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A review on Antimicrobial Assessment of Coumarin-Based Compounds

Anand Kumar Yadav[1] (Ph.D.)
Krishna Bahadur B.K. [2]

Abstract

Coumarins are a frequent component of many medicinal plants like tonka bean, bitter orange, cinnamon, clover, bilberry, peaches, and plums and are members of the benzopyrone family. Various pharmacological activities have been shown by natural and synthetic coumarins. The significant pharmacological variety of coumarins is being used for the treatment of infectious diseases, cardiovascular disorders, inflammation, neurodegenerative disorders, and cancer. These advantages for human health are due to the substantial structural variation of coumarins. Their antibacterial properties were initially discovered in 1945 and found that they could inhibit the growth of different bacterial strains. Bioavailability is the absorption of a drug from the digestive system after the oral dose is administered. Coumarins prevent the growth or kill the microbes through various modes of action. Every year, invasive infections caused by human fungal pathogens claim the lives of more than a million people, making them covert killers. To effectively prevent or cure life-threatening fungal illnesses, however, research in this area has not advanced quickly enough. Natural and synthetic coumarins show effective inhibition of gram-positive and Gram-negative bacterial strains, fungi, and viruses. This special issue's goals of study are to summarize the current research on coumarin derivatives, their antibacterial and antifungal properties, and to offer suggestions for further study in the area. The current study provides an overview of coumarins' biological capabilities, availability, and origin while also taking into account the key mechanisms underlying their therapeutic effects. Natural coumarins such as umbelliferone, esculetin have good antimicrobial activities. But most of the synthetic coumarin derivatives exhibited excellent antimicrobial properties.

Keywords: Coumarins, Antibacterial potency, Antifungal potency, Antimicrobial resistance, Bioavailability,

Introduction

Currently, microbial (bacterial, fungal, viral) infections are the major cause of death globally and a common illness found at community health centers and hospitals (Sayed et al., 2023). Coumarins are members of the benzopyrone group, frequently present in a variety of therapeutic plants, but they are particularly abundant in Dipteryx odorata (Tonka bean). Numerous pharmacological activities,

1. Asst. Professor, Department of Chemistry, Patan Multiple Campus, Tribhuvan University
Correspondence: aky4chem@gmail.com
2. Asst. Professor, Department of Chemistry, Patan Multiple Campus, Tribhuvan University
Email: krishnamahar300@gmail.com

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such as antibacterial, antifungal, antiviral, anticancer, anticoagulant, antimalarial, anti-inflammatory, Alzheimer's disease inhibition, have been demonstrated by natural as well as synthetic coumarins (Sharifi-Rad et al., 2021). Coumarins are secondary metabolites found in a wide variety of plant species, and are most prevalent in the Apiaceae, Rutaceae, Asteraceae, and Fabaceae families (Yadav et al., 2025).

They are intriguing compounds for various study domains because of their conjugated double-ring structure (Carneiro et al., 2021). The ubiquitous coumarin scaffold (2*H*-1-benzopyran-2-one) and its derivatives have an intriguing range of pharmacological characteristics (Zhang & Xu, 2019). Some coumarin derivatives, after being granted regulatory approval by the Food and Drug Administration, are in medical trial. These include esculin, warfarin, dicoumarol acenocoumarol, trioxsalen and phenprocoumon (Citarella et al., 2024).

The strong antioxidant activity of 6,7-Dihydroxycoumarin, which is a naturally occurring and synthetic coumarin derivative, makes it of great interest for human use (Marques et al., 2015). The extensive range of biological activities and applications of coumarins can be attributed to their capacity to form noncovalent interactions with various enzymes and receptors in living beings (Yadav et al., 2025).

The discovery of penicillin in the 20th century led to the belief that bacterial illnesses could be readily managed. Nonetheless, doctors have had to deal with infectious diseases that are constantly developing and reappearing, which have a major impact on public health. Humans can contract zoonotic agents by direct touch, scratches, bites, arthropod vectors, eating contaminated food, or coming into contact with corpses or soil or water contaminated with fecal matter. The diseases caused by different bacteria are like diarrhea, pneumonia, lung infection, gastric ulcers, and miscarriages (Vouga and Greub, 2016).

Every year, over a million people die from fungal-associated infections, most notably brought on by *Cryptococcus species, Aspergillus,* and *Candida*. In fact, even with antifungal therapies, these neglected infections are generally very difficult to treat, and the associated mortality is still very high (Janbon et al., 2019).

A common form of small-molecule peptide found in nature, antimicrobial peptides are a part of nearly every living organism's innate immunity. They are crucial in thwarting the invasion of alien microbes. Antimicrobial peptides exhibit a variety of antibacterial properties against viruses, bacteria, fungi, and other microbes. They do not readily cause the emergence of drug resistance and are effective against strains that are resistant to conventional antibiotics (Li et al., 2022).

Antimicrobial resistance is the capacity of microrganisms to adapt and thrive after medicines are administered. Multidrug resistance is developed and become more prevalent owing to the over use of antibiotics, cause higher mortality. The mechanism of antimicrobial drugs are inhibition of metabolic processes, inhibition of nucleic acid synthesis, and inhibition of protein synthesis. There is a prime importance of developing new drugs which can work as antibacterial agents but with mechanism different from the present antimicrobial drugs (Sayed et al., 2023).

Objectives of this review

The present study seeks to compile the antibacterial and antifungal potencies of natural and synthetic coumarins. To evaluate the mode of action of various antimicrobial compounds. To compare

the antimicrobial activities of coumarins with the reference drugs such as ampicillin, ciprofloxacin. This article will be beneficial to the researchers of same field.

Conceptual framework

It is hypothesized that both natural and synthetic coumarins are versatile pharmacophore having broad spectrum antimicrobial efficacies. Their potential against the resistant microbial strains could be enhanced by selective structural modifications.

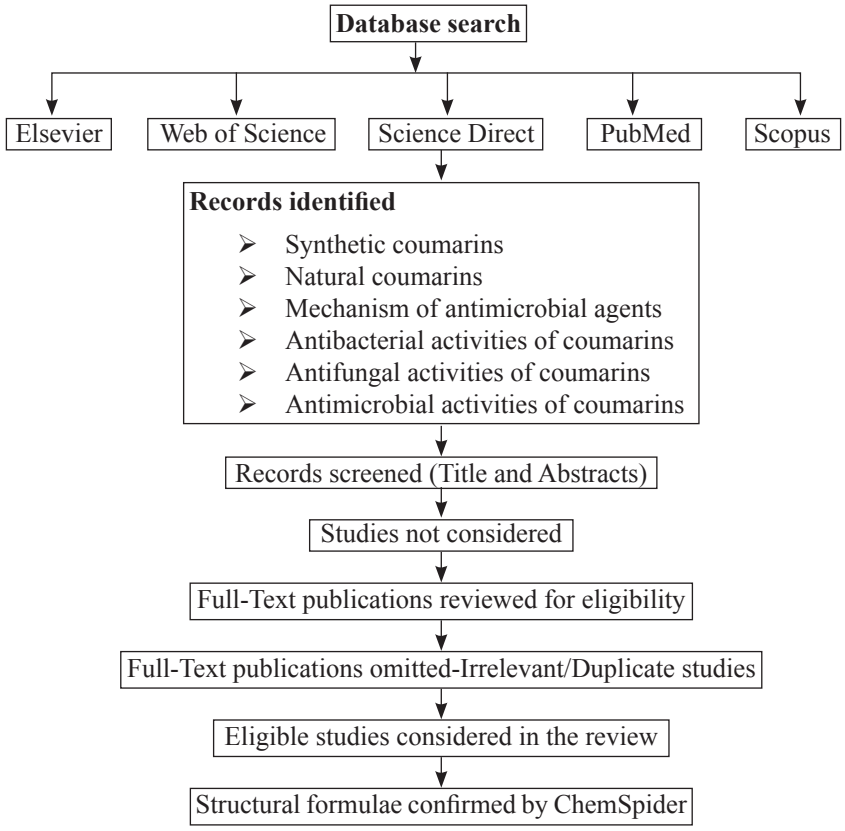
Research questions

Which coumarins have showed significant antimicrobial activities?

Which type of microbes are more susceptible to the coumarins?

What are the limitations and future perspectives of coumarin derivatives as antimicrobial agents?

Review methodology



Results and Discussion

Mode of action of antimicrobial agents

Antimicrobial agents destroy the cellular membrane of microbes and destabilize it. Cellular contents are leaked from the cells and eventually, cells die. Antimicrobial drugs that influence bacterial metabolism or interrupt essential processes, including protein synthesis and DNA

replication. Interference can cause cellular malfunction and ultimately bacterial death. Amino and other reactive functional groups may help denaturation of bacterial proteins. Proteins' structural integrity may be compromised by interactions with amino acid residues, which would reduce their functionality. Bacterial mortality is caused by the disruption of essential cellular functions due to protein denaturation (Betti et al., 2024).

Certain antioxidant chemicals may have an antibacterial impact by causing the intracellular production of reactive oxygen species (ROS), in bacteria. ROS, including H_2O_2 and superoxide anions (O_2*), can cause oxidative deterioration to biological components such as proteins, lipids, and DNA. This oxidative stress affects bacterial defense mechanisms, resulting in cellular damage and, eventually, death (Betti et al., 2024).

By adhering to the outer surface of the cell wall, metal ion of a complex obstructs respiration, prevents the production of proteins. So, the growth of the microorganisms is hindered, ultimately leading to their death (Patil et al., 2015).

Antibacterial and antifungal potency of synthetic coumarin derivatives

Pyrazoles, pyridines, and thiazoles containing a coumarin moiety were synthesized as new antimicrobial agents and the synthetic chemical molecules were tested for their antimicrobial efficacy. Compound 1 (**Fig. 1a**) was determined to be the most effective against *Bacillus pumilis* having a minimum inhibitory concentration of 7.69 µmol/mL. Compound 2 (**Fig. 1b)** showed antibacterial activity against *Enterobacter cloacae*, comparable to that of the reference drug Ciprofloxacin (Sayed et al., 2023).

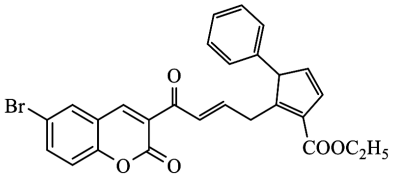


Fig 1: Ethyl (E)-2-(4-(6-bromo-2-oxo-2H-chromen-3-yl)-4-oxobut-2-en-1-yl)-3-phenylcyclopenta-1,4-diene-1-carboxylate

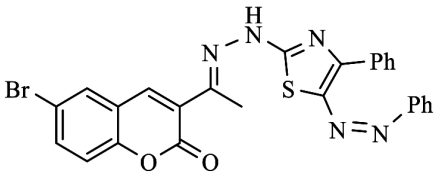


Fig 1b: 6-Bromo-3-((E)-1-(2-(4-phenyl-5-((Z)-phenyldiazenyl) thiazol-2-yl)hydrazineylidene) ethyl)-2H-chromen-2-one

Some new 4-hydroxycoumarin derivatives were synthesized and they were examined for their antimicrobial activities. After 48 hours, compound 3 (**Fig. 2a**) showed the good antibacterial efficacy on the tested bacterial cultures. On investigation using a tested method, compound 4 (**Fig. 2b)** showed a stronger ability to inhibit the growth of the fungus *Candida albicans*, with minimum inhibitory concentration of 0.13 µg/mL for both compounds (Mladenovic et al., 2009).

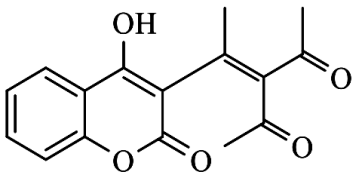


Fig 2a: 3-(1-(4-hydroxy-2-oxo-2H-chromen-3-yl) ethylidene)pentane-2,4-dione

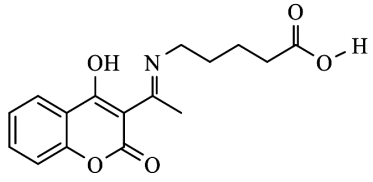


Fig 2b: (E)-5-((1-(4-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)amino)pentanoic acid

The antimicrobial activity of novel synthetic coumarin thiosemicarbazones were evaluated using the agar dilution method against fungal strains (*Aspergillus niger, Aspergillus clavatus, and Candida albicans*), gram-negative bacterial strains (*P. aeruginosa, E. coli*) as well as gram-positive bacterial strains (*S. aureus, S. pyogenes*). The tested compounds exhibited excellent potency. The compound 5 (**Fig. 3**) exhibited better activity against E. coli at MIC of 62.5 µg/mL (Vekariya et al., 2017).

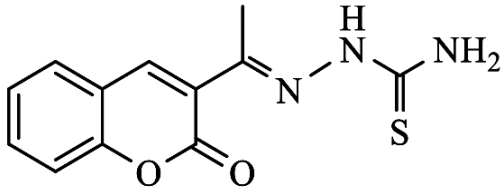


Fig 3: (E)-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)hydrazine-1-carbothioamide

New Schiff bases 6 and 7 (**Fig. 4a, 4b**) with coumarin moiety and their Cu(II), Co(II), and Ni(II) metal complexes were chemically synthesized and assessed for their antifungal, antibacterial, and DNA cleavage activity using *in vitro* assays. Their antimicrobial potency was found to be excellent to moderate against the tested microbes. Zone of inhibition against fungi (*A. niger, Candida, Rhizopus*) and against bacteria (*E. coli, Proteus, S. aureus, P. auregenosa, Salmonella, Klebsiella*) was found as 5-14 mm (Patil et al., 2015).

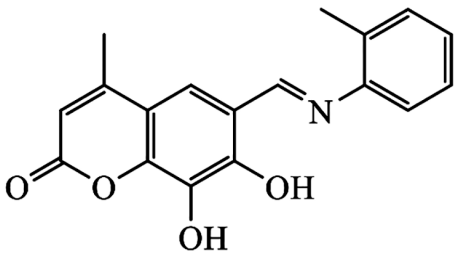


Fig 4a: (E)-7,8-dihydroxy-4-methyl-6-((o-tolylimino)methyl)-2H-chromen-2-one

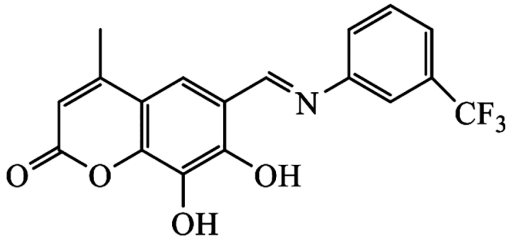


Fig 4b: (E)-7,8-dihydroxy-4-methyl-6-(((3-(trifluoromethyl)phenyl)imino)methyl)-2H-chromen-2-one

The newly synthesized derivatives 8-12 (**Fig. 5a-5e**) of 4-hydroxycoumarin were characterized by spectroscopic and analytical techniques. Antimicrobial investigation of these compounds were carried out in dose dependent manner. They showed good potency against tested Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*E. coli, P. vulgaris, K. pneumoniae, P. aeruginose*) and fungi (*A. niger, C. albicans*). The zone of inhibition (ZOI) against bacteria was found as 6-27 mm. The percentage of inhibition against fungi was found 6-26%. DPPH radical scavenging assay was conducted to examine the antioxidant properties, and it was determined 27-91%. The compounds with azomethene group (5c, 5d and 5e) exhibited better antimicrobial activities than coumarin alone. It may be due to azomethene group helps to interact and disrupt bacterial cell membrane which results in cell death (Betti et al., 2024).

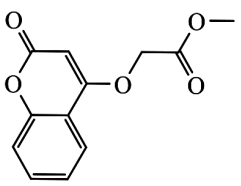


Fig 5a: Methyl 2-((2-oxo-2H-chromen-4-yl)oxy)acetate

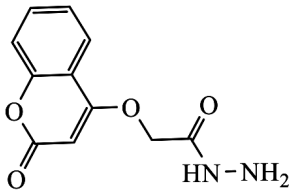


Fig 5b: 2-((2-oxo-2H-chromen-4-yl)oxy)acetohydrazide

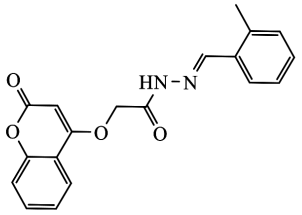


Fig 5c: (E)-N'-(2-methylbenzylidene)-2-((2-oxo-2H-chromen-4-yl)oxy) acetohydrazide

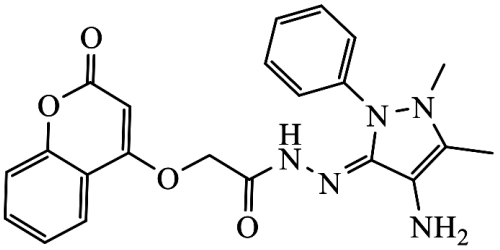


Fig 5d: (Z)-N'-(4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-ylidene)-2-((2-oxo-2H-chromen-4-yl)oxy)acetohydrazide

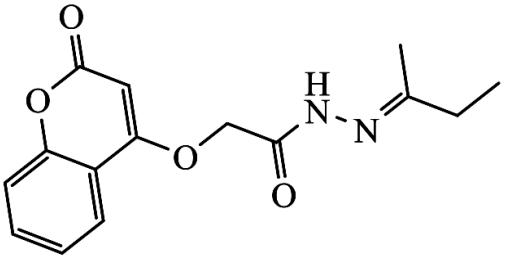


Fig 5e: (E)-N'-(butan-2-ylidene)-2-((2-oxo-2H-chromen-4-yl)oxy)acetohydrazide

The formation of 4-hydroxycoumarin derivatives 13-18 (**Fig. 6a-6f**) was confirmed by spectroscopic and analytical techniques. The newly formed compounds were examined for their antimicrobial potency targeting *Candida albicans*, *Escherichia coli, Bacillus subtilis, Staphylococcus aureus and Pseudomonas aeruginosa* (Naik et al., 2019). The compounds showed significant antifungal and antibacterial efficacy against the tested microorganisms, but less than that of the reference drug ampicillin and Flucanazole (Naik et al., 2019).

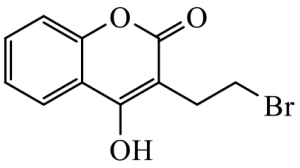


Fig 6a: 3-(2-bromoethyl)-4-hydroxy-2H-chromen-2-one

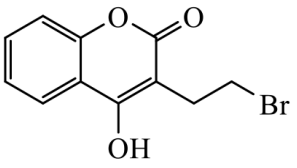


Fig 6b: 3-(4-bromobutyl)-4-hydroxy-2H-chromen-2-one

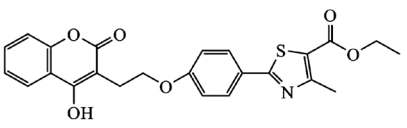


Fig 6c: Ethyl 2-(4-(2-(4-hydroxy-2-oxo-2H-chromen-3-yl)ethoxy)phenyl)-4-methylthiazole-5-carboxylate

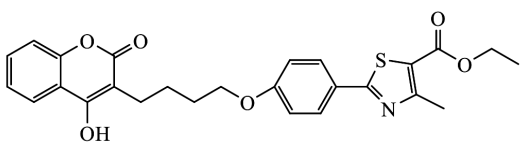


Fig 6d: Ethyl 2-(4-(4-(4-hydroxy-2-oxo-2H-chromen-3-yl)butoxy)phenyl)-4-methylthiazole-5-carboxylate

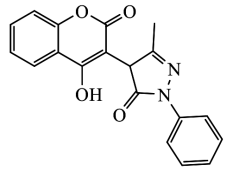


Fig 6e: 4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one

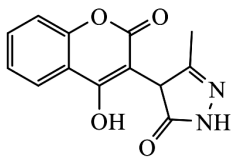


Fig 6f: 4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one

Antibacterial and antifungal potency of natural coumarins

It has been found that coumarins can fight off both Gram-negative and Gram-positive bacteria. Long-chain coumarin derivatives, such as ostruthin and ammoresinol, demonstrated greater effectiveness against *Staphylococcus aureus, Micrococcus luteus, Bacillus megaterium*, and *Micrococcus lysodeikticus*. 7-Hydroxycoumarin (umbelliferone) isolated from the grassy leaves of Pilosellas plant. It is used against brucellosis caused by gram-negative bacteria, *coccobacilli*. Esculetin (6,7-dihydroxycoumarin has showed antifungal and bacteriostatic activities. 3-Phenylcoumarin and dafnoretin (a biscoumarin) are used as anti-HIV and anti-hepatitis B virus. Phytoalexins can be extracted from Eupatorium ayapana (Asteraceae family) and are used to limit or eliminate pathogens such as viruses, insects, and bacteria. Antogenol, isolated from Aegle marmefos, imperatorin (furanocoumarin), isolated from Angelica dahurica, demonstrated stronger efficacy against *Enterococcus faecium* and *Shigella dysenteriae* bacteria, respectively. A coumarin derivative, oatrithin, isolated from Angelica pubescens, furanocoumarins, imperatonin and psoralen have been found to work potently against the fungi such as *Sclerotinia sclerotiorum*, *Rhizoctonia solani*, *Phytophthora capsici, Fusarium graminearum*, and *Botrytis cinerea* (Sharifi-Rad et al., 2021).

The broth microdilution assay was employed to examine the antimicrobial effectiveness of some selected natural and synthetic coumarins. The test was performed against methicillin-resistant *Staphylococcus aureus* (MRSA), a hospital isolate, and clinically relevant gram-negative and gram-positive bacteria. Compound 19 (**Fig. 7**) exhibited good activity with a low MIC value (125 and 62.5 µg/mL), particularly against two strains (Irish-1 MARSA and Irish-2 MARSA) of the *Staphylococcus aureus* (Smyth et al., 2009).

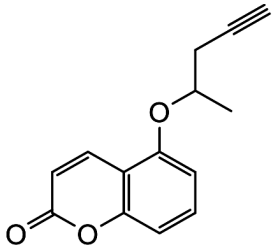


Fig 7: 5-(pent-4-yn-2-yloxy)-2H-chromen-2-one

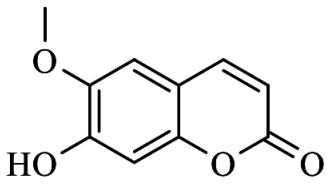


Fig 8: 7-hydroxy-6-methoxy-2H-chromen-2-one

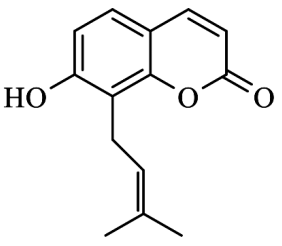


Fig 9: 7-hydroxy-8-(3-methylbut-2-en-1-yl)-2H-chromen-2-one

A naturally occurring coumarin called scopoletin (7-hydroxy-6-methoxycoumarin, **Fig. 8**) has demonstrated antifungal capabilities against plant yeast infections. However, it is still unknown whether this coumarin has antifungal efficacy against clinically significant fungal species like *C. tropicalis*. One of the most significant biofilm-forming fungus species that is linked to invasive mucosal candidiasis globally is *Candida tropicalis*. Scopoletin was isolated from Mitracarpus frigidus, a plant species (Rubiaceae family).The antifungal potency and mechanistic pathway of scopoletin against a multidrug-resistant *Candida tropicalis* (ATCC28707) was investigated, both planktonic and biofilm forms. The determination of MIC values, time-kill kinetics, and cell density were used to assess fungal planktonic growth inhibition. The efflux pumps, sorbitol, ergosterol, nucleotide leakage bioassays were used to examine the mechanisms of action. The positive control was fluconazole. MIC value for scopoletin was found as 50 µg/L, whereas 250 µg/L for fluconazole (Lemos et al., 2020).

Broth microdilution assay was used to evaluate antifungal property of 40 coumarins (35 natural occurring, two with little modification and 3 commercially available) against the selected fungal strains, such as *Aspergillus fumigatus* (ATCC 16913), *Fusarium solani* (ATCC 36031), and *Candida albicans* (ATCC 14053). Out of the tested compounds, osthenol (**Fig. 9**) having long alkenyl group exhibited most potent antifungal activity against *Fusarium solani* and *Aspergillus fumigatus* with MIC values 125 µg/mL and 250 µg/mL, respectively (Montagner et al., 2008).

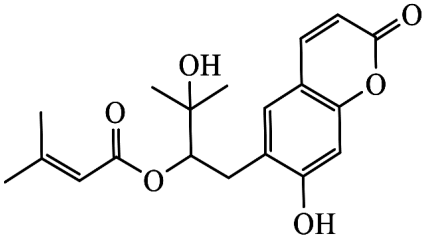


Fig 10a: 3-hydroxy-1-(7-hydroxy-2-oxo-2H-chromen-6-yl)-3-methylbutan-2-yl 3-methylbut-2-enoate

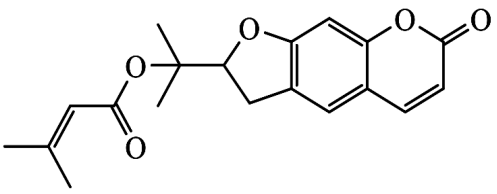


Fig 10b: 2-(7-oxo-2,3-dihydro-7H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-methylbut-2-enoate

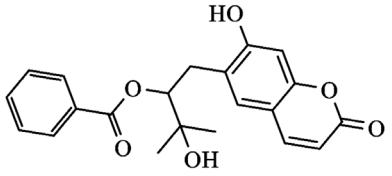


Fig 10c: 3-hydroxy-1-(7-hydroxy-2-oxo-2H-chromen-6-yl)-3-methylbutan-2-yl benzoate

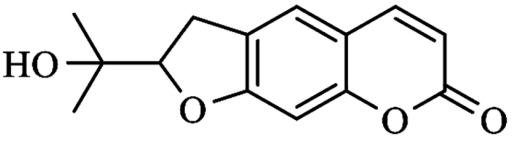


Fig 10d: 2-(2-hydroxypropan-2-yl)-2,3-dihydro-7H-furo[3,2-g]chromen-7-one

Some coumarins (**Fig. 10a -10d**) were extracted and isolated from the roots and aerial parts of Ferulago species using different solvent extract like methanol, ethylacetate, dichloromethane and butan-2-ol. Different analytical and spectroscopic techniques were implemented to characterize the isolated compounds. Their antimicrobial activities were examined against gram-positive and gram-negative bacteria and also against a yeast C. albicans (Karakaya et al., 2019). The growth inhibition of E. coli, S. aureus, B. subtilis, and P. aeruginosa was found at MIC 62.5 µg/mL, whereas the inhibition in growth of C. albicans was observed at 31.25 µg/mL. Among the tested compounds, the compound isolated from F. pachyloba showed the best efficacy (Karakaya et al., 2019).

Conclusion

Coumarin derivatives exhibited good to excellent antibacterial and antifungal potencies. Some coumarin compounds are in clinical trials (Warfarin for the treatment of thromboembolic disorders, Geiparvarin for the treatment of blood clots, COTI-2 for the treatment of solid tumors, clorobiocin and novobiocin agianst bacterial infection) whereas some showed antimicrobial properties better than that of the reference drug (Ciprofloxacin) used during the investigation. The structure-activity relationship shows that substitutions like long-chain alkyl, heterocyclic groups, halogens, hydroxides, and alkoxy enhance the antimicrobial efficacy. It has been found that the coumarin derivatives act as antimicrobial agents by inhibition of enzymes, disruption of biofilm, membrane integrity, and alteration of nucleic acid synthesis. Some of the challenges are, limited *in vivo* test, metabolic instability, poor selectivity, poor solubility, and toxicity. The synthetic and natural coumarins are significant scaffolds in search of new antimicrobial agents. The structural modification will increase the antimicrobial activities of coumarin-based compounds. The coumarin derivatives can be synthesized and proven to be better antimicrobial agents with more effective and fewer adverse effects.

Conflicts of Interest

The authors declare no conflict of interest.

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