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REVIEW ON: "COUMARINS: A Unique Scaffold with Versatile Biological Behaviour"

[1*]Vaishnavi U. Kale, [1]Vaishnavi S. Balinge, [2]Dr. Anjali M. Wankhade, [3]Nikhil S. Wagh,

[1]Students, Vidyabharti college of Pharmacy, Naidu marg Camp, Amravati MH INDIA 444-602
[2]Professor, Vidyabharti college of Pharmacy, Naidu marg Camp, Amravati MH INDIA 444-602
[3]Student, Vidyabharti college of Pharmacy, Naidu marg Camp, Amravati MH INDIA 444-602

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Abstract:
The Tonka bean, from which coumarin was first isolated in 1820, is represented by the word "coumarins," which also refers to "coumarou." A natural substance obtained from plants called coumarin (2H-1-benzopyran-2-one) is well known for its pharmacological effects, including antibacterial, antifungal, antiviral, antitubercular, anticancer, antihypertensive characteristics that are anti-adipogenic, anti-hyperglycemic, antioxidant, and neuroprotective. dietary contact with Benzopyrones are significant since they are present in many foods, including seeds, nuts, coffee, and vegetables, wine and tea. Considering the known low toxicity, relative affordability, availability in the diet, and Given that coumarins are present in many herbal treatments, it would be wise to consider their characteristics and other applications. It consists of categorization and pharmacologic factors like absorption.

Keywords: *Coumarin, Tonka Beans, Benzopyrene, Toxicological Studies, Antiadipogenic*

Corresponding author:
Vaishnavi U. Kale,
Students, Vidyabharti college of Pharmacy,
Naidu marg Camp, Amravati MH INDIA 444-602

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INTRODUCTION:

It has been determined that coumarins are secondary metabolites produced by fungus, bacteria, and plants. The term "coumarins" refers to the Tonka bean, also known as "coumarou," from which coumarin was first isolate in 1820. 1,2-benzopyrone, or less, is the name of the archetypal chemical. It has been extensively researched and is frequently found as lactone and -hydroxycinnamic acid. The Coumarins first discovered in tonka beans, and are reported in over 150 different species spread out over almost Among the 30 families, some of the most significant are the Rutaceae, Umbelliferae, and Clusiaceae. Apiaceae, Guttiferae, Caprifoliaceae, Oleaceae, and Nyctaginaceae. numerous, diverse, and New chemical analogues with fantastic drug-use potential have been discovered by organic resources. Combinatorial chemistry and high-throughput screening can be used to design and synthesise novel pharmacological analogues, but this is still a difficult endeavour for researchers. Benzopyrone, which has a benzene ring attached to a pyrone ring, is related to coumarin. The coumarin-belonging benzo-pyrones and the flavonoids-belonging benzo-pyrones are two subclasses of the benzopyrones, respectively [1].

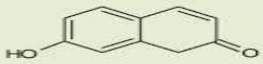
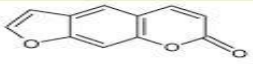
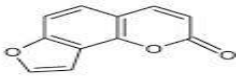
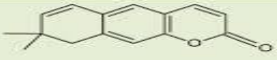
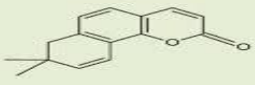
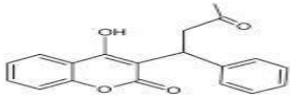
The coumarins are present in all parts of the plant, but they are most abundant in the fruits (Bael fruits (Aeglemarmelos), Tetrapleuratetraptera TAUB (Mimosaceae), bilberry, and cloudberry), seeds (tonka beans), and pods (Calophyllumcerasiferum Vesque and Calophylluminophyllum). Linn, the leaves (Murrayapaniculata), the roots (Ferulagocampestris), and afterwards latex of the tropical rainforest tree and Phellodendronamurense var. wilsoniiGreen tea and other foods like chicory contain the bacterium Calophyllumteysmannii var. inophylloide. Furthermore, they found in significant concentrations in various essential oils, including lavender oil, cinnamon bark oil, and cassia oil[2].

The prevalence of coumarins in different areas of the plant may be influenced by seasonal variations and environmental factors. Thoughts on coumarins' potential uses include waste materials, bacteriostats, fungistats, and even plant growth regulators. by-products of Bourgaud evaluates coumarin. Due to a variety of factors, coumarins come in different kinds in nature. substitutions and conjugations result in permutations; nonetheless, majority of the Studies on coumarin and its major metabolite have been conducted in the areas of pharmacology and biochemistry.7-hydroxycoumarin, a human metabolite Earlier pharmacological research on coumarin has been examined in certain cases, but in other cases, more recent Detailed analyses cover the incidence, chemistry, and biological characteristics of both Natural coumarins, both straightforward and complex[3]

Classification of Coumarins

Natural coumarins are mainly classified into six types based on the chemical structure of the compounds. The physicochemical properties and therapeutic applications of natural coumarinsdepend upon the pattern of substitution [4-7].

TABLE: CLASSIFICATION OF COUMARIN

Classification	Features	Examples
Simple coumarins	Hydroxylated, alkoxylated or alkylated at benzene ring	 7-hydroxycoumarin
Furanocoumarins	Furan ring attached to the benzene ring. Linear or Angular forms are described	 Psoralen  Angelicin
Pyranocoumarins	Pyran ring attached to the benzene ring. Linear or Angular forms are described	 Xanthyletin  Seselin
Phenylcoumarins	Substitution on the pyrone ring, often at position C3 or C4	

PHARMACOKINETICS OF COUMARINS:
ABSORPTION & DISTRIBUTION:
When administered orally to humans, coumarin is quickly absorbed from the digestive tract and transported throughout the body. When dissolved in water, coumarin and 7-hydroxycoumarin are both less soluble (0.22 and 0.031%, respectively). Low bioavailability in vivo. Coumarin and 7-hydroxycoumarin, however, exhibit increased partition values as 21.5 and 10.4%, respectively, in aqueous solution, which is acceptable for the quick absorption of substances It also combines the ability to traverse lipids due to its nonpolar nature. Bilayers easily through passive diffusion The liver's initial metabolism of coumarin involves just reaching the systemic circulation intact between 2% to 6%. Due of coumarin's limited bioavailability along with its brief half-life (1.02 h per oral vs. 0.8 h intravenous), has made the coumarin is a prodrug, with 7 hydroxycoumarin, the principal therapeutic component [8-13].

METABOLISM:
The metabolic fate of coumarins has been the subject of extensive research by pharmacologists. Understanding the potential coumarin-induced harm on metabolism requires this investigation. Initially, cytochrome (CYP) P450-linked enzymes metabolise coumarin. Live microsomes include the CYP2A6 mono-oxygenase enzyme system, which causes hydroxylation to produce 7-hydroxycoumarin. Phase II conjugation process producing a glucuronide follows. 7-hydroxycoumarin is related to conjugation. When compared to the activity in the livers of other mammals, the 7-hydroxylase activity in human liver microsomes is unusually high. While non-existent in human microsomes, coumarin 3-hydroxylase activity is abundant in rodent microsomes. It is no table that all six possible hydroxylation locations can be used to break down coumarin a carbon. The metabolic product 7-hydroxycoumarin, however, has acquired recognition since it is created by humans and is simple to examine. The carbon hydroxylation by expanding the ring, three causes further metabolism and produces two additional by products, o- and o-hydroxyphenyl acetic acid, respectively. It must be mentioned that genetic and environmental variables lead to differences in CYP2A6 expression between persons, which results in inter individual variances in coumarin metabolism. The various studies proclaimed that some drugs, including various coumarin analogs are metabolized chiefly by CYP2A6. Many substrates and inhibitors currently known to be metabolized by or interfered with CYP2A6 in vitro and in vivo have been illustrated by Pelkonen . Nowadays, spectrofluorometry, high-performance liquid chromatography and capillary electrophoresis are employed for the analysis of many metabolic products. Recent in vitro studies include tissue slices, hepatocytes, subcellular fractions, and purified, and cDNA-expressed enzymes.

Various investigations suggested that CYP2A6 is primarily responsible for the metabolism of specific medications, including different coumarin analogs. There are numerous substrates and inhibitors that can either interfere with or be metabolised by Pelkonen has provided examples of CYP2A6 in vitro and in vivo. In the present, spectrofluorometry, Capillary electrophoresis and high-performance liquid chromatography are used for the examination of several metabolic products. Recent in vitro research on hepatocytes, tissue slices, enzymes that are cDNA-expressed, purified, and subcellular fractionated [14-16].

BIOLOGICAL ACTIVITY OF COUMARIN:
Antitubercular Activity:
With respect to the H37Rv strain, Tandon investigated the anti-tuberculosis (TB) potential of a number of amino and acyl amino coumarins. The MBCs, fractional inhibitory concentration index values, and cytotoxicity of the analogues were also evaluated. The least restrictive concentrations (MICs) for a clinical isolate of Mycobacterium that is drug-sensitive and drug-resistant. Additionally, TB was assessed. The test chemical underwent electron and fluorescence microscopy. To determine the target site, treated mycobacterial samples underwent further analysis. 7-Amino-4-methylcoumarin (7-amino-4-methyl-2H-chromen-2-one; NA5) shows the lowest MIC was 1 mg/L for methyl coumarin against the strain H37Rv[17].

With a MIC of 0.12 g/ml, compound (3a) demonstrated remarkable anti-TB activity. Compounds (3a, 3f) showed strong antibacterial action, while compounds (3a, 3b, and 3f) showed only moderate antifungal activity. Crystal X-ray analysis was used to determine the structural analysis of produced substances. Diffraction analysis and a molecular docking study against the M. tuberculosis 4DQU enzyme displayed amazing binding interactions [17-19].

Anticancer Activity:
The current standard of care for cancer patients is a combination of chemotherapy, radiotherapy, and surgery. Specific cancer types, such as Hodgkin's lymphoma, testicular cancer, and various leukaemias, have been successfully treated with these regimens.

Coumarins should not be utilised not just to treat cancer, but also to treat radiotherapy's adverse effects. A recent investigation Journal of In Applied Pharmaceutical Science, the effectiveness of the coumarin/troxerutin combination was examined. Therapy for patients having head and neck surgery to protect the mucosa and salivary glands radiotherapy. The findings imply that coumarin/troxerutin has a beneficial impact on the course of treatment. of mucositis and radiogenic siala/dentis. The use of coumarin and its 7-hydroxycoumarin derivative as reports that these agents had produced objective results in certain people led to the development of cancer agents, people with cancer that has spread. According to reports, coumarin and 7-hydroxycoumarin have some anti-cancer properties and have shown objective responses in some patients with advanced malignancies. Benci produced and examined the antitumoral potential of new 1,2,4-triazole derivatives (compounds 3-6), 4,5-Purine (Compounds 8–13) and dicyanoimidazole (Compound 7) coumarin derivatives and their Analogs of acyclic nucleosides. the outcomes of testing for antitumoral substances performed on human tumour cell lines, revealed that chemical 6 had a somewhat effective antiproliferative effect on the HeLa cell line. Compound 10 was only modestly active against the HeLa (IC50: 33 M), but compound 9 was (IC50: 35 M). HepG2 and SW620 cell lines had IC50 values of 25 and 35, respectively. Cheng compiled and clarified SAR.

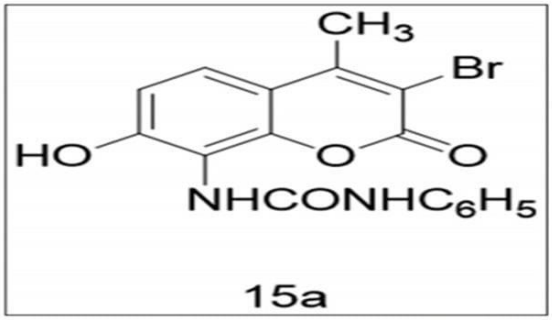


Figure 1: Structure of most active compound (15a) from novel 3-bromo-4-methyl-7-methoxy-8-amino substituted coumarins, benzoxazoles, and /or benzoxazine-8-ones.

Several different coumarin compounds that have anti-tumor necrosis factor (TNF) activity. Compounds 9 and 10 in particular shown impressive anti-proliferative action against a number of cancer cell lines, whereas compounds 12 and 15 demonstrated outstanding selectivity for HUVEC. Consequently, these analogues can be used as a model for creating new, non-toxic angiogenesis inhibitors and small-molecule ligands that target HUVEC [20-25].

Antimicrobial Activity :

Al-Haiza synthesized Pyrimidino [5`,4`-6,5] -pyridino[3`,2`- 6,5] -and pyrrolo[3`,2`-5,6] 4H-pyrano-[3,2-c] [1] benzopyran-6-one derivatives (5-7 and 10) by reacting 2-amino -4-(p-bromophenyl)-3cyano(carboethoxy) -4H,5H-pyrano[3,2-c] benzopyran-5ones(3a,b) with a variety of reagents . Alkylation of (3b) with either 2-furoyl chloride or chloroacetyl chloride produced 2-N-substituted derivatives (9a, b). Benzofurano [3,2-b] 4H-pyran derivative (was also prepared and investigated for antimicrobial activity. López-Rojas synthesized a novel series of 26 compounds having coumarin-1,2,3-triazole conjugates with varied alkyl, phenyl, and heterocycle moieties at C-4 of the triazole nucleus using a copper(I)-catalyzed, Huisgen 1,3-dipolar cycloaddition reaction.

The antifungal and antibacterial efficacy of each analogue was examined, and the findings showed that compound (4k) was a powerful antifungal agent while compound (4e) was a powerful antibacterial agent. The drug (4k) works by preventing the formation of ergosterol in using an ergosterol extraction and quantitation assay method, C. albicans was identified.The most potent substances, 4e and 4k, have no cytotoxic effects on a human cancer cell line[25-27].

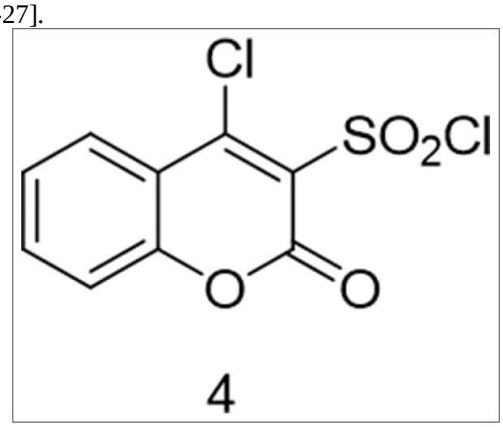


Figure 2: The structure of 4-chlorocoumarin-3-sulfonyl chloride

Antibacterial Activity:

The series of ring-opened products created by the reaction of 4-hydroxy and 7-hydroxycoumarin derivatives with activated aziridines analog. 3-carboxy coumarin amide dimer derivatives were also created by reacting aliphatic alkyl: Alkyl diamines and amines containing benzotriazol-1-yl N, N-Diisopropylethylamine and oxytripyrrolidino phosphonium hexafluorophosphate. A few of these substances' and their dimer derivatives' antibacterial activity was examined using modified imidazole containing coumarin analogs was produced for use in

micro-plate antibiotic susceptibility tests. Escherichia coli, Staphylococcus aureus, and other microorganisms were tested for antibacterial activity against the structure. Flavobacterium cloumnare and Streptoccus agalactiae. Following the principles of green chemistry, derivatives of 2,3-diyhdro-1,3,4-thiadiazoles, pyrazoles, and coumarin containing benzofuran were created, and their antibacterial properties were tested. Schiff bases, chalcones, hydrazones, and hydrazinylthiazoles derivatives included in 8-formyl-7-hydroxy-4-methyl coumarin derivatives were synthesised, and their antibacterial activity was reported by Hamid and Kubba. The findings demonstrated that new chalcones with a phenyl group in the structure exhibited outstanding effectiveness against Gram-negative bacterial strains. However, against Gram-positive bacterial strains, hydrazone and cyclized hydrazinyl thiazole derivatives showed good action. [28- 34]

Antihyperlipidemic Activity:

By using the Duff reaction on naphthalene-1-ol, Shashidhara designed and produced derivatives with both coumarin and indole moieties in a single molecule. This reaction was then carried out in a Knoevenagel-type reaction with the proper active methylene compounds. they were examined for hypolipidemic potential. Furthermore, these coumarin aldehyde derivatives were Iodine in acetonitrile is electrophilically replaced with appropriate indoles to create coumarinbis-indoleanalogs. Likewise, a different group of coumarinbis-indoleanalogs was also additional set of coumarinbis-indole analogs were created starting with 2-sec-butylphenol. In the hyperlipidemic hamster, these compounds were tested for hypolipidemic action. model. As far as coumarin is concerned, a pharmacophore is focused, and the The presence of ethyl ester and derivatives with substitution at position three both play important roles. is chosen for profound activity over methyl.

Unsubstituted indoles, on the other hand, were found to have a better activity profile than substituted indoles. One of the 12 investigated substances had plasma triglyceride levels that were reduced by 55% overall (R=-C2 H5 and R1 = R2 =-H). a 20% increase in total cholesterol (TC), along with a 42% increase in the HDL-C/TC ratio greater degree than any of the reference statins in hyperlipidemic rats [35].

Anticonvulsant Activity:

Siddiqui created numerous coumarin derivatives of heteroarylsemicarbazones by combining aryl aldehydes or ketones with heteroaryl hydrazine carboxamide. Pentylenetetrazole was used to test the analogues for their anticonvulsant activity. Maximum electroshock seizure tests were performed at dose levels of 30, 100, and 300 mg/kg. in addition to researching the signs of neurotoxicology. Having three compounds with 3,4-Cl.C6 H3, At a dose of 30 mg/kg, OCH3-C6-H4 and 4-Br-C6-H4 showed the strongest anticonvulsant effect. in contrast to phenytoin [36].

Tyrosine Inhibitor Activity:

Using the classic Perkin reaction and dicyclohexylcarbo dimide as a catalyst, Fais created coumarin-resveratrol hybrids from o-hydroxybenzaldehyde's (or their methoxy substituted counterparts) and the corresponding aryl acetic acids investigating the SAR with a dehydrating agent. These analogues displayed what the IC50 values indicated. action that inhibits tyrosinase. The most common form of 3-(3,4,5-trihydroxyphenyl)-6,8-dihydroxycoumarin powerful substance (IC50: 0.27 mM) compared to umbelliferone (IC50:0.42 mM). The kinetic research discovered that the substance caused tyrosinase to be inhibited non-competitively and the number. The amount, kind, and position of free hydroxyl groups are crucial factors in biological activity [37].

CONCLUSION:

Coumarins and its analogs obtained from either natural or synthetic sources exhibited vital biological potential.The coumarins are of great interest due to their biological properties. The key role of coumarin derivatives in plants and animal biology has not been explored until now. The study of novel approaches employed to design and synthesize coumarin analogs bearing essential biological activities along with the study of SAR in addition to the proposed mechanism of action is incorporated in this review. Therefore, this review will help the researchers to design novel coumarinanalogs by careful understanding of SAR studies incorporated in this review**.**Their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive for further backbone derivatisation and screening as novel therapeutic agents.Both coumarin and coumarin derivatives have shown promise as potential inhibitors of cellular proliferation in various carcinoma cell lines.

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