihydrofurocoumarins, pyranocoumarins (linear and angular), phenylcoumarins, and biscoumarins.

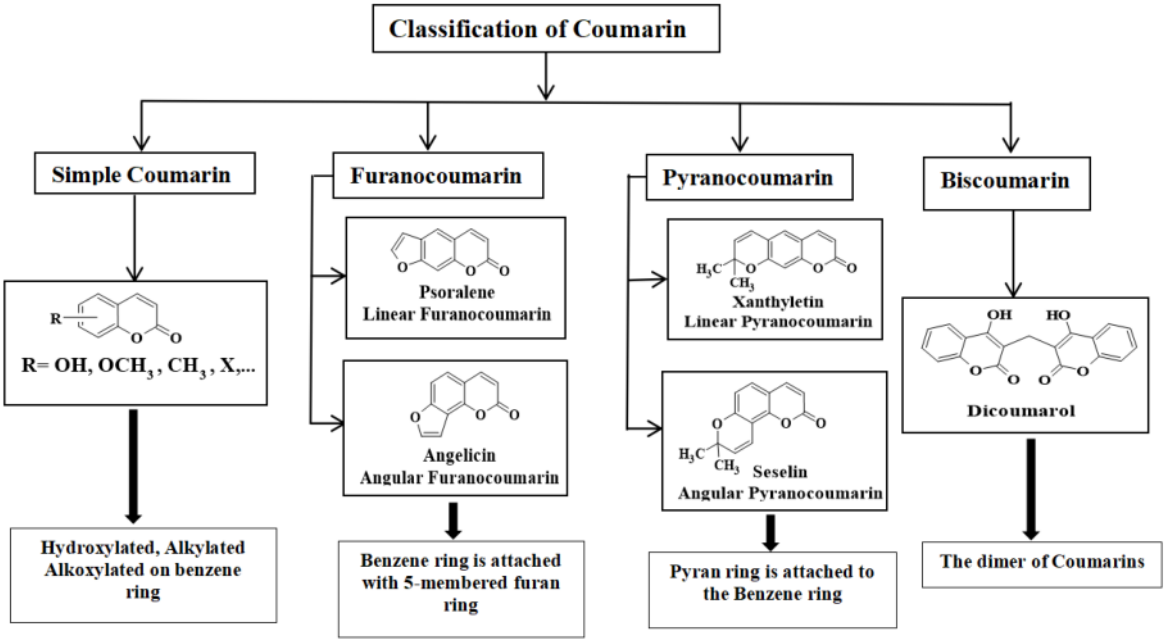


Figure 3: Classification of coumarin[4]

3-Phenylcoumarins are a subclass of coumarins, which are a well-studied group of compounds with a wide range of pharmacological interests. Coumarins are a class of molecules that can be either naturally occurring or synthetically produced. Additionally, due to the aromatization of the ring, a connection between 3-phenylcoumarins and steroid hormones, particularly with estrogens, can be formed. These factors make 3-phenylcoumarins a privileged scaffold in medicinal chemistry[5].

2.1 Chemical structures behind the Pharmacological effects in natural Coumarins.

In plants, coumarin can be found in both free and glycosidic forms bonded to a glucose molecule as an aglycone. The significant structural heterogeneity of coumarins explains the wide range of pharmacological effects that are advantageous to human health.

a) Scopoletin, a chemical found in *Viburnum prunifolium* and *angelica*, has hypotensive and spasmolytic characteristics. It can prevent the spastic contraction of smooth gastrointestinal and genitourinary muscle.
b) Two coumarins from the *Ammi visnaga* species, Khelline and Visnagine, show spasmolytic and antianginal effects on the smooth muscle of the coronary vessels.
c) Umbelliferone, a coumarin found in the resins of several Umbelliferae species and the grassy aerial parts of Pilosella, is used as a sunscreen and has antibrucellosis and antibiotic properties.
d) Esculetin, a coumarin found in chestnut leaves, has anti-inflammatory and phlebotonic properties that help to improve venous tone by reducing capillary permeability and increasing their resistance. It also prevents the production of proinflammatory chemicals such prostaglandins, thromboxanes, and leukotrienes that cause allergy, inflammatory, and asthmatic reactions.
e) Phytoalexins are plant-derived coumarins with general protective properties to fungal infection, physical injury, chemical damage, or a pathogenic progression. The main function of phytoalexins is to constrain or destroy the attacking agents like bacteria, viruses, and insects[6].
f) Fraxidin exhibited antihyperglycemic action and prevented the production of inducible nitric oxide synthase.
g) Coumarin is used to treat oedema and has anti-inflammatory properties. By promoting phagocytosis, the generation of enzymes, and consequently proteolysis, this helps remove protein and oedema fluid from wounded tissue.
h) Against clinically isolated strains of Gram-positive and Gram-negative bacteria like *Staphylococcus aureus, Salmonella typhi, Enterobacter cloacae*, and *Enterobacter aerogenes,* Aegelinol and Agasyllin exhibited significant antibacterial activity. A wide range of Gram +ve bacteria, including *Bacillus megaterium, Micrococcus luteus, Micrococcus lysodeikticus,* and *Staphylococcus aureus*, are intolerant to the effects of Ammoresinol and Ostruthin.
i) Imperatorin showed anti-cancer properties. By using wound healing and transwell assays, osthole is effective at preventing the migration and invasion of breast cancer cells. Matrix metalloproteinase's promoter and enzyme activity were efficiently inhibited by osthole in luciferase and zymography testing, which may be one of the reasons why Osthole limits migration and invasion.
j) *Calophyllum lanigerum* var. austrocoriaceum and *Calophyllum teysmannii* var. inophylloide (King) P. F. Stevens (Clusiaceae) extracts were used to isolate pyranocoumarins like Pseudocordatolide C and Calanolide F. Both of them have depicted anti-HIV activity[7].

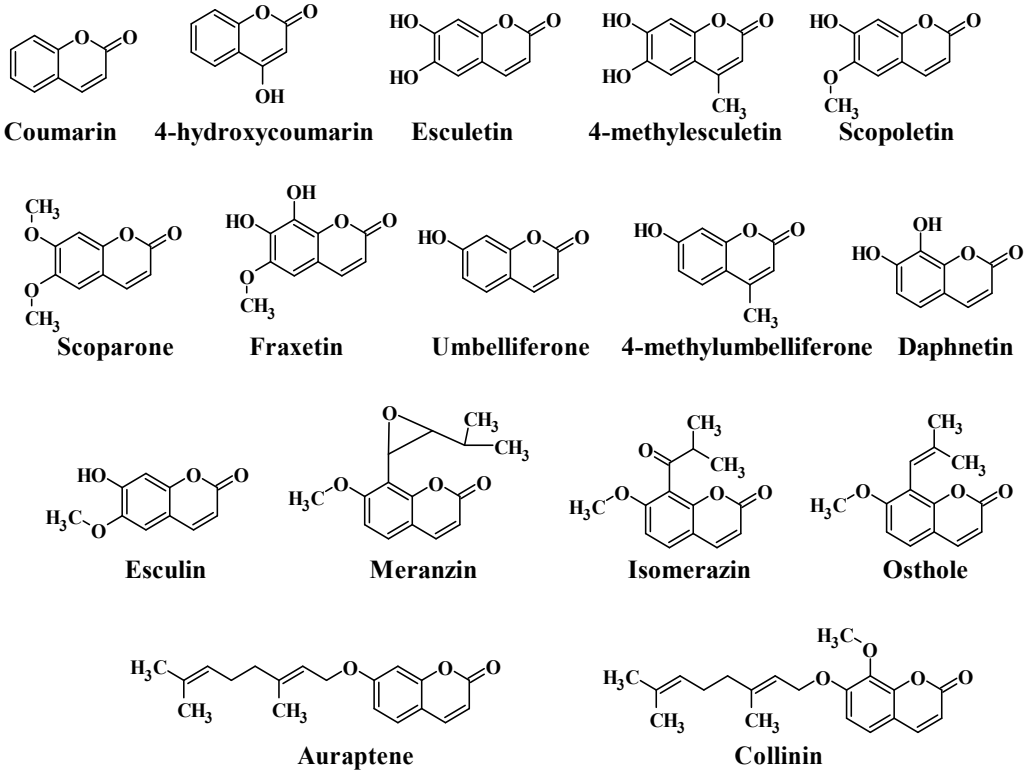


Figure 4: Structures of biologically active coumarins[8]

2.2 Pharmacokinetics Study of Coumarin

The biological processes of absorption, distribution, metabolism, and excretion are all included in the study of pharmacokinetics, which focuses on the dynamic movements of foreign substances, or coumarins, as they pass through the body. Numerous pharmacological properties of natural coumarins have been investigated, including their anti-inflammatory, antioxidant, neuroprotective, and anti-tumor properties. Coumarins are quickly absorbed from the gastrointestinal tract (GIT) and distributed throughout the body upon oral consumption. Coumarin and 7-hydroxycoumarin dissolve weakly in water. It was found that coumarins can easily permeate across lipid bilayer layers since they are non-polar. A clinical pharmacokinetic investigation found that only 2%–6% of 7-hydroxycoumarin entered the systemic circulation after being completely absorbed from the gastrointestinal tract and quickly processed by the liver in the first pass. The precursor of 7-hydroxycoumarin, coumarin, is not very bioavailable and has a brief half-life. According to pharmacokinetic studies, 35% and 47% of 7-hydroxycoumarin bind to plasma proteins.

The dietary component coumarin is significantly metabolized by the human liver to produce excretable 7-hydroxycoumarin. Even so, it is regarded as safe when regularly ingested in food. Because of its potential association with hepatotoxicity, which is especially apparent in rats, coumarin has both toxicological and clinical importance. The pharmacokinetics of coumarin were modelled after its virtual oral delivery to humans. Using specific species allometric scaling constants, the biotransformation of coumarin to o-hydroxyphenylacetic acid (by 3, 4-epoxidation)

and the modified monitoring equivalents of coumarin were calculated. The available plasma concentrations from rat studies were used to compute human coumarin equivalents. The rapid *in vitro* metabolic clearance for humans (about 50 times faster than for rats) was measured using rat and human liver preparations for both *in vitro* and *in vivo* interpretation. The metabolic ratios to 7-hydroxycoumarin and o-hydroxyphenylacetic acid were established at major (0.9) and minor (0.1) levels, respectively, to account for the whole clearance of coumarin in order to reproduce human physiologically based pharmacokinetics (PBPK). The maximum projected concentrations of coumarin that have been reported were used to create the human plasma concentration curves using PBPK models. Advanced dose using PBPK modelling proved useful in evaluating human risk because there was little evidence of coumarin's toxicological effects in humans under the prevalent assumptions [9].

3. Literature Survey

Sumi Hwang investigated the variety of potential pharmacological effects of 7-methoxy-5-geranyloxycoumarin and bergamottin extracted from lime by synthesizing several coumarin derivatives with a geranyloxy group and comparing their bioactivities. This study used both weak and strong base additives, such as K_2CO_3, Cs_2CO_3, and Ag_2CO_3, to explore the reaction between 7-hydroxycoumarin and geranyl bromide in the synthesis of the geranyloxycoumarin derivative. By treating different hydroxycoumarins with geranyl bromide under ideal reaction conditions, we were able to get 95% yields for the O-alkylated geranyloxycoumarin derivatives. Nevertheless, at mildly optimized reaction circumstances, 4-hydroxycoumarin and geranyl bromide produced 3,3-Bis((E)-3,7-dimethylocta-2,6-dien-1-yl)chromane-2,4-dione (E)-2-((E)-3,7-dimethylocta-2,6-dien-1-yl)-1-(2-hydroxyphenyl)-5,9-dimethyldeca-4,8-dien-1-one (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one. According to reports, the keto enol tautomerism of 4-hydroxycoumarin produces a variety of coumarin derivatives, which is why compounds like 3,3-Bis((E)-3,7-dimethylocta-2,6-dien-1-yl)chromane-2,4-dione (E)-2-((E)-3,7-dimethylocta-2,6-dien-1-yl)-1-(2-hydroxyphenyl)-5,9-dimethyldeca-4,8-dien-1-one and (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-2H-chromen-2-one are formed. This work isolated bergamottin, isopimpinellin, 5-geranyloxy-7-methoxy coumarin, and 5,7-dimethoxy coumarin from lime peel. Additionally, utilizing optimized Cs_2CO_3, acetonitrile, and room temperature (20 ± 5), coumarin derivatives and geranyloxycoumarin, which are anticipated to have a variety of biological functions, were synthesized in excellent yields. Eight species of food-poisoning bacteria were used in the antibacterial screening of coumarin derivatives, geranyloxycoumarin derivatives, and the coumarin component of lime peel. The minimum inhibitory concentration (MIC) of the coumarin derivative with good activity was determined. The 5,7-Dihydroxy-4-trifluoromethylcoumarin and 7-hydroxy-4-trifluoromethyl coumarin derivatives' antibacterial activity was verified as a consequence of the MIC measurement. These findings support the antibacterial action of coumarin derivatives including CF3 and OH substituents against food-poisoning microorganisms. Only 1,2,3-triazole-coumarin derivatives have been shown to have antibacterial activity against *Enterococcus faecalis*. Nonetheless, coumarin derivatives shown antibacterial activity on *B.*

cereus, S. aureus subsp. aureus, M. luteus, S. enteritidis, and *S. boydii*, according to the results of the antibacterial screening carried out in this investigation.

Furthermore, it was reported that no antibacterial action was seen when the water-soluble coumarin quaternary ammonium chloride was synthesized against Gram-positive *B. subtilis* and Gram-negative *E. coli* bacteria. However, compound 7,8-Dihydroxy-4-trifluoromethylcoumarin's antibacterial screening results indicated that it was active against *E.coli*. This experiment led to the measurement of the MIC of the 5,7-Dihydroxy-4-trifluoromethylcoumarin derivative in *E. coli* at a concentration of 2.9 mM because their antibacterial activity was verified, the data obtained here suggest that 5,7-Dihydroxy-4-trifluoromethylcoumarin and 7-hydroxy-4-trifluoromethyl coumarin derivatives, which contain CF3 substituents, can be used as natural antibacterial agents. We think that if the several derivative synthetic chemicals we have suggested are used in additional study, the large-scale synthesis of coumarin derivatives with antibacterial activity will be feasible. Therefore, in this investigation, we used a coumarin synthesis method to try to find a method with a high recovery rate and then used a coumarin derivative to confirm the antibacterial activity. It is anticipated that these findings will offer valuable insights into the antibacterial action of water-soluble coumarin derivatives containing fluorine. It is anticipated that by creating more derivatives using structure–activity relationships, beneficial circumstances to improve antibacterial activity would be discovered in the future[10].

Chang Jia *et, al.* discovered that coumarin could lower strain viability and hinder cell development. The characteristics of yeast apoptosis, such as phosphatidylserine (PS) externalization, DNA fragmentation, cytochrome c release, and metacaspase activation, were identified in order to investigate the pattern of cell death. The findings indicated that coumarin treatment caused PS exposure on the outer leaflet, nuclear condensation and DNA breakage, Cytochrome C release from the mitochondria to the cytosol, and metacaspase activation, indicating that coumarin caused apoptosis in *Candida albicans*. Contrary to our findings, other research has shown that coumarin harms *Candida albicans* cells by creating holes in the cell wall and that necrosis and cytoplasmic material leakage cause cell death. This could be caused by variations in the *C. albicans* strains employed, different culture media, incubation temperature, and duration of coumarin treatment. As is well known, mitochondria are both the source and the target of reactive oxygen species (ROS), and both ROS and mitochondria are crucial for apoptotic processes.

Oxidative stress causes the mitochondrial permeability transition pore (PTP) to open during apoptosis. This opens the mitochondrial outer membrane permeabilization (MOMP), which releases cytochrome c and other proapoptotic factors and activates metacaspase. Additionally, ROS can directly cause apoptosis in a way that is dependent on metacaspase. In this investigation, coumarin-treated *Candida albicans* cells showed aberrant mitochondrial shape, reduced mitochondrial membrane potential, and increased ROS levels, suggesting that coumarin caused ROS accumulation and mitochondrial malfunction. Ca^{2+} is integrally linked to apoptosis in addition to ROS. Apoptotic stimuli frequently result in an increase in cytosolic Ca^{2+} in mammalian cells, which is fueled by either intracellular calcium release or external calcium influx. Among

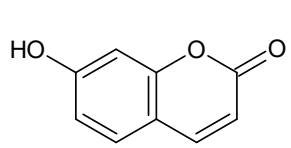
these, PS externalization depends on the release of Ca^{2+} from lysosomes. MCU complex-dependent absorption then quickly transfers cytosolic Ca^{2+} to mitochondria. This Ca^{2+} signal may cause PTP to open under oxidative stress, releasing cytochrome c and other proapoptotic substances that eventually cause apoptotic bodies to develop and cell death. Apoptotic stimuli may cause enough mitochondrial Ca^{2+} to undergo the permeability transition, which is accompanied by elevated ROS and cytosolic Ca^{2+} levels, even though yeast mitochondria lack the MCU complex.Ca^{2+} levels in the cytosol and matrix equilibrate and stabilize PTP in its open conformation after it opens, producing matrix swelling, damage to the outer mitochondrial membrane, and the release of proapoptotic proteins, all of which result in cell death. According to our research, coumarin administration led to an increase in Ca^{2+} in the cytosol and mitochondria, which may have a role in apoptosis[11].

By administering a dose of 200 mg/kg body weight orally or 100 mg/kg intraperitoneally, Singh *et, al*. showed that the coumarin derivative i.e, antifungal molecule N, N, N-Triethyl-11-(4-methyl-2-oxo-2Hbenzopyran-7-yloxy)-11-oxoundecan-1-aminium bromide coded as SCD-1(synthetic coumarin derivative 1), this compound exhibited potent activity against pathogenic Aspergilli (MIC90 15.62 mg/mL) and could improve the survival of *Aspergillus fumigatus* infected mice and reduce the colony counts in critical organs, suggesting that SCD-1 could be a potential treatment for aspergillosis. The antifungal activity of coumarin or its derivatives against *Candida albicans in vitro* was the primary focus of earlier research. It's uncertain how effective these substances are *in vivo*. In order to assess coumarin's anti-Candida efficacy *in vivo*, infected mice were given it by Oral-Gastric (OG) gavage. The findings demonstrated that the infected mice's survival was extended by the 40 mg/kg coumarin dose. Additionally, toxicity tests revealed that coumarin was low-toxic to human umbilical vein endothelial cells (HUVECs) and non-toxic to mice at the 40 mg/kg level. These findings suggest that coumarin is a safe and efficient treatment for *Candida albicans* infections[12].

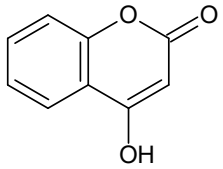
Hsia CW *et, al.* in this work shows that esculetin, a coumarin derivative, suppresses human platelet activation by impeding the generation of hydroxyl radicals, the PLCγ2–PKC cascade, Akt activation, and eventually platelet activation. Esculetin may therefore serve as a crucial therapeutic agent in the prevention of thromboembolic disorders. Esculetin (10–80 μM) was highly efficient in preventing platelet aggregation induced by collagen (1 μg/mL) and arachidonic acid (AA; 60 μM), but not by thrombin (0.01 U/mL) or prostaglandin endoperoxide 9,11-dideoxy-11α,9α-epoxymethanoprostaglandin (U46619). At a concentration of 80 μM, esculetin totally prevented platelet aggregation caused by collagen and AA. Esculetin's 50% inhibitory concentration (IC_{50}) against collagen-stimulated platelet aggregation was 50 μM. Therefore, esculetin's IC_{50} (50 μM) and maximal concentration (80 μM) were employed to investigate its potential processes in platelet activation triggered by collagen, an essential endogenous platelet activator that plays a significant role in arterial thrombosis. The solvent control, 0.1% dimethyl sulfoxide (DMSO), had no effect on platelet aggregation. According to this study, esculetin successfully prevents arterial thrombogenesis *in vivo* and has antiplatelet efficacy for human platelets. Esculetin's absorption, distribution, metabolism, and excretion in rat plasma and tissues were assessed in a prior work to

investigate its pharmacokinetics. They discovered that esculetin's half-life in plasma was 45 minutes, and its maximal plasma level was higher five minutes after oral administration. Esculetin's pharmacokinetic profile so indicates that it may be rapidly disseminated and removed from tissues, as well as that it is rapidly absorbed and elisecated from plasma. To get the necessary plasma concentrations that can prevent in vivo platelet activation, esculetin taken normally from natural sources would not be sufficient. Esculetin may be a novel antithrombotic agent in humans since it is said that long-term consumption of adequate natural food products or nutritional supplements is best to prevent atherothrombotic occurrences. By blocking the PLCγ2–PKC–Akt cascade and the production of hydroxyl radicals, esculetin prevents platelet activation, which in turn prevents platelet aggregation. According to this research, esculetin may be used therapeutically as a novel treatment for thromboembolic conditions[13].

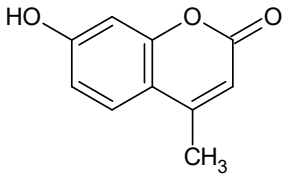
N.Prahadeesh *et, al*. in their research work synthesized and characterized four simple coumarin compounds using UV, IR, 1H and 13C NMR spectra. All of the produced coumarins demonstrated antioxidant activity by reducing ferric ions and scavenging hydrogen peroxide. The simple coumarins' antioxidant activity is shown to be in the following decreasing order: 7-hydroxy coumarin, 4-hydroxy coumarin, 7-hydroxy 4-methyl coumarin, and coumarin.



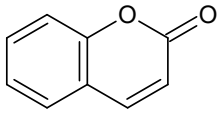
7-Hydroxy coumarin



4-Hydroxy coumarin



7-Hydroxy 4-methyl coumarin



Coumarin

The sequence of antioxidant activity is comparable for both ferric reducing ability and hydrogen peroxide scavenging ability. Compared to parent coumarins, hydroxyl coumarins are more active. The hydroxyl functional group enhances the antioxidant activity of coumarin and demonstrates an efficient scavenging ability. On the coumarin skeleton, the hydroxyl group at position seven is more efficient at scavenging H_2O_2 and reducing ferric ions than that at position four. The ferric reducing capacity of 7-hydroxy coumarin is roughly twice that of 4-hydroxy coumarin. The antioxidant activity of coumarin rings is also significantly influenced by their electron delocalizing mechanism. The coumarin ring system's methyl functional group at position four interferes negatively with both the ferric reducing capacity and the H_2O_2 scavenging activity. Nevertheless, all of the investigated simple coumarins have low antioxidant activity to scavenge H_2O_2 and ferric ions when compared to the standard reference, ascorbic acid[14].

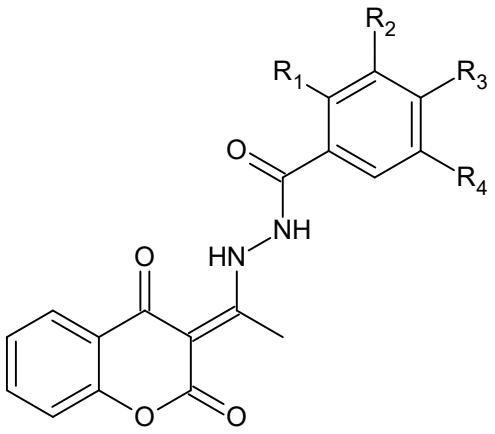
Manda R R *et, al.* Synthesized a series of new 7-{3-[3-(Benzylidene-amino)-[1,2,4]triazole-1-yl]-propoxy}-4-methyl-chromen-2-one molecular hybrids 7(a–k) using molecular hybridization approach. The synthesized new benzylidene-triazole tethered coumarin molecular hybrids were characterized by spectroscopic studies and elemental analysis. Molecular modelling studies against tubulin alpha beta hetero dimer protein have been used to investigate the antifungal activity of coumarin molecular hybrids in terms of tubulin inhibitors. The findings undeniably showed that

coumarin molecular hybrids with 2,4-dihydroxy and indole substituted antagonists had a considerable binding affinity. Additionally, *in vitro* antifungal investigations against three fungal strains—*Candida albicans, Aspergillus niger,* and *Aspergillus fumigatus*—were carried out using the broth dilution method. The outcomes, which are in line with docking models, strongly demonstrate the antifungal activity of indole and 2,4-dihydroxy substituted molecules. Among all the synthesized molecular hybrids, indole and 2,4-dihydroxy substituted compounds exhibit exceptional antifungal activity, with Minimum Inhibitory Concentration (MIC) values of 31.25 µg/ml and 62.5 µg/ml for *C. albicans* and 31.25 µg/ml for *A. niger*, respectively. These values are significantly higher than griseofulvin and fluconazole. The current study unequivocally shows the potential effectiveness of synthetic indole and 2,4-dihydroxy substituted coumarin molecular hybrids as lead compounds for the synthesis of novel drugs against resistant strains for the treatment of fungal infection.

Treating fungal infections is still a difficult issue worldwide. The shortcomings of the current antifungal medications highlight the need for the development of antifungal medications with new targets as an essential approach for the effective treatment of fungal infections. In order to investigate their antifungal efficacy, they have coupled triazole and coumarin moieties in the current study using a "molecular hybridization" strategy, taking into account their pharmacological significance. According to the study, 7(a–k) compounds 7j and 7e exhibit exceptional antifungal activity towards *C. albicans* [MIC: 31.25, 62.5 µg/ml] and *A. niger* [MIC: 31.25, 62.5 µg/ml], which is significantly higher than Griseofulvin [MIC: 62.5, 125 µg/ml] and fluconazole [MIC: 62.5,31.25 µg/ml]. Molecular modelling investigations, which showed compounds 7e and 7j to have a greater binding affinity with binding scores of -1.5 and -10.7 kcal/mol tubulin alpha beta hetro dimer protein, further corroborated the results. Therefore, the synthesized compounds (Z)-7-(3-(3-((2,4-dihydroxybenzylidene)amino)-1H-1,2,4-triazol-1-yl)propoxy)-4-methyl-2H-chromen-2-one (7e) and (Z)-7-(3-(3-(((1H-indol-2-yl)methylene)amino)-1H-1,2,4-triazol-1-yl)propoxy)-4-methyl-2H-chromen-2-one (7j) may be prospective lead pharmacophores in the drug discovery process for the creation of stronger antifungal medications[15].

Sijovinic D *et, al*. studied the synthesis of two new compounds with promising antimicrobial and anti-inflammatory properties using precursors that contain pyrogallol and coumarin units.The compounds pyrogallolcoumarin hybrids(PCHs) (E)-N′ -(1-(2,4-dioxochroman-3-ylidene)ethyl)-2,3,4-trihydroxybenzohydrazide (PCH-1) and (E)-N′ -(1- (2,4-dioxochroman-3-ylidene)ethyl)-3,4,5-trihydroxybenzohydrazide (PCH-2) were characterized by using various spectroscopic methods in combination with the DFT methods. Antimicrobial and anti-inflammatory activities were evaluated, by testing PCHs against 13 different types of microorganisms and soybean lipoxygenase. The specific mechanisms of anti-LOX activity was determined by performing molecular docking and molecular dynamics studies. With a minimum inhibitory concentration (MIC) of 31.125 µg/mL, these compounds exhibited the strongest antibacterial activity against *Proteus mirabilis* ATCC 12453. In addition, three standard bacterial species were chosen to evaluate the antibiofilm activity of tested substances. The findings demonstrated that PCH-2 had the greatest impact on *Staphylococcus aureus* ATCC 25923 biofilm formation (BIC50 at 378

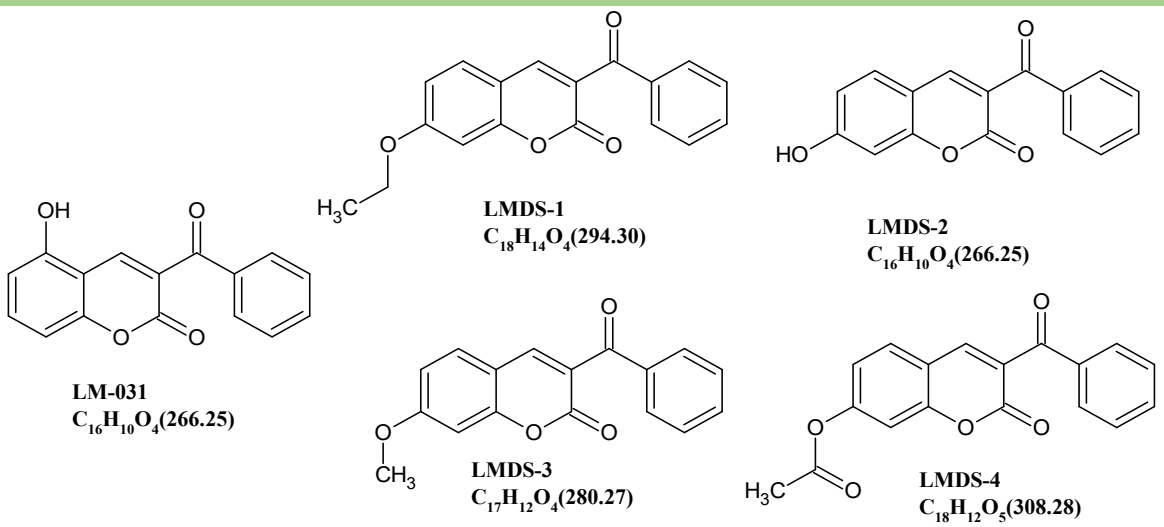
µg/mL). With IC_{50} values for PCH-1 = 38.12 µM and PCH-2 = 34.12 µM, the anti-LOX studies show that PCHs have outstanding activity.



	R1	R2	R3	R4
PCH-1	-OH	-OH	-OH	-H
PCH-2	-H	-OH	-OH	-OH

An analysis of the antimicrobial activity of both drugs revealed that their antibacterial activity was superior to their antifungal activity. In comparison to PCH-1, PCH-2 shown superior effectiveness against the biofilm development of specific bacteria. The acquired experimental results demonstrate the substantial inhibitory impact of the investigated substances. Furthermore, the studied compounds were found to create several hydrogen bonds with amino acid residues in the protein's active site through in silico study. These interactions support the compound–protein complex's stability and, hence, its inhibitory impact. Future study should concentrate on examining mechanisms of action, evaluating the compounds' efficacy *in vivo* and toxicity, and optimising their characteristics for possible clinical uses because the examined compounds demonstrated promising antibacterial and anti-LOX potential[16].

Te-Hsien Lin *et, al*. studied the Hyperphosphorylation and aggregation of the microtubule binding protein tau a neuropathological hallmark of Alzheimer's disease/tauopathies.Brain-derived neurotrophic factor (BDNF), tropomycin receptor kinase B (TRKB), and cAMP-response element binding protein (CREB) signalling are all altered by tau neurotoxicity, which contributes to neurodegeneration. Therefore, substances that activate TRKB may have positive effects on tauopathies. A coumarin derivative called LM-031 has shown promise in enhancing BDNF signalling in neuronal cells that exhibit the pro-aggregated ΔK280 taumutant.This work examined how LM-031 analogues interact with TRKB to produce neuroprotective effects in SH-SY5Y cells that express the ΔK280 tauRD-DsRed folding reporter. Reactive oxygen species and tau aggregation were decreased by all four LMDS drugs.



Among these, LMDS-1 and -2 increased neurite outgrowth and decreased caspase-1, caspase-6, and caspase-3 activities; the effect was considerably reversed by TRKB knockdown. ERK inhibitor U0126 or PI3K inhibitor wortmannin treatment reduced p-CREB, BDNF, and BCL2 in these cells, suggesting that LMDS-1/2 has neuroprotective effects via activating TRKB downstream ERK, PI3K-AKT, and CREB signalling.

Additionally, LMDS-1/2 showed that they may quench the intrinsic fluorescence of tryptophan residues in TRKB's extracellular domain, strengthening their contact with the protein. According to their findings, LMDS-1/2 may be used to treat tauopathies and Alzheimer's disease via triggering TRKB signalling.

This study found that in ΔK280 tauRD SH-SY5Y cells, the TRKB signalling pathway is disrupted, leading to downregulation of BCL2 and BDNF, overexpression of BAX, overproduction of ROS, and impairment of neurite outgrowth. LMDS-1/2 has neuroprotective effects on these cells via binding to TRKB, triggering its downstream ERK, PI3K-AKT, and CREB signalling pathways, and decreasing caspase activity. Their neuroprotection against tau aggregation was impaired by blocking either the ERK or PI3K-AKT signalling pathways, suggesting that both signalling pathways are essential for shielding neurones from tau-mediated neurotoxicity. Future research in animal models of tauopathies or other neurodegenerative diseases will be required to confirm their promise in treating patients with AD and tauopathies, as the effects of LMDS-1/2 were only investigated in cell models[17].

Abdul Amir H. Kadhum *et, al*. Synthesized the two coumarins, namely *N*-(4,7-dioxo-2-phenyl-1,3-oxazepin-3(2*H*,4*H*,7*H*)-yl)-2- (2-oxo-2H-chromen-4-yloxy)acetamide and *N*-(4-oxo-2-phenylthiazolidin-3-yl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide, and characterized by using various spectroscopic methods and elemental analysis techniques. The synthesized compounds showed that they have improved antioxidant properties than ascorbic acid[18].

Bhakti Davda *et, al*. Synthesized a series of novel coumarin derivatives (3a–3e) and characterized for their biological activities, including anti-inflammatory, antioxidant, and anticancerproperties. This study concluded that compounds 3b (p-methoxy) and 3e (p-hydroxy) demonstrated selective inhibition of COX-2 over COX-1 and considerable suppression of albumin denaturation, suggesting their potential as anti-inflammatory drugs. Antioxidant activity: 3b and 3e showed excellent antioxidant qualities in both DPPH and ABTS assays, with 3b emerging as the most effective radical scavenger. Anticancer activity: In cytotoxicity tests, compounds 3e and 3b showed the best results, with low IC_{50} values against the MCF-7 and HeLa cell lines. Significantly, 3e demonstrated strong selectivity for cancer cells compared to normal WI-38 cells, suggesting intriguing anticancer potential. The most potent derivatives, 3b (p-methoxy) and 3e (p-hydroxy), had outstanding pharmacological profiles in a variety of assays, indicating their potential for additional preclinical and clinical research. These chemicals' structural alterations seem to improve their biological activity, with electron-donating groups like hydroxy and methoxy helping to boost their antioxidant and anticancer properties.These results imply that 3b and 3e may be used as lead molecules for the creation of multitargeted medications that can treat cancer, oxidative stress, and inflammation all of which are connected to a number of chronic illnesses[19].

V. S. V. Satyanarayana *et, al*. the new Schiff base 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N′-(substitutedmethylene)acetohydrazides (4a-p) have been synthesised by reaction of 2-[(4-Methyl-2-oxo-2H-chromen-7- yl)oxy]acetohydrazide with aryl/hetero aromatic aldehydes under conventional and microwave irradiation methods. The compounds 4c-l i.e. 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(3-nitrobenzylidene)acetohydrazide (4c), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-hydroxybenzylidene)acetohydrazide (4d), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-hydroxy-3-methoxybenzylidene)aceto hydrazide (4e),2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-dimethylaminobenzylidene)aceto hydrazide (4f), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(2,5-dimethoxybenzylidene)acetohydrazide (4g), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(3-chlorobenzylidene)acetohydrazide (4h), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[3,4-dimethoxybenzylidene]acetohydrazide (4i), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-bromothiophen-2-yl)methylene]aceto hydrazide (4j), 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-chlorofuran-2-yl)methylene]aceto hydrazide (4k) and 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-nitrofuran-2-yl)methylene]aceto hydrazide (4l) were tested for antibacterial acivity by disc diffusion method, showing moderate to potent inhibition.Preliminary antibacterial screening using the paper disc method revealed that compounds 4c, 4e, 4g, 4h, 4j, and 4l were effective against every type of bacteria. It was discovered that the synthetic compounds' antibacterial efficacy against pathological and standard strains was comparable (statistically negligible difference). The majority of the substances showed modest to moderate antibacterial activity. *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm), *Staphylococcus aureus* ATCC 25923 (1000 ppm), *Escherichia coli* ATCC 25922 (1000 ppm), and *Klebsiella pneumonia* ATCC 13883 (1000 ppm) were all successfully inhibited by compounds 4c–l. The most effective compounds against *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm), *Staphylococcus aureus* ATCC 25923 (150 ppm), *Bacillus subtilis* ATCC 29212 (150 ppm), *Klebsiella pneumoniae* ATCC 13883 (150 ppm), and *Bacillus subtilis* ATCC 29212 (150 ppm),

were compounds 4k-l, 4j, 4c, 4h, and 4e. Compounds 4d, 4g, 4i, and 4f were the most active against *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm) and *Escherichia coli* ATCC 25922 (1000 ppm), respectively.

The most effective compounds against the screened gram positive and gram negative standard and pathogenic bacterial strains were discovered to be compounds 4k, 4l, and 4e. Based on the findings mentioned above, they have determined that compounds 4g, 4l, and 4k were the most effective since these compounds prevent *Staphylococcus aureus* and *Pseudomonas auregenosa* from growing to diameters of 18, 15, and 16 mm[20].

4. Emergence of Metal Complexes:

Among the many bioactivities that coumarins exhibit are anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscicidal, antihelmintic, sedative and hypnotic, analgesic, and hypothermic effects. Aflatoxin B1; 7,12-dimethylbenz(a)anthracene and N-methyl-N-nitrosourea-induced mammary carcinogenesis in rats have also been demonstrated to be inhibited by coumarins. Due to its capacity to suppress human immunodeficiency virus, coumarin derivatives have been evaluated for the treatment of HIV. Many *in vitro* and *in vivo* investigations have looked into the potential use of coumarins in the treatment of cancer since the late 1980s. Based on the structure of coumarin where there exists delocalization of π-electrons (resonance effect), the potential for this molecule to be used as chemical inhibitor can be established. Since the discovery of cisplatin, medicinal metal complexes have gained attention as a promising research field. Since then, a large number of complexes have been produced and examined in many biological systems. Metal complexes play an essential role in pharmaceutical sciences for their multiple and important activities and it is well known that copper complexes have a wide range of biological effects[21].

4.1 Catalytic property of Metal Complexes:

Metal complexes are crucial to industrial, medicinal, and agricultural chemistry. For the synthesis of complex compounds known as Schiff bases, which are condensation products of primary amines and aldehydes or ketones (RCH=NR′, where R & R′ indicates alkyl and/or aryl substituents), a ligand-a metal surrounded by a cluster of ions or molecule-is being used. Oxygenation, hydrolysis, electro-reduction, and decomposition processes can be catalyzed by aromatic Schiff bases or their metal complexes. In the oxygenation of alkene, four coordinated Co (II) Schiff base chelate complexes exhibit catalytic activity. Phenols (naphthol) are oxidized by metalloporphyrins. Some copper complexes made with amino acids increase hydrolysis rate (10–50 times) more than a simple copper (II) ion. The synthetic iron (II) Schiff base complex has catalytic properties for oxygen electro-reduction. Some metal complexes of a polymer-bound Schiff base exhibit catalytic activity on the oxidation of ascorbic acid and the decomposition of hydrogen peroxide. Cyanohydrins cobaltate complexes exhibit catalytic activity.

4.2 Diverse Pharmacological activity of Metal Complexes:

Thallium (I) combined with benzothiazolines, exhibits antibacterial activity against pathogenic bacteria. Different metal complexes in the 2nd and 4th oxidation states synthesized with aniline interact differently with various microorganisms. Mo (IV) and Mn (II) metal complexes containing the ligands hydrazine carboxamide and hydrazine carbothiamide exhibit antibacterial action against *Xanthomonas compestris* and *S. aureus*, respectively. *E. coli, S. aureus, B. subtilis*, and *B. pumpilis* are all affected to the antibacterial effects of tridentate Schiff bases and their metal complexes. *Coli bacillus* and *Pseudomonas aeruginosa* are resistant to the antibacterial effects of N-5 chlorosalicylidiene tauriene Schiff base and its Cu, Ni complexes. Thallium (I) complexes with benzothiazolines, copper (II) complexes of benzoylpyridine Schiff base, ruthenium (II) complexes with Schiff base salicyladmine and Oxovanadium (IV) complexes with triazole, all these metal complexes exhibit antifungal properties. Salicylaldehyde, 2,4-dihydroxybenzaldehyde, glycine, and L-alanine were used to synthesise Schiff bases, which have been shown to have anticancer action. Their order of reactivity with metal complexes is Ni>Cu>Zn>Co. Amido-Schiff base acts as a thrombin inhibitor after complexsation with Cu (II) and Fe (II). Reproductive physiology may be altered by Schiff bases of hydrazine, carboxoamide, and hydrazine, as well as metal complexes of dioxo Mo (IV) and Mn (II)[22].

4.3 Importance of Metal Complexes of Coumarin:

Metal complexes with coumarin-based ligands have been thoroughly examined for their cytotoxic effects because there is a tremendous demand for new therapeutic medicines for treating cancer. The most effective metal-ion-incorporated coumarin-based compounds are bi-functional Platinum (IV) complexes with COX inhibitory capabilities or Ir (III)-COUPY conjugates as promising photosensitizers in photodynamic treatment directed at cancer stem cells. Contrarily, the development of novel antimicrobial drugs is another major area of research in which coumarin-based metal complexes are assessed due to the rise in the number of multi-drug resistant microbial infections.

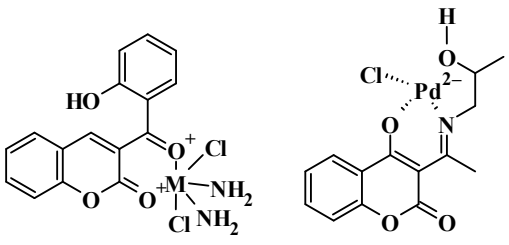


Figure 5: Structures of metal complexes

In addition, the most recent developments in the synthesis of metal complexes with coumarin-based ligands have led to the development of probes or sensors practical applications for detecting diverse

biological analytes under physiological conditions. The development of coumarin-based copper (II), iridium (III), or europium (III) complexes as fluorescence probes or PEC sensors for bioanalysis has attracted tremendously[23].

Sadia Rehman *et, al.* synthesized zinc metal complexes of dicoumarol derivatives. All these metal complexes were subjected to spectral studies like IR, NMR, MS, elemental analyses and conductance studies and then they were screened for antimicrobial activities against gram negative bacteria *Escherichia coli, Salmonella typhus*, *Agrobacterium tumefaciens*, *Erwinia carotovora, Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, gram positive bacteria *Staphylococcus aureus, Bacillus subtilis*, *Bacillus atrophaeus* and fungal strain *Candida albicans*. It was observed that most of the metal complexes showed moderate activities against Gram negative bacteria whereas they were more active against gram positive bacterial and fungal strains[24].

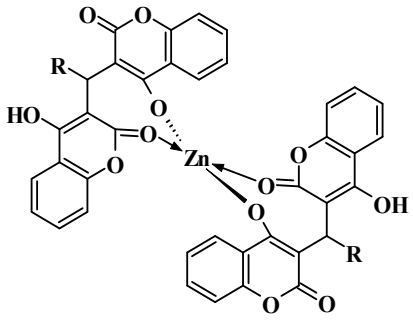


Figure 6: Structure of Zinc complexes of dicoumarols

Karekal Mahendra Raj *et, al.* synthesized Cu(II), Co(II), Ni(II) and Zn(II) complexes of ligands 5-substituted-N[1]-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)-3-phenyl-1H-indole-2-carbohydrazides and performed the various spectroscopic techniques like, IR, ^{1}H NMR, ESI-mass, UV–Visible, thermogravimetry–differential thermal analysis, magnetic measurements, molar conductance and powder-XRD data. Later the compounds were evaluated for their antimicrobial potency where the metal complexes were screened for their antibacterial and antifungal activities by the minimum inhibitory concentration (MIC) method. Studies demonstrated that the metal complexes were more effective than free ligands[25.]

Ramesh S. Yamgar *et, al.* performed the condensation reaction of schiff base 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde with dimethyl amino propylene diamine and N-methylamino propylene diamine and another condensation of schiff base ethyl 2-(3-formyl-4-hydroxyphenyl)-4-ethyl-1,3-thiazole-5- carboxylate with dimethylamino propylene diamine to synthesize the respective metal complexes. The combination of 1H NMR, 13C NMR, IR, and mass spectroscopy was used to characterise these Zn(II) metal complexes. It was concluded that the metal complexes moderately showed antimycobacterium activities when compared to that of standard Pyrazinamide and Streptomycin[26].

Jyotirmaya Sahoo *et, al.* synthesized metal complexes from 3-aryl-azo-4- hydroxy coumarin analogues and the structural characterization of the complex was done using various instrumental methods. It was reported that among all the metal complexes, cobalt complexes of (E)-3-((4-chlorophenyl) diazenyl)-4-hydroxy-2H-chromen-2-one and (E)-3-((4-methoxyphenyl) diazenyl)-4-hydroxy-2H-chromen-2-one exhibited potential antimicrobial activity when compared to their ligands[27].

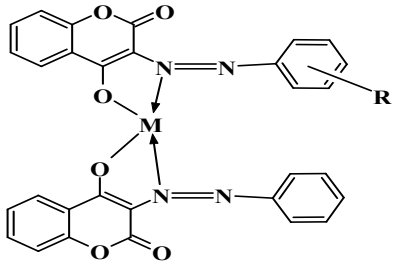


Figure 7: Chemical structure of metal complexes

Mohammad Usman *et, al.* evaluated metal complexes for potential antitumor chemotherapeutic drugs by synthesizing a copper complex of coumarin derivative and it was characterised using single crystal X-ray diffraction analysis and other spectroscopic methods. The metal complex showed very good activity for MCF-7 (breast cancer) and moderate activity on HepG2 (liver cancer) cell lines when cytotoxic activity was tested *in vitro*[28].

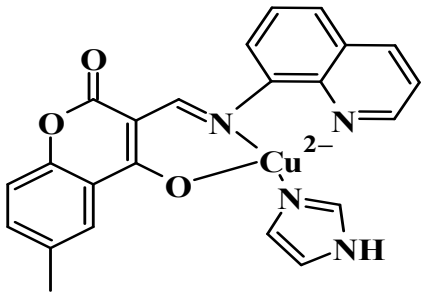


Figure 8: Structure of copper complex of coumarin

Dejan A. Milenkovic *et, al.* studied three coumarin ligands; L1, L2, and L3 namely ((3-(1-((3-chlorophenyl)amino)ethylidene)-chroman-2,4-dione)), ((3-(1-((4-chlorophenyl)amino)ethylidene)-chroman-2,4-dione)) and ((3-(1-(phenylamino)ethylidene)-chroman-2,4-dione)) respectively along with their corresponding palladium(II) complexes. All these compounds were examined for their binding affinity towards the SARS-CoV-2 virus and they were undergone molecular docking studies which reported that the binding affinities of L2, L3, and all of the complexes were higher than those for chloroquine and cinanserin, two FDA approved drugs. The results of the toxicity studies also demonstrated that C2 and L2 fall under

toxicity class V, which indicates that they might be dangerous if consumed, in contrast to FDA-approved medications, which were far more hazardous[29].

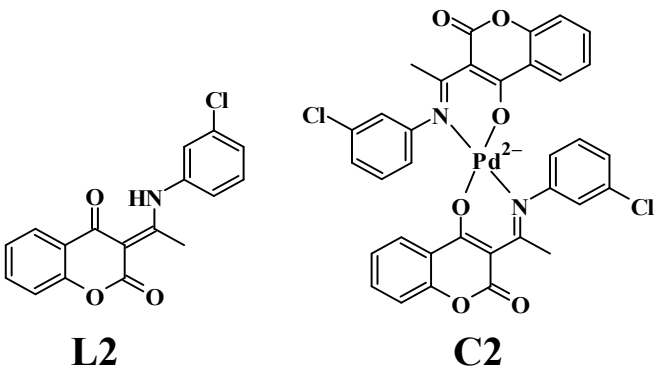


Figure 9: Structure of Ligand and Metal complex

Akshata S. Menasinakai *et, al.* synthesized copper metal complexes and characterized them by the spectral analyses. Later the complexes were screened against breast cancer cell line (MDA MB 231) with standard Paclitaxel using MTT assay method. All compounds underwent *in-vitro* anticancer activity whose reports concluded that compounds of copper complex of 7-(2,5-dimethoxybenazylideneamino)-4-methyl-2H-chromen-2-one, copper complex of 7 - (4 - dimethylaminobenazylideneamino)-4-methyl-2H-chromen-2-one, 7-(2,3-dichlorobenazylideneamino)-4-methyl-2H-chromen-2-one and 7-(3-hydroxybenazylideneamino)-4- methyl-2H-chromen-2-one showed good activity compared to standard.

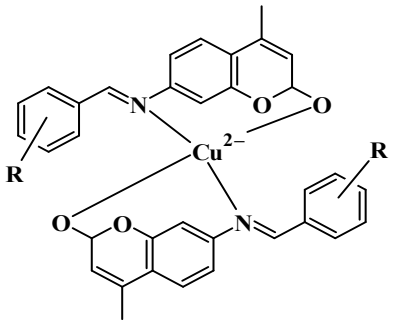


Figure 10: Structure of copper metal complex[30].

Hayet. Belbah *et, al.* explored the formation and stability of a novel synthesized coordination complex involving nickel as the transition metal and daphnetin or 7,8-dihydroxycoumarin (DAPH) as the ligand, a theoretical investigation is conducted using the Gaussian 09 so| |ware and the TD-DFT calculation method.The complex has a tetradentate square planar structure with four dative bonds, specifically at the Ni–C]O locations, produced between the nickel ion and the DAPH ligand. This result was confirmed by the vibrational frequencies of the NI-DAPH complex, which showed a significant increase in the wavenumber linked to the benzopyrone ring's carbonyl.

The identification of the electrophilic site at the nickel ion and the nucleophilic site at the oxygen atoms of the carbonyl groups was made easier by analysing the energies of the HOMO and LUMO frontier orbitals, atomic charges, and molecular electrostatic potentials of the Ni–DAPH complex. Among the four suggested configurations of the Ni–DAPH complex, theoretical research was essential in determining which was the most stable.

In conclusion, compared to free daphnetin, the complex formed between nickel and daphnetin shows a significantly stronger antioxidant capability. The coordination of the metal ion, which both stabilises reactive intermediates and promotes redox reactions—both essential for efficient free radical scavenging—is responsible for this increased activity.

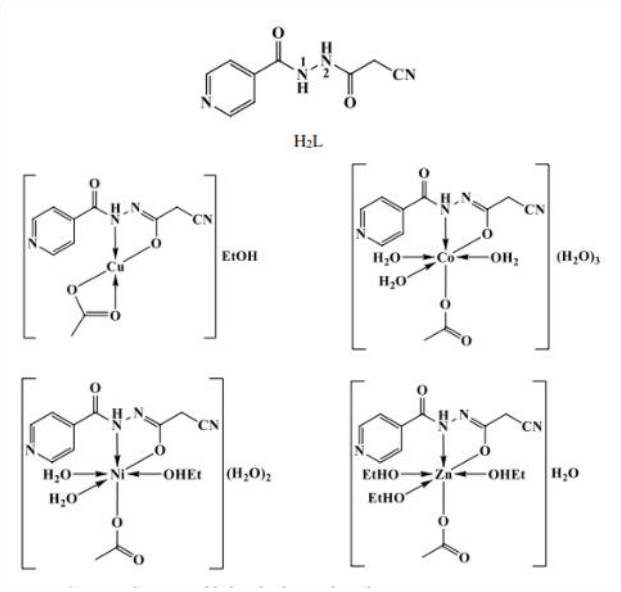
The antioxidant qualities of the investigated complexes were assessed using molecular docking methods, and the findings suggested that these complexes would be useful inhibitors of the HEME-proteins cytochrome C peroxidase (CCP) and ascorbate peroxidase (APX). The [Ni–DAPH] complex's promising antioxidant activity creates new opportunities for pharmacological applications, especially in the creation of novel antioxidant drugs for therapeutic use. The Ni-DAPH despite some infractions of Lipinski's criteria, the complex shows superior ADMET characteristics compared to the DAPH molecule alone. As a result, it is a viable option for biological applications in the future applications. Consequently, it is a good option for biological applications in the future[31].

Mirela Jevti´ *et, al.* Synthesized the palladium(II) complex (CC)by performing the reaction between (E)-3-(1-((4-hydroxy-3-methoxyphenyl)amino)ethylidene)-2,4-dioxochroman-7-yl-acetate (CL) and potassium tetrachloropalladate (II) produced, which was both experimentally and theoretically characterised using IR and NMR spectra. Human cervical carcinoma HeLa, ovarian cancer A2780, hormone-dependent breast cancer MCF7, and colorectal cancer HCT116 lines were used to test the cytotoxicity of CL and CC. Spectrofluorimetric analysis was used to track how the substances under investigation interacted with HSA. Molecular docking simulations were used to evaluate the binding mechanism in the active pocket. The optimised structure matched the experimental one, as demonstrated by a low mean absolute error between theoretical and practical data. A reasonable selectivity index for cancerous cells was demonstrated by both substances. The evaluated drugs' affinity for binding to the HSA was determined. In comparison to CL, the molecular docking revealed a significantly smaller change in the Gibbs free energy of binding for CC. While molecular docking showed that CC had the strongest activity against alpha-fetoprotein, the acquired data showed that CL and CC have good binding characteristics to HSA and significant effects on a number of cancer cell lines[32].

Hamed Ghanbar *et, al.* synthesized two novel copper (Cu) complexes, [Cu(L)(L′)(H2O)2] (1) and [Cu(L)(Im)H2O] (2), where L=pyridine-2,6-dicarboxylic acid, L′ = 2,4-diamino-6-hydroxypyrimidine, and Im= imidazole.These were investigated for their sonochemical synthesis, spectroscopic analysis, and biological activity. Analytical methods such as single-crystal X-ray structure determination, FTIR, PXRD, TGA and DTA, SEM, TEM, and EDS were used to

characterise the complexes' structures. There was a six-coordinated Cu^{2+} ion in compound (1) and a five-coordinated Cu^{2+} ion in complex (2). The crystal structures showed triclinic (P-1) and monoclinic (C2/c) space groups, respectively. Hydrogen bonding and π–π stacking interactions, which were crucial in stabilising the structures and forming the distinctive supramolecular architecture, were the primary determinants of the zero-dimensional (0D) supramolecular networks displayed in both complexes. Significant antioxidant activity was shown by both complexes, indicating their potential to neutralise free radicals and minimise ailments associated with oxidative stress. According to the ASTM F756-00 standard, haemolysis percentages were less than 2%, suggesting non-hemolytic behaviour. MCF-7 and fibroblast cell lines showed minimal cytotoxicity. They show little antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli*. These results imply that the obtained Cu^{2+} complexes have an enormous amount of potential for use in drug delivery and cancer therapy. The development of multifunctional materials for a variety of scientific and medical uses, as well as the progress of supramolecular chemistry, are both facilitated by this research[33].

Mohamed H Abdel-Rhman *et, al*. synthesized the novel ligand (H_2L), N'-(2-cyanoacetyl)isonicotinohydrazide,by reacting the isonicotinic hydrazide with 1-cyanoacetyl-3,5-dimethylpyrazole.From its spectral data, the free ligand's keto-form has been elicited. The ligand produced 1:1 (M: L) metal complexes with the acetate salts of Cu(II), Co(II), Ni(II), and Zn(II), according to elemental studies and mass spectra. Spectral studies of the complexes showed that the ligand behaved as a mononegative bidentate through the deprotonated enolized acetyl oxygen and hydrazonyl N1.Furthermore, the ligand had lower LUMO and higher HOMO energies than metal complexes, signifying an electron-donating nature, according to DFT quantum chemical simulations. Additionally, the ligand was more effective than doxorubicin against the HepG2 and HCT-116 cell lines in *in-vitro* anticancer studies, however the metal complexes were less effective.



Structures of ligands and its metal complexes[34]

Ahmed K. Hijazi *et, al.* synthesized A set of metal(II) complexes of the general formula [MPy6][B(C6F5)4]2 where (Py = pyridine, M = Mn (1), Fe (2), Co (3), Ni (4), Cu (5), Zn (6)) by direct reaction of metal halides and pyridine in the presence of Ag[B(C6F5)4].Various kinds of methods, consisting of elemental analysis (EA), electron paramagnetic resonance (EPR) spectroscopy, thermogravimetric analysis (TGA), ultraviolet–visible (UV–Vis) spectroscopy, 11B-NMR, 1H-NMR, and FT-IR spectroscopy, were used to characterise the complexes in order to ensure their purity. For each synthesized complex, the antimicrobial and antifungal activities against various bacteria and fungi were examined. When compared to the reference antibiotic, oxytetracycline (positive control), the synthesized complexes showed varying effectiveness and broad-spectrum antibacterial activity. With a minimum inhibitory concentration (MIC) of 4 µg/mL, [ZnPy6][B(C6F5)4]2 (complex 6) demonstrated remarkable antibacterial activity against *Streptococcus pyogenes*, surpassing the control (MIC = 8 µg/mL). With MIC values of 8 µg/mL, Complexes 1, 2, and 4 i.e. [MnPy6][B(C6F5)4]2 , [FePy6][B(C6F5)4]2 and [NiPy6][B(C6F5)4]2 respectively shown excellent action against *Klebsiella pneumoniae, Streptococcus pyogenes,* and *Shigella flexneri*. On the other hand, complexes 3, 5, and 6 i.e. [CoPy6][B(C6F5)4]2 , [CuPy6][B(C6F5)4]2 , and [ZnPy6][B(C6F5)4]2 respectively showed the least activity (MIC = 512 µg/mL) against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, respectively. With MIC values of 8 µg/mL, which are equal to those of the positive control, fluconazole, complexes 5 and 6 showed the strongest antifungal activity against *Candida albicans*. Each complex had an overall octahedral coordination geometry, according to density functional theory (DFT) studies; complexes 3, 4, and 5 showed tetragonal distortions.

All the metal complexes are [MnPy6][B(C6F5)4]2 (1), [FePy6][B(C6F5)4]2 (2), [CoPy6][B(C6F5)4]2 (3), [NiPy6][B(C6F5)4]2 (4), [CuPy6][B(C6F5)4]2 (5), and [ZnPy6][B(C6F5)4]2 (6)[35].

Tahmeena Khan *et, al*. studied about the mixed ligand–metal complexes of $CuSO_4 \cdot 5H_2O$ and $ZnSO_4 \cdot 7H_2O$ with salicylaldehyde thiosemicarbazone (2-hydroxybenzaldehyde thiosemicarbazone) as primary ligand and imidazole (im), pyridine (py) and triphenylphosphine (PPh3) as secondary ligands through a general preparatory route. FTIR, UV, 1H-NMR, and molar conductance methods were used to characterize the ligand and complexes. Molinspiration, SwissADME, and admetSAR software were used in computational research to determine the physicochemical parameters, bioactivity scores, absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters. PyRx automated docking program was used to perform molecular docking with Mproof SARS-CoV-2 (PDB i.d.6LU7), Aspartate Kinase (PDB i.d.5YEI), and Transforming Growth Factor β (PDB i.d. 3KFD). The Agar well method was used to test the antibacterial activity. Nearly all of the complexes had clogP values smaller than 5, indicating their bioavailability, according to computational results. The complexes' bioactivity values ranged from moderate to good. Imidazole was the secondary ligand in the mixed ligand complexes that showed comparatively high FCsp3, suggesting that they could be lead candidates. Significant binding affinities against the individuals selected proteins were shown by $[Zn(C_8H_9N_3OS)(PPh_3)_2(SO_4)]$

and [$Cu(C_8H_9N_3OS)(im)_2(SO_4)$]. Additionally, the ligated [$Cu(C_8H_9N_3OS)(im)_2(SO_4)$] and aspartate kinase molecular modelling results demonstrated compact folding, few deviations, and notable stability. The frontier molecular orbitals (FMOs) gap provided additional evidence of the ligand's stability. Molecular stability was demonstrated by the energy gap (− 0.423 eV). With zones of inhibition of 11, 11, and 10 mm, respectively, the ligand was effective against L. monocytogenes, S. aureus, and E. coli. The minimum inhibitory concentrations (MIC) of [$Cu(C_8H_9N_3OS)(im)_2(SO_4)$] against the chosen bacterial strains ranged from 32 to 128 µg/mL[36].

Abazari, A., *et, al.* synthesized a series of bisimine derivatives (3a–j) through condensation with structurally diverse amines, achieving yields of 68–95%. Their distinct structures were validated by spectroscopic characterisation like NMR, IR, and MS where 3,3'-((1E,1'E)-((6-amino-1,3,5-triazine-2,4-diyl)bis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-hydroxy-2 H-chromen-2-one) [3j] stood out as a promising candidate with anticancer activity similar to doxorubicin but better selectivity against MCF-7 and A549 cell lines. Compound 3,3'-((1E,1'E)-hydrazine-1,2-diylidenebis(ethan-1-yl-1-ylidene))bis(4-hydroxy-2 H-chromene-2-one) [3a] showed the strongest antibacterial activity among the investigated derivatives, with the lowest minimum inhibitory concentration (MIC) values against Gram-positive pathogens. Notably, 3,3'-((2E,12E)-3,6,9,12-tetraazatetradeca-2,12-diene-2,13-diyl)bis(4-hydroxy-2 H-chromen-2-one) [3c] exceeded ascorbic acid in radical scavenging (96.7% DPPH inhibition), and 1,3-bis((E)-1-(4-hydroxy-2-oxo-2 H-chromen-3-yl)ethylidene)thiourea [3f] (a thiourea analogue) showed broad-spectrum antifungal effectiveness (MICs: 1.95–31.25 µg/mL). Strong interactions between lead compounds 3,3'-((1E,1'E)-((azanediylbis(ethane-2,1-diyl))bis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-hydroxy-2 H-chromene-2-one) [3b], 3,3'-((2E,12E)-3,6,9,12-tetraazatetradeca-2,12-diene-2,13-diyl)bis(4-hydroxy-2 H-chromen-2-one) [3c] and 3,3'-((1E,1'E)-((6-amino-1,3,5-triazine-2,4-diyl)bis(azanylylidene))bis(ethan-1-yl-1-ylidene))bis(4-hydroxy-2 H-chromen-2-one) [3j] (3b, 3c, and 3j) and important therapeutic targets (FGFR1, cIAP1-BIR3) were found using molecular docking, indicating a dual inhibitory mechanism. These results highlight coumarin bisimines' potential as adaptable platforms for treating diseases linked to oxidative stress and antibiotic resistance[37].

5. Conclusion:

This review gives a broad overview of the varied pharmacological uses of metal complexes and of coumarin compounds individually as well as several metal complexes fused with the coumarin compounds. The significant increase in the number of papers and studies addressing the potential applications of coumarin-based metal complexes in therapy and medicine in recent years is an unexpected manifestation of their impact on the scientific world. It is a collection of all the uses and recent advancements in the research and use of coumarin-metal complexes as anticancer, antimicrobial, antifungal, anti-inflammatory, antioxidants as well as anti-TB agents.

However, with the proliferation of multi-drug resistant microbial diseases, another major area of research in which coumarin-based metal complexes are assessed is the development of novel

antimicrobial drugs. In medicinal chemistry, metal complexes of Schiff bases with coumarin pharmacophores have been significant. Over the past three decades, a number of metal complexes of coumarin derivatives have been synthesized, and the majority of them show notable pharmacological characteristics.

Metal complexes with coumarin-based ligands have been thoroughly investigated for their cytotoxic effects in light of the urgent need for new therapeutic agents to treat malignancies. However, due to the increase of multi-drug resistance microbial infections, another major area of research that considers coumarin-based metal complexes is the development of novel antimicrobial drugs. The valuable and promising compounds that contain coumarin-metal complexes may also be used as the basis for the synthesis of anti-neurogenerative drugs. We anticipate that this evaluation will be beneficial for the continued development of metal complexes based on coumarin in the field of medication development.

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