Natural and Synthetic Coumarins and their Pharmacological Activity

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ABSTRACT
Coumarins are a structurally diverse group of natural substances derives from plants that display a host of bioactivities. In this paper, we will introduce the reader to coumarins and their applications as medicinal substances. The great diversity in coumarin structure will be discussed along with their extensive use as pharmaceutical agents. Coumarins display a wide range of antimicrobial activity and applications of coumarins as antifungal and antiviral agents will be addressed. Other properties of coumarins such as their role in neuroprotection, anticancer, and as antioxidants will also be reviewed.

Keywords: coumarins, antimicrobial agents, neuroprotection, natural products in medicine

Introduction
Coumarins form an extensive group of natural substances known as secondary metabolites. They are found in over 150 different species of plants belonging to almost 30 different families. The families containing the highest content of coumarins are: Rutaceae, Clusiaceae, Guttiferae, Caprifoliaceae, Oleaceae, Nyctaginaceae and Apiaceae. 1 Coumarin compounds accumulate in large quantities in fruits (such as citrus fruits), vegetables (e.g., celery), roots, flowers and leaves. In smaller quantities they are isolated from bark and stems.2

Coumarins, in addition to occurring in vascular plants, are also found in bacteria and fungi such as novobiocin and coumermicin which are known antibiotics synthesized by bacteria. In contrast, Aspergillus flavus is a source of aflatoxin, a highly carcinogenic substance with acoumarin ring in its structure.3

Structural diversity of coumarins
The structural diversity of natural coumarins is the basis for classifying them into four groups:
1. coumarin derivatives, e.g. simple coumarin, compounds formed by two rings: benzene and α-pi-ron. Substituents are often hydroxyl, methoxy and aliphatic groups, at the C7, C6 and C3 positions of benzopyrone (Fig. 1).

Figure 1. Chemical structure of coumarin

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2. **isocoumarin derivatives**, formed by benzene rings and α-isopirone. They have substituents in positions C3, C6, C7 and C8 (Fig. 2). They are isolated mainly from fungi: *Artemisia, Aspergillus, Fusarium, Penicillium, Stremtomycetes* and the few plants belonging to families: *Compositae, Leguminoseae* and *Myriaceae*.4

![Figure 2. Chemical structure of isocoumarin](image1)

3. **furanocoumarin derivatives**, (Fig. 3) formed by the coupling of the coumarin ring with the furan ring at the C6-C7 position (psoralen type, Fig. 3A) or in the C7-C8 position (angelicin type, Fig. 3B).

![Figure 3. Chemical structure of furanocoumarin](image2)

![Figure 3A. Psoralentype](image3)

![Figure 3B. Angelicintype](image4)

4. **pyrancoumarin derivatives**, coumarine ring is condensed with pyran ring (Fig. 4). Ring condensation at the C6-C7 position is defined by the xanthyletin-type (Fig. 4A), or in position C7-C8 a seselin-type (Fig. 4B).

![Figure 4. Chemical structure ofpyrancoumarin](image5)

![Figure 4A. Xanthyletin-type](image6)

![Figure 4B. Seselin-type](image7)

**Pharmacological Activity of Coumarins**

Coumarins are a group of biologically active compounds. They are produced by living organisms (plants, fungi and bacteria) as secondary metabolites. Their activities are, among others, anti-inflammatory, antithrombotic, antimicrobial, antifungal, antiviral (including anti-HIV), anticonvulsant, antioxidant, and antitumor.1

**Anti-inflammatory activity of coumarins**

Coumarins (1,2-benzopyrone) have anti-inflammatory properties and have been used to treat oedema, helping wound healing. This removes protein and oedema fluid from injured tissue by stimulating phagocytosis and proteolytic enzyme production.5 Esculetin exhibited anti-inflammatory activity in rat colitis.6 Also, esculetin inhibits the cyclooxygenase and lipoxygenase enzymes, which results in an anti-inflammatory effect.7

**Anticoagulant activity of coumarins**

Vitamin K is a co-catalyst for the carboxylation reaction of the glutamic acid residue with γ-carboxyglutamic acid. The carboxylation process affects the further normal activity of coagulation factors II, VII, IX and X. Warfarin interferes with the cycle of vitamin K metabolism, resulting in liver deposition of partially carboxylated and decarboxylated proteins. These proteins are characterized
by decreased procoagulant activity. Coumarins interfere with the carboxylation process of C and S protein, causing a procoagulant effect.1

It has been shown that the warfarin - coumarin derivative, used as an oral anticoagulant, negatively affects the γ-carboxylation of glutamate residues of bone proteins. As a result of its action in pregnant mothers and those taking warfarin preparation, the fetal skeleton develops abnormally.6

Warfarin has shown particularly promising results in the treatment of SCCL (Small Cell Carcinoma Lung) a tumour cell type that is characterised by a coagulation-associated pathway.9

**Antimicrobial activity of coumarins**

Most coumarins have very low antimicrobial activity, but compounds having long chain hydrocarbon substitutions such as ammomasolin and ostruthin have a high activity towards gram (+) bacteria and show antimicrobial activity on *Bacillus megaterium*, *Micrococcus luteus*, *Micrococcus lysodeikticus* and *Staphylococcus aureus*.

Anthogenol, a coumarin derivative isolated from green fruits *Aegle marmelos* (L.), exhibits antimicrobial activity against bacteria of the genus *Enterococcus*.1 Imperatorin shows high activity towards *Shigella dysenteriae*.10

Pyranocoumarins such as grandivittin, agasyllin, aegelinol benzoate and osthole isolated from the root *Ferula lagoscampestris* (Besser) Grecescu (*Apiaceae*) show activity towards both gram (+) and gram (-) bacteria, for example on *Staphylococcus aureus*, *Salmonella typhi*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Helicobacter pylori*.11

Coumarins are mainly isolated from higher plants, but some of them have been discovered in microorganisms. Examples include novobiocin, coumerycin, and chartreusin. Novobiocin, a secondary metabolite of *Streptomyces niveus* and *Streptomyces spheroides* exhibit very high activity towards gram (+) organisms such as *Corinebacterium diptheriae*, *Staphylococcus aureus*, *Streptomyces pneumoniae*, *Streptomyces pyogenes* and *gram(-) organisms such as *Haemophilus influenzae*, *Neisseria meningitides* and *Pasturella*. Coumerycin, structural similar to novobiocin, exhibits almost 50 times more potency against bacteria belonging to *Escherichia coli* strains and *Staphylococcus aureus* strains. Alsochartreusin, isolated from *Streptomyces chartreusis*, shows activity towards gram (+) bacteria, but due to its toxicity, chartreusin has not been tried for treatment.1

**Antifungal activity of coumarins**

The broad spectrum of antifungal activity is shown by fraxinol, a derivative of coumarin isolated from celery plants. This derivative demonstrates activity against *Rhizoctonia solani* [Kühn], *Phytophthora capsici* [Leonian], *Botrytis cinerea* [Pers.], *Sclerotinia sclerotiorum* [de Bary] and *Fusarium graminearum* [Patch].13 A number of coumarins have been tested for antifungal activity, and the three most effective ones are psoralen, imperatorin, and ostruthin.14

**Antiviral activity of coumarins**

Coumarin derivatives can also have a reverse transcriptase (RT) inhibitory effect and show antiviral activity on *HIV* and *Fusarium graminearum* (*Clusiaceae*), belong to pyranocoumarin, inhibit RT activity and completely deactivate the replication process of HIV-1.15,16 Others coumarin derivatives – inophyllum B and P obtained from an giant African snail *Achatina fulica* ([Férussac]) significantly inhibit RT activity in HIV-1 cell cultures.17

Aminomethyltrimethyl psoralen (AMT) is used as a photo-sterilizing agent and is added to blood products followed by exposure to UVA radiation. AMT has inactivated DNA and RNA viruses.18 Sancho et al. showed that imperatorin also inhibits either vesicular stomatitis virus or gp-160-enveloped recombinant HIV-1 infection in several T-cell lines and in HeLa cells.19

**Antihypertensive activity of coumarins**

Scopoletin, a coumarin isolated from the fruits of *Tetraptera reticulata* (*Mimosaceae*), in laboratory animals shows a smooth muscle relaxant effect on blood vessels resulting in a drop in blood pressure. A similar action was shown by dihydromammaea; a coumarin isolated from the seed of the tree *Mammee africana* ([L.]) (*Guttiferae*).1

Visnadine – pyranocoumarin, an active ingredient extracted from the fruit of *Ammi visnaga*, exhibited peripheral and coronary vasodilator activities. It is used adjunctively to treat angina pectoris.20

**Antioxidant activity of coumarins**

Coumarin antioxidant activity is manifested by the ability to inhibit reactive oxygen species (ROS) and to capture them. Studies in rats have shown that the inhibition of xanthine oxidase - the enzyme responsible for xanthine biosynthesis, is directly proportional to the amount of hydroxyl groups that are contained within the molecule.21

Coumarin compounds can directly affect the properties of antioxidant enzymes. Luczaj et al. have demonstrated the effect of coumarin on superoxide dismutate, catalase, and glutathione peroxidase activity in plasma, liver, kidney and brain of rats.22,23 Following administration of esculetin and 7-hydroxycoumarin in mice, increased levels of vitamin E, vitamin C and glutathionewere found.24 It has been shown that fraxin in 0.5 mM concentration protects human umbilical vein endothelial cells (HUVEC) against oxidative stress caused by hydrogen peroxide.25

The antioxidative and cytopreparative character of fraxetin has been demonstrated. It effectively prevents...
oxidative stress-induced apoptosis of neuroblastoma cells—which can be used in the treatment of Parkinson's disease and other neurodegenerative diseases.26

Neuroprotective activity of coumarins
Alzheimer’s disease (AD) is a degenerative and progressive neurological disorder. It is characterized by variable levels of cholinergic enzymes and the formation of senile plaques containing β-amyloid proteins in cerebral tissue. In patients with Alzheimer’s disease is observed decreased or unchanging levels of acetylcholinesterase (AChE), level of second enzyme butyrylcholinesterase (BChE) increase. Therefore, the levels of AChE and BChE enzymes are considered to be crucial in the treatment of this disease. Orhan et al. have demonstrated significant inhibition of acetyl- and butyrylcholinesterase levels after application with bergapten, xanthotoxin, scopoletin, umbelliferone, and 4-methylumbelliferone.27

Recent computer techniques have allowed the design of an amine-substituted coumarin derivative. The synthesized compound 3-(4-[(benzyl(ethyl)amino)methyl]phenyl)-7-[4-(diethylamino)butoxy]-2H-chromen-2-one exhibits neuroprotective activity, expressed in AChE inhibition, and is a potential candidate for Alzheimer’s disease treatment.28

Osthole present among others in Cnidiummonnieri (L.) fruits is a commonly used substance in traditional Chinese medicine. Chen et al. investigated the effect of osthole on the demyelination process in the central nervous system of mice in an experimental model of multiple sclerosis.29 The results showed that osthole delayed disease progression and could find use in the treatment of multiple sclerosis.29

The use of coumarins in the treatment of skin diseases and of the hematopoietic system diseases
Therapeutic use has been found for two furanocoumarin derivatives 5-MOP (5-methoxypsoralen) as an N-acetyltransferase inhibitor and 8-MOP (8-methoxypsoralen) in phototherapy for psoriasis and vitiligo.

In treatment of the skin disorders vitiligo, psoriasis and atopic inflammation, bergapten has also been successful.30-31 Human keratinocytes of the NCTC-2544 line were exposed to bergapten, xanthotoxin, scopoletin, umbelliferone, and 4-methylumbelliferone.27

Very effective psoriasis treatment was achieved using xanthotoxin and the PUVA method which involves administering xanthotoxin gel directly onto the patient’s skin and then irradiating with UVB light.33,34

The Jurkat cell line (T-cell leukemia line) and normal lymphocytes were exposed to 8-MOP and then exposed to UVA light. There was a marked induction of apoptosis and a significant increase in caspases: 8 and 9 (initiator caspases) and 3 and 7 (effector caspases).35 This method, called photophoresis, which uses extracorporeal irradiation of blood cells previously exposed to 8-MOP, has been implicated in therapy for autoimmune diseases, such as T-cell lymphoma.36 Photophoresis increases apoptosis in lymphocytes, causing them to die and induce the formation of postapoptotic vesicles with anti-inflammatory properties.37 Another feature of xanthotoxin used in vitiligo treatment is the ability to induce skin regepment. Coumarin increases the intracellular concentration of calcium ions and affects the organization of actin fibers in the cytoskeleton of melanocytes, which in turn leads to their migration.38

Anticancer activity of coumarins
In research on GLC (small cell lung carcinoma) and COLO 320 (colorectal cancer) cell lines, it has been shown that the cytotoxicity of coumarin is due to the presence of at least two phenolic groups at the 6,7- or 6,8-position in the ring of the molecule.39 The proliferation of the 786-O and A-498 (kidney cancer) and DU145 and LNCaP (prostate cancer) cells line were inhibited by coumarin and its hydroxyl derivative, umbelliferone.40,41

Several hydroxylated and methoxylated coumarin derivatives were tested for their relative cytotoxicity on four human HSC-2 tumor cell lines, HSC-3 (oral squamous cell carcinoma), A-375 (melanoma) and HL-60 (promyelocytic leukemia). It has been shown that the cytotoxicity of 6,7-dihydroxycoumarin towards HL-60 tumor cells can be further enhanced by substituting the -OH in 3 and/or position 4.42 Similar conclusions were made by Budzisz et al. by QSAR regression analysis of the relationship between biological activity and physicochemical properties of test compounds. The cytotoxic effect increases with increasing hydrophobic substituents in 2, 3 and 4 positions of the benzopyrene ring.43 The cytotoxic activity of organometallic coumarin complexes (umbelliferone, mendixan, warfarin, coumarchlor, and nifflcoumar) towards P3HR1, K-562 and THP-1 leukemia cells lines were confirmed.44 Nitrocoumarin derivatives of 7-hydroxy–6-nitrocoumarin and 7-hydroxy–3,6,8-trinitrocoumarin exhibited cytotoxic activity against tumor cells of the melanocytic line (SK-MEL-31).41 On the other hand, 8-nitro-7-hydroxycoumarin induced apoptosis of leukemic cell lines K562 and HL-60.45

Coumarin derivatives exhibit specific cytotoxicity, which is closely related to the chemical structure of their molecules.41 Attempthve have been made to synthesize a coumarin-like compound with selective and targeted action on tumor cells. Extremely cytotoxic heterocyclic coumarin derivatives which have 1,2,4-triazole, 4,5-dicyanoimidazole or purine groups have been obtained. In addition, the 1,2,4-triazole-3-carboxamide derivative exhibited particular selectivity to HeLa human epithelial
It has been observed that combination therapy with dicumarol, coupled with a chemotherapeutic agent, can improve efficacy and reduce toxicity compared to coumarin alone. The use of the dicumarol with taxol complex has antiproliferative effects on the hedgehog larvae (Strongylocentrotus purpuratus) [Stimpson]. The positive result was explained by the synergism of the cytostatic and dicumarol. The authors suggest that the future of the development of combined pharmacotherapy may be the basis of modern chemotherapy.

It has been found that coumarins eaten in human diet can positively affect the body. Observations indicate that even if present at low levels in apiaceous vegetables, imperatorin, trioxsalen and isopimpinellin may contribute significantly to CYP1A2 inhibition and potentially decreased procarcinogen activation.

**Conclusion**

Coumarins are a large group of biologically active compounds commonly used in natural medicine.

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Xanthonylethin isolated from *Erythrinvariegata* [L.], stimulated gastric cancer cells of the SGC-7901 line, induced apoptosis and cell cycle arrest. It was noted that this action was associated with DNA damage. The process of apoptosis in cells was caused by mitochondrial damage and the cell cycle was stopped in phase S.55

In cancer therapy, a very important issues are angiogenesis, i.e. the formation of blood vessels within the tumor and metastasis. The 7-diethylaminocoumarin derivatives exhibited activity as angiogenesis inhibitors towards tumor cells and were highly selective to normal HUVEC (human umbilical vein endothelial cells).56 In other studies, the synthetic brominated coumarin derivative showed cytotoxic and anti-proliferative effects on EAC (Ascitic Carcinoma) and DLA (lymphoma) carcinoma cell lines. Inhibition of blood vessel formation and stimulation of apoptosis has also been observed.57

**Cells** (cervical cancer).41 In contrast, the presence of the 2-amino-6-chloropurine group conditioned the cytostatic effects on HepG2 (hepatoma) and SW620 (colon) cells line, leading to mutations in the p53 gene.46

Osthole stops proliferation of human breast cancer cells MCF-7 and MDA-MB231 by inhibiting metalloproteinases in the outer cell matrix, slowing down the migration and further invasion of tumor cells.47,48

Grandivittin, agasylalin, agelinol benzoate and felamidin, four natural coumarins isolated from *Ferulagocampsis* *(Apiaceae)*, and several synthetic ester derivatives of agelinol were tested against four tumor cell lines. Some of them were shown to be marginally cytotoxic against the A549 lung cancer cell line.49 From *Canophyllundispar* (Clusiaceae), eight 4-phenylfurano coumarin derivatives were isolated that showed significant cytotoxicity to cervical cancer (KB).50

Panno et al. stimulated bergapten on breast cancer cells MCF-7 (human adenocarcinoma cell line) and SKBR-3 (malignant breast cancer cell line). Bergapten, independently of photoactivation, caused cell cycle arrest in G0 / G1 phase, inserting breast cancer cells into the pathway of apoptosis, and counteracting the stimulating effect of IGF-I/E2 on MCF-7 cell line growth.51 Further study of the team, conducted on human breast cancer cells MCF-7, ZR-75 and SKBR-3, confirmed the antiproliferative and apoptotic effects of bergapten and its UV-activated derivative.52 Molecular studies of mammary gland cells have determined the function of the membrane estrogen receptor α (ERα). ERα is involved in the normal development of the mammary gland as well as in the tumor-resistant MCF-7 breast cancer resistant to tamoxifen. Stimulation with bergapten causes ERα to decrease with anti-tumor and mitogenic effects.53 Recent studies show that bergapten induces the metabolic reprogramming of breast cancer cells MCF-7 pathways and ZR75. Therapy with bergapten causes changes in metabolic pathways, inducing cell death.54

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